Lionel Trottet · Howard Maibach

Dermal Drug Selection and Development

An Industrial Perspective

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To Elena, Silvia, Claudia and Luca

Preface

Delivery of drugs through skin has been an attractive area for research and for pharmaceutical companies as it can offer larger therapeutic window compared to systemic delivery.

Dermal drug development started back in the 1950s with corticosteroids as, despite impressive efficacy, corticosteroids use was limited because of the serious adverse events observed when administered systemically for long periods. The efficacy of topically delivered hydrocortisone then paved the way to further corticosteroid drug developments. Over the years the successful development of retinoids, vitamin D3 derivatives and immuno-suppressors has further proved the dermal potential for drug target classes with difficult safety profile.

In the last 15 years, the strong move of the pharmaceutical industry to focus on new mechanisms of action—rather than "me too" approaches—has multiplied the number of new target classes that could address skin diseases. Moreover because of the risk of target-related toxicity, a fair number of drug candidates for various targets are being abandoned as no viable indication for a systemic use can be found. This has created a renewed interest among the pharmaceutical industry to investigate the dermal route for these failed molecules.

Unfortunately, the desired profile of a dermal drug candidate is somewhat different to that of a systemic drug candidate. Moreover, if know-how to select and develop an oral/systemic drug is well established it is much less so for a dermal drug. All this together can often lead to the selection of poor drug candidates.

Offering the perspective from the industrial side, *Dermal Drug Selection and Development* aims to describe how the pharmaceutical industry faces the selection of dermal drugs complete with the challenges and opportunities of the field. It covers the various parameters important to consider when choosing a drug candidate, some tricks and pitfalls as well as the scientific gaps that exist in the drug selection process such as dermal pharmacokinetics and the resulting uncertainty for drug discovery teams.

The first chapter of the book allows the reader to get a grasp of what is at stake with the development and selection of a candidate medicine in general and the particular elements linked to a dermal drug. Chapter 2 then reviews the historical

development of the major classes of topical drugs. In Chap. 3, the learnings from past topical drug development are listed with a particular focus on the key factors affecting the efficacy of a dermal drug. In the following chapter, the dermal and oral/systemic drug discovery processes are compared. Dermal pharmacokinetics, dermal efficacy assessment as well as therapeutic index assessment and their gaps are then discussed in Chaps. 5, 6 and 7. Some interesting approaches in these three chapters are described which should hopefully help drug discovery teams in their drug candidate selection. A chapter is then dedicated to the dermal formulation. Chapter 9 lists the four main approaches that a pharmaceutical company may decide to take when developing a new dermal drug. In the next chapter, the various criteria to select a dermal drug candidate are discussed and an example of a screening cascade is given. Chapter 11 is somewhat provocative listing 14 quotations and rules that could be useful during the selection and development of a dermal drug. The final chapter tries to weigh the pros and cons of dermal drug development and gives some perspectives of potential emerging approaches which could make such development even more successful.

Acknowledgements

First, I wish to acknowledge the exceptional support and guidance that I have received from Adrian Davis, who introduced me to the field of topical drug delivery and to dermatology 22 years ago and whom I worked with closely for many years. I also thank Jonathan Hadgraft, my Ph.D. supervisor, for the various discussions on topical drug delivery and for his support and patience during my Ph.D. I am grateful to Howard Maibach who convinced me to write this manuscript many years ago and then helped to write it, improve it and get it to publication. I would like to thank the team at Springer for their support and dedication to publish this book. I should add finally that the interactions in various forms with colleagues within GSK, the industry and in the academia have influenced, in one way or another, the content and thinking around this manuscript. I am therefore thankful to my colleagues at the GSK and Oncodesign François Hyafil Research Center in France, to my ex--colleagues at the GSK Consumer Healthcare Research Center in Weybridge (UK), as well as to Adam Watkinson, Adrian Williams, Amyn Sayani, Andrew Renwick, Annette Bunge, Brian Barry, Charles Heard, Craig Newby, Christian Surber, Christine Parker, Dominic Sanderson, Larry Jolivette, Lotte Groth, Mark Brown, Mark Levick, Mike Roberts, Leandro Santos, Peter Eddershaw, Richard Guy, Simon Blake, Simon Gallagher, Simon King, Simon Taylor, Sukhdev Bangar, Sanjay Kumar, William Higuchi and Tim Carter.

Contents

Chapter 1
Introduction

In this chapter, the manner a new drug is discovered and selected as well as the costs, challenges and risks around the selection of a candidate molecule are discussed. As candidate quality impacts attrition in later phases of development this concept is developed as well. The aim is to frame the key aspects of drug candidate selection in general to place into context the challenges that a drug discovery team would face for the selection of a dermal drug candidate. Finally, specific risks and opportunities for selecting such a dermal drug candidate are presented.

1.1 Developing a New Medicine

Developing a new drug, whether a small or large molecule, whether for local delivery or systemic delivery, is a complex process which can take 12–15 years and cost in excess of $1 billion [1, 2].

The process to develop a new drug is divided in several steps and mainly aims at minimizing the substantial risks inherent to such a development. It follows broadly five stages [2] as shown in Fig. 1.1. The first is a research stage during which the target, the mechanism of action is considered and studied. Such research often occurs in academia. Once the mechanism of action is associated with a disease, a second stage can begin where a pharmaceutical/biotech company could decide to start a drug discovery project aiming at finding a candidate molecule. If the candidate molecule is found, the project will move into a preclinical development stage where various efforts especially in safety assessment, pharmaceutics development and chemical development will occur. Then the clinical phases will start and eventually, if successful, a New Drug Application will be filed to regulatory bodies.

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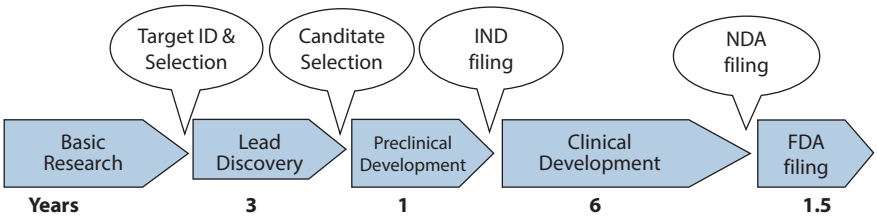

Fig. 1.1 Drug discovery process from target ID and validation through to filing of a compound and the approximate timescale for these processes. *FDA* food and drug administration; *IND* investigational new drug; *NDA* new drug application. From [2]

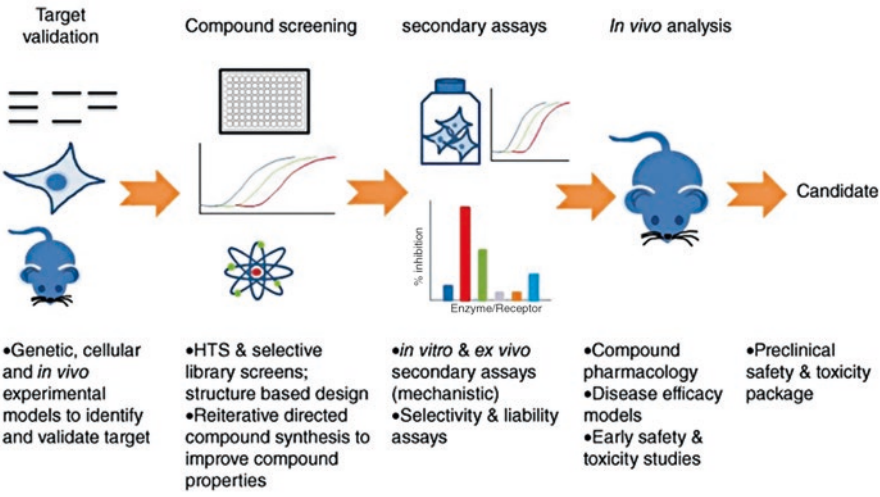

Fig. 1.2 Overview of the drug discovery assays. From [2]

Within this process, drug discovery (lead discovery in the previous figure) is the stage during which the drug molecule will be designed, synthesised, assessed and selected. It will involve efforts from disciplines such as biology (in vitro and in vivo pharmacology), medicinal chemistry, pharmacokinetics and safety assessment. Many assays will be performed during this drug discovery phase (Fig. 1.2).

The early molecules obtained after a high throughput screening (HTS) are most of the time minimally active and not selective, and often with undesirable pharmacokinetic properties (low bioavailability, high systemic clearance). To obtain sustained systemic target engagement would require to dose such molecules several times a day at doses exceeding 10 g with a risk of having off target side effects. The drug discovery phase will, therefore, be an iterative phase—as described in Fig. 1.3,

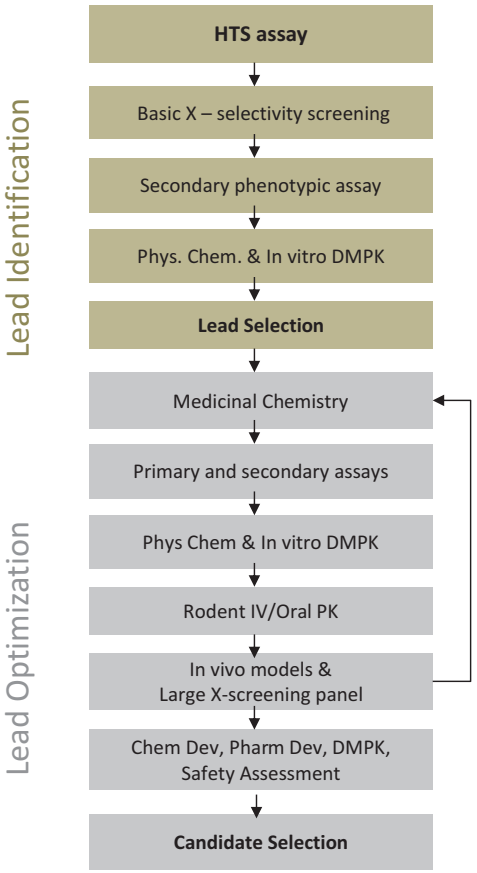

Fig. 1.3 Example of a screening cascade during the lead identification-optimization phases (= Drug Discovery)

where new molecules will be synthesized and optimized on selectivity, potency and pharmacokinetic properties in order to obtain, ideally, a selective molecule with once daily administration with a projected dose inferior to 100 mg.

Once the candidate is selected the die is cast when it comes to the risks on the molecule being progressed. A bad selected candidate is unlikely to make it to the market despite all efforts from the program team during the preclinical and clinical phases that will follow its selection.

Indeed, such phases do not compare various molecules in order to select the best one but they just work on, the one selected at the candidate selection stage. So the quality of the selected molecule will not change in the preclinical and clinical phases.

The preclinical phase is a preparation phase for the clinical phases where large quantity of drug material is synthesized, where the toxicology profile and metabolism profile of the candidate are further explored and where the formulation is prepared.

The clinical phases will aim at confirming that the pharmacology is the expected one and that the therapeutic window is sufficient to progress to a medicine. The Phases 1 and 2 with a relatively low number of subjects and patients will increase the comfort level to answer these questions before the large Phase 3 studies, involving many more patients.

1.2 Key Risks at the Candidate Selection Stage

The quality of the molecule selected will impact the attrition that will be incurred in the following expensive clinical phases. The major risks that are being taken forward at the candidate selection stage (for a new mechanism of action) are on the therapeutic window (i.e., the difference in drug plasma exposure in between the beneficial effects and the undesired ones) and on the translation of the pharmacology for the targeted disease. For research program working on a known and proven mechanism of action, these risks are much lower.

In order to decrease these risks the project team will pay special attention to three elements:

1. Good literature and genetic data are available, sufficient in vitro biology and in vivo pharmacology studies have been conducted to allow a good comfort level that the expected pharmacology will translate into beneficial pharmacology in the targeted disease.
2. The quality of the assessment of predicted exposure that will lead to good target engagement. This consists in assessing three fundamentals aspects often quoted as the three pillars [3] represented in Fig. 1.4: (1) target exposure, (2) target bind-

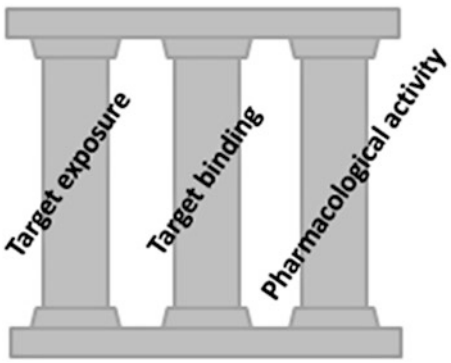

Fig. 1.4 Three pillars concept for assessing target engagement

ing and (3) pharmacological activity. Getting the right assessment on these three pillars will anchor the target exposure required and therefore help to estimate the therapeutic window and to predict the dose.

3. The safety profile for the projected exposure in man has been well assessed and appears to offer a reasonable therapeutic window. The therapeutic window assessment will be of good quality if the predicted required exposure to achieve efficacy has been well assessed.

1.3 Attrition in the Pharmaceutical Industry

The pharmaceutical industry has the particularity compared to most industries to have a high percentage of its research projects that will fail even after several years of development. As seen previously, a molecule reaches the clinical phase most often after at least 3 years of research. Despite substantial efforts and risks being discharged by then, from Phase 1 to market, the overall success rate to market is only 7.5% for a small molecule and 15% for a biologics [4]. Most risks that the candidate molecule carries after its selection are being discharged during the first two clinical phases (Fig. 1.5) [5].

Whether the candidate failures are flagged with "lack of efficacy" or "safety issue," these two reasons represented 70% of the Phase 2 failures in the period 2008–2010 (Fig. 1.6) [6].

These two reasons of failure mirror the two major risks discussed earlier that are being taken forward at the candidate selection stage (for a new mechanism of action)

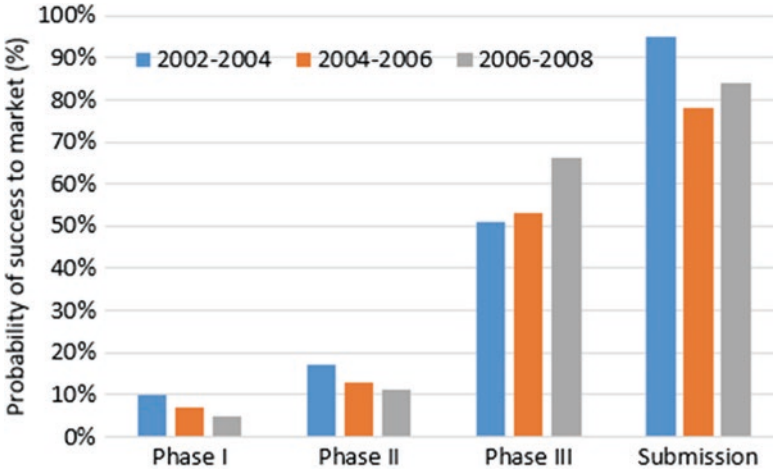

Fig. 1.5 Probability of success to market from key milestones

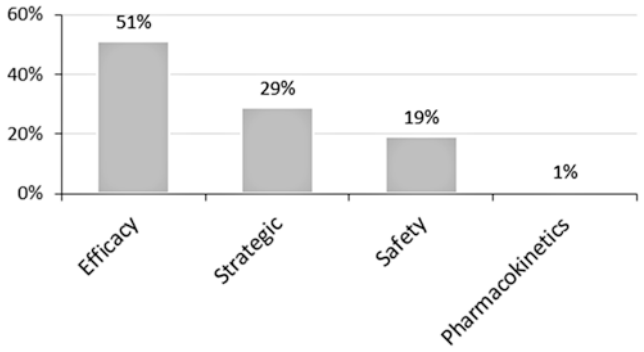

Fig. 1.6 Reasons of Phase 2 failures: 2008–2010

which are: (1) the translation of the pharmacology for the targeted disease and (2) the therapeutic window.

1.4 Evolution of the Pharma R&D Over the Last Two Decades

Despite improved processes, assays and criteria used to reduce attrition since the early 90s, external reasons have increased the attrition rate in the pharmaceutical industry over the past two decades. The three principal factors are: (1) increased focus on safety from regulatory bodies characterised for example with longer phase 3 studies, (2) requirement for many NDA filing to have outcome studies and (3) probably the most important one, requirement by the payors to demonstrate superiority to standard of care.

The first two reasons have increased attrition, cost and time to market and pushed the industry to abandon some assets because of the increased risks and lower expected return on investment on these assets which pushed further the attrition rate up. On the other end, the pressure from payors to demonstrate superiority to standard of care has pushed the industry to move into new mechanisms of action which have had as well a large impact on attrition rates.

Indeed, moving into new mechanisms of action means taking much higher risks. Developing a new drug with a known and proven mechanism of action mainly meant that the key risks of target related toxicity and wrong pharmacology for the targeted disease indication were already discharged. With a “me too” or “me better” drug discovery program, which represented a large number of drug discovery projects in the 80s and 90s, the focus was most often to have an improved pharmacokinetic profile, to decrease the dose and to improve selectivity versus the first in class drug. The drug discovery processes improvement since the early 90s have allowed researchers to gain confidence at an early stage (before candidate selection) that such criteria would be met in the clinical Phases 1 and 2.

With a new mechanism of action, however, increased confidence on the criteria of low dose, selectivity and good pharmacokinetic profile have still to be met, but the risk related to the translation of pharmacology for the indication has to be managed, as also is the toxicological risk associated with the target.

The risk on the pharmacology can be difficult to assess. First, more than 50% of results in published papers on new drug targets cannot be reproduced [7]. This can mislead the decision taken by the pharmaceutical program team to progress on a new target. However, this can be discharged most often during the early phase of the drug discovery stage. It will cost time and money but is before the clinical phases start. A more difficult task is the translation of animal models into human diseases, as this can only be tested in a clinical proof of concept study in man (Phase 2 study most often). Attrition in that case will be flagged with "lack of efficacy".

Many new mechanisms of action will lead to target related unacceptable side effects. Figures on that important cause of attrition are however unavailable. A large number of such new mechanism of action programs will be stopped before candidate selection when it is assessed that the therapeutic window will not be high enough to envisage a medicine for that target. However, a fair number of new target assets will progress in Phases 1 and 2 as it can be difficult to know whether the therapeutic window will be viable or not at a pre-candidate stage (often because of uncertainty on the required exposure in man to explore the mechanism of action). The difficulty then is that the maximum dose—limited by the toxicology observed in preclinical species—at which the candidate drug will be given to patients may not allow to fully explore and test the mechanism of action as showed in Fig. 1.7 [8]. For example, with an inhibition mechanism, if the maximum clinical dose tested can only achieve 60% of inhibition—because of side effects limitation—while 90% or more would have been required to exert the desired pharmacology, the mechanism

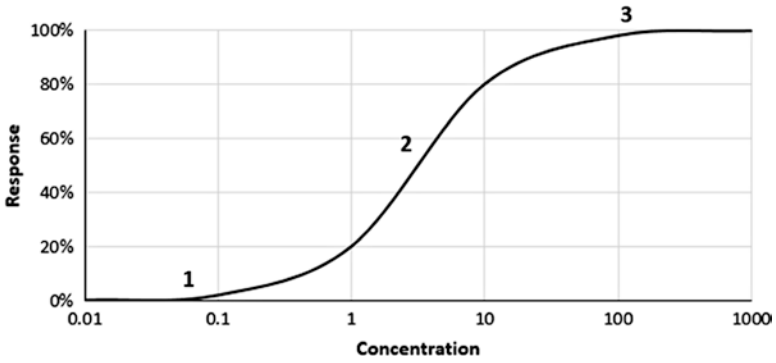

Fig. 1.7 Concentration-response curve. Region '1', limited to no efficacy which cannot allow to conclude whether poor compound or a flaw in the mechanistic hypothesis. Region '2', some efficacy which may have been limited by safety. Region '3', full target engagement which allows to understand the mechanistic hypothesis

of action will not have been fully explored. Target related toxicity can therefore lead to program termination flagged with "safety issue" or flagged with "lack of efficacy" because the target could not be sufficiently engaged.

New mechanisms of action and failure due to "safety issue" or "lack of efficacy" as shown earlier (Fig. 1.6) [6] can go therefore hand in hand.

Overall, the pharmaceutical industry is therefore faced with the following dilemma: The need to accept higher attrition in its R&D phases if it wants improved drug efficacy over standard of care and therefore reimbursed medicines by the payors.

1.5 Pharma R&D Productivity in Decline

One would have thought that the advances in the understanding of the molecular basis of diseases which have expanded the number of plausible new targets in recent decades, would have translated into higher R&D productivity. However as seen earlier, this move into new mechanisms of action has increased attrition, which, expectedly, has had a consequence on the R&D productivity. Although R&D output, measured as approved New Molecule Entities (NMEs), remained relatively constant during the period 1997–2013 (Fig. 1.8) [9], inflation adjusted R&D costs increased manyfold giving rise to the marked decline in the overall R&D Productivity during the period 1997–2013 (Fig. 1.9) [9].

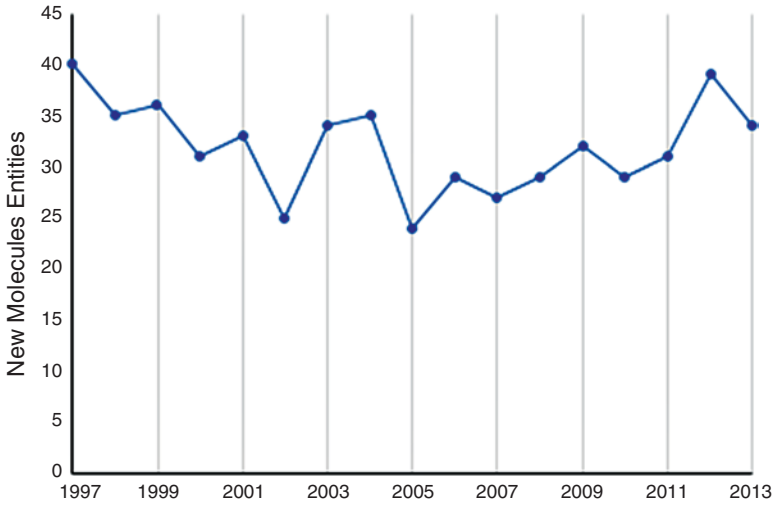

Fig. 1.8 Number of new molecule entities (NMEs) approved by the FDA from 1997 to 2013

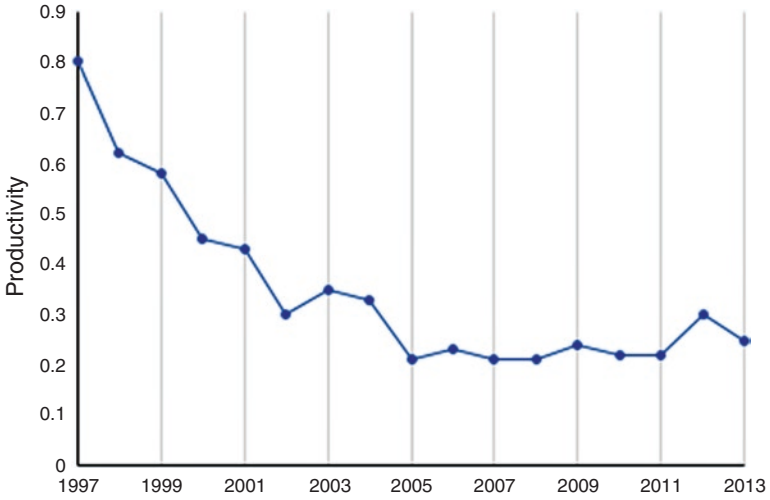

Fig. 1.9 Pharmaceutical R&D productivity 1997–2013. R&D productivity is expressed as the number of new molecule entities (NMEs) per $US billion R&D spent per annum

1.6 Cost of Pharma R&D and Cost Up to Candidate Selection

In 2010, Paul et al. [1] published the individual costs of drug development (Fig. 1.10). They took into account the cost per phase, the attrition rate of each phases (p(TS)), the duration of each phase and cost of capital. The estimated cost of R&D for the launch of one compound was about $1.8 billion in 2010 from this analysis.

If we focus on the early phases up to candidate selection, the total cost of a candidate for a successful program will be $13.5 million (target to hit + hit to lead + lead optimization). Taking into account the cumulative attrition rates (80%, 75% and 85%) in these early phases, the R&D cost to get a candidate is therefore $26.5 million.

Terminating a single lead optimization program before or just after candidate selection is a substantial loss for the Pharma company which will have invested in that program. As seen previously, such termination can happen for various reasons but most often it happens when target related toxicity prevents further progression for the target. By that time, highly potent and candidate like molecules will have been identified. A large asset that often contains several chemical series is then lost. This can give big incentives for Pharma companies to repurpose such failed lead optimization programs in an area where target related toxicity may not be an issue. Repurposing such assets in a dermal indication where systemic exposure is avoided can often be considered.

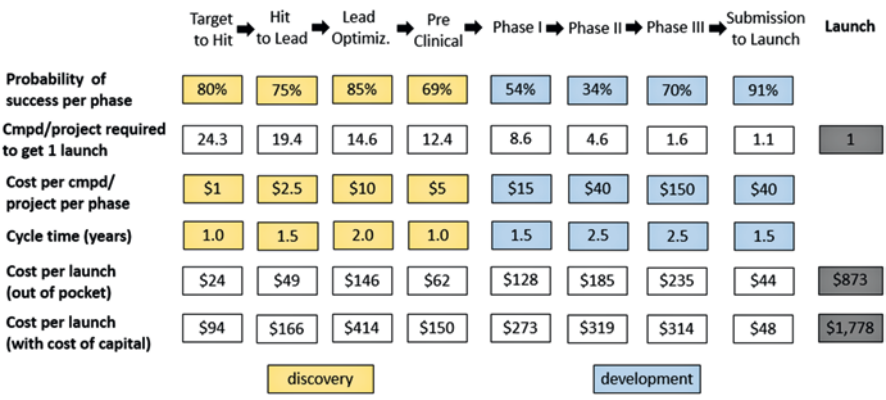

Fig. 1.10 R&D model yielding costs to successfully discover and develop a single new molecular entity (cost: in $ million)

1.7 Increased Risks in Developing a Topical Drug

For topical dermatologicals the attrition figure for a success rate from candidate selection to the market is not available. As will be seen later on, if the process to develop and select a candidate systemic molecule is well established, it is not so for a topical candidate as the prediction of target engagement (the three pillars [3]) so crucial to define the dose and go/no go decision is largely absent with a topical project.

In overall risk and failure of systemic molecules at Phase 2, (see Fig. 1.6) pharmacokinetics issues represents now only about 1% of these failures [6] demonstrating the quality of the process in place to discharge the DMPK (Drug Metabolism and PharmacoKinetics) risk.

It is particularly interesting to go back to the early 1990s where pharmacokinetics represented about 40% of failure of clinical asset. At this time the pharmacokinetic science was just emerging and was being developed by the industry. Attrition dropped then to 10% in 10 years thanks to the emergence within the industry of the right screening tools to understand pharmacokinetics and remove early the molecules displaying inappropriate DMPK properties [10] (Fig. 1.11).

With a topical dermatological project, the proportion of projects failing due to inappropriate properties is not known but it is likely high for two reasons:

1. Topical pharmacokinetics is not or poorly understood (see Chap. 5). It is therefore as if the industry is at a stage before 1990 as in most cases a "No Go" criteria based on DMPK (Drug Metabolism and Pharmacokinetics) are not used. and
2. Skin is an impermeable barrier compared to the intestine leading to large difference in permeation across compounds up to a 1 million fold difference (see Table 1 in Chap. 6).

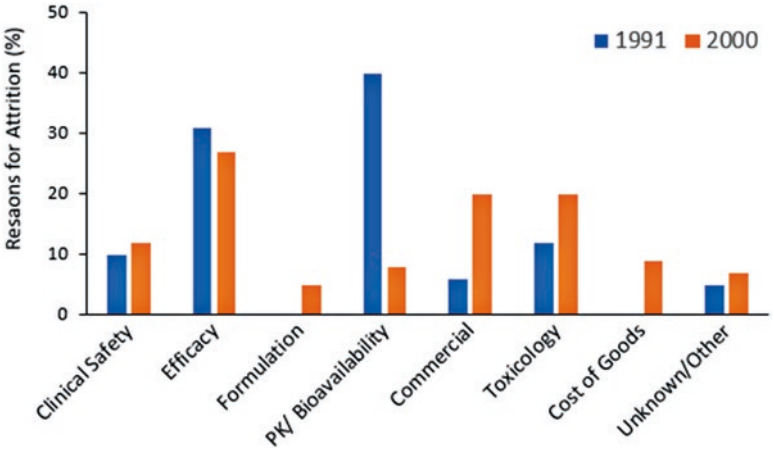

Fig. 1.11 Reasons for attrition (1991 and 2000)

Pharmacokinetics represents therefore a large un-discharged risk for molecules progressing in the clinic. As a consequence inappropriate pharmacokinetics will translate into a large risk for target engagement which will remain until the read out of the clinical proof of concept study.

Other risks specific to a topical have to be discharged as well, such as, the 2-years shelf life and the difficult hydrolysis stability in solution, as well as the local photo-toxicology and the local skin toxicology.

Overall the lack of knowledge from non-specialised pharmaceutical companies to develop a dermal compound will tend to put the bar of success higher than it could have been if the right process, criteria and knowledge would have been applied by the research program team.

Pragmatism in the industry is another aspect that will increase risk and attrition for the successful development of a dermal medicine. Most often the industry will consider the move towards a topical indication after the research project has reached a road block No Go decision often linked to target related toxicity or sometimes because of poor translation of the pharmacology to the targeted disease. At this point in time, the research program team will, most often, have developed a single molecule. This molecule will look like a good molecule for a systemic delivery, the toxicology package will be available and sufficient API (Active Pharmaceutical Ingredient) material will have been synthesised by then. The natural vision at this stage will most often be that the research team would only consider this molecule as a topical candidate, as large cost on this asset would have been spent and would not have to be spent if no other molecule is considered. This approach can work sometimes but often fails because the criteria to develop and progress a topical are different to the one for a systemic compound.

1.8 Increased Opportunities to Develop a Topical Drug

As just described, there are in some areas of the topical drug development some increased risks with a topical versus a systemic one. There are, however, some strong opportunities. Three are listed below:

1. Reduced risk of toxicity
   The most recognised one is the decreased risk of toxicity. This is well proven by key topical target classes such as corticosteroids, immunosuppressors, retinoids and vitamin D3 derivatives which have side effects difficult to manage if given systemically for long period but which are effective and mostly safe when given topically.
2. Large number of assets to test
   The move of the pharmaceutical industry to new mechanisms of action means more mechanisms to test are available. Moreover because of the high risk of target related toxicity, large number of asset molecules for various targets end up being abandoned as no viable indication for a systemic use can be found. Some of these molecules could be of interest for a skin disease as systemic toxicology would not be an issue in most cases.
3. Competitive advantage by better selecting topical candidates
   As seen previously, if there are increased risks with a topical because of poor understanding of successful criteria to select a candidate, on the other end these risks will become opportunities if they can be better understood and if a better risk discharge cascade can be put in place. Indeed this would allow the following:

   - To revisit mechanisms of action where the pharmacology was right but the compound was not right (no target engagement achieved).
   - To improve current proven effective mechanism where pharmacology had not been fully exerted because the target was not fully engaged (only partial efficacy achieved).
   - To improve compliance by having a more powerful topical drug which would allow formulations in possibly inferior delivery vehicle but more aesthetically pleasing medicine for the patient (e.g., clobetasol propionate the most potent corticoid).

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Chapter 2
Choosing Topical Drug Candidate: Historical Overview

2.1 The Pragmatic Topical Drug Development Approach: An Existing Oral/Systemic Drug is Further Developed as a Topical

Historically most topical drug classes seem to have been originally developed following the pragmatic principle that, "if an existing drug with an interesting pharmacology is effective orally/systemically, and the target is in the skin, it could well work topically without giving side effects and, therefore, would deserve to be tried topically".

The next paragraphs review the development of the "first in their class" topical drugs. Most of the major classes of topical drugs are reviewed with the aim of understanding how the first molecule of each class was selected.

2.1.1 Local Anaesthetics (<1900)

Local anaesthetics can be considered as the oldest class of synthetic topical drugs as most of the molecules of this class were first synthesised in the first half of the twentieth century or before [cocaine (plant extract 1860), benzocaine (1895), procaine (1906), butacaine (1920), amylocaine (1928), dibucaine (1931), tetracaine (1932), lidocaine (1948), prilocaine (1960)] [1, 2].

Natives of the Andes region of Peru were the first known users of a local anaesthetic by chewing the leaves of the Coca shrub that produced both numbness of the tongue and intense central nervous system stimulation [3]. In 1860, Niemann reported the extraction of cocaine from the coca shrub [2]. Local anaesthetic properties of cocaine were first noted a decade later after its introduction by a Peruvian army surgeon [3].

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It is difficult for such an old drug like cocaine to grasp how its pharmacological/medical use as a local anaesthetic was generated. Indeed one could interpret in different ways the facts presented in the previous paragraph. The pragmatic approach described in the introduction to this section is therefore difficult to demonstrate for this class of drug.

It is noteworthy, that most of these drugs are not indicated for use on skin but on the eyes or on mucosal membranes. It is only recently, that topical treatments indicated for skin anaesthesia have been introduced: Ametop® (tetracaine), and EMLA® (lidocaine + prilocaine). This does suggest that the history of local anaesthetic development for an intact skin anaesthesia indication has not been straightforward.

2.1.2 Corticosteroids (1952)

Topical corticosteroids constitute the most important class of topical drugs available. They are considered as the most effective and the most widely used treatment of dermatoses. They form as well one of the oldest topical drug class (appearing in the 50s) and the largest one with more than 20 molecules marketed [4].

The history of corticosteroids begins after the demonstration in 1927 that crude extracts of adrenal tissue could maintain life in adrenalectomised animals. In 1936, Kendall's compound E (later to be known as cortisone) isolated from adrenal cortex was proved to be effective in a non-specific test. Over the next decade, synthesis of this compound as well as other adrenal cortex isolated compounds (like hydrocortisone) took place. Eventually in 1949, Kendall's compound E was administered orally in two patients with rheumatoid arthritis, an inflammatory disease [5]. That year, compound E (cortisone) and compound F (hydrocortisone) of Kendall are first listed in the Index Medicus under the heading Adrenal Preparations [6]. In 1951, oral cortisone was reported to be effective in treatment of dermatology conditions [7]. At the same time, cortisone acetate ointment is tried but failed to deliver benefits [8–10] as it is not metabolised to hydrocortisone in skin. The first effective topical corticosteroid trial comes a year later with topical hydrocortisone reported by Sulzberger and Witten [11].

Hydrocortisone, an existing molecule (an endogenous compound) is the first topical corticosteroid to be developed successfully. The pragmatic concept to try topically an effective existing molecule does apply for the first successful drug of this important topical drug class.

2.1.3 Retinoids (1962)

For dermatoses, the next important class of topical drugs developed after the corticosteroids were the retinoids. This class of compounds is largely used for the treatment of psoriasis and acne.

As for the corticosteroids, the history of retinoids starts in the 20s when in 1925, Wolbach and Howe demonstrate that deprivation of vitamin A in animals and man led to hyperkeratosis [12]. In the 40s, the oral administration of large doses of vitamin A is tried with varied success to treat various dyskeratotic disorders like acne or ichthyosis [13–15]. In the 50s, topical vitamin A shows some sign of effectiveness in some dermatoses but was found to be ineffective for psoriasis [16]. Eventually, the function of the acid metabolite form of vitamin A was elucidated [17, 18], and led to the successful testing of topical vitamin A acid in dyskeratotic disorders such as ichthyosis, acne and psoriasis [19–22].

As for the corticosteroids, vitamin A acid, an endogenous molecule shown to be active orally for dyskeratotic disorders was then later found to be effective topically on the same disorders, showing again the use of the pragmatic approach.

2.1.4 Antifungals (1967)

Topical antifungals represent another important class of topical drugs not used to treat dermatoses but fungal infections. This is, with the topical corticosteroids and NSAIDs, one of the largest class (>15 molecules marketed) [1].

If, for the two previous classes a clear historical starting point could be set, various "treatments" for fungal infections have, however, been around for a long time. For the purpose of this historical review, one could suggest that the family of currently available antifungals should be considered. There are nowadays two main classes of topical antifungals available: the imidazole type (fungistatic) and the allylamine type (fungicidal), the latter being the newer class which is slowly taking over the old imidazole class. The imidazole class appeared in the mid 60s with Etonam [23, 24], shortly followed in just a few years by clotrimazole, miconazole, econazole, isoconazole and many others.

The literature on this class suggests that contrary to the retinoids and corticosteroids, the drug development path followed has been to first test topically the effectiveness of the drug before testing it orally.

2.1.5 NSAIDS (1971)

Non Steroidal Anti Inflammatory Drugs (NSAIDs) constitute another large class of topical drugs, Dromgoole in 1994 lists 18 topical NSAID molecules [25]. Their topical efficacy remains controversial despite successful controlled trials. Indeed, the study of pain is and has always been difficult due to the subjective nature of the measured end-point. The need of controlled trials is, therefore, even more important for such a class than for others.

The history of NSAIDs starts with aspirin—one of the oldest synthesised molecule of the pharmacopoeia (1853). In the first part of the twentieth century other

NSAIDs were synthesised: fenbufen (1936), felbinac (1946), phenybutazone (1951). Eventually, the NSAIDs burst occurs in the 1960s (indomethacin (1963), benzydamine (1964), ibuprofen (1964), diclofenac (1966), ketoprofen (1968), piroxicam (1970)…). These drugs are primarily developed for oral use as analgesics but several reached the market as well in a topical formulation and it is likely that a few were tried topically in uncontrolled trials before the 1970s.

Among this large list, the systematic review of topical NSAIDs clinical trials by Moore et al. [26] shows that the first NSAID with proven topical efficacy in a controlled trial is benzydamine, a molecule first synthesised in Italy in 1964. In 1965, benzydamine efficacy in traumatology after oral delivery was established by several controlled studies [27, 28]. The topical use of benzydamine was justified in 1968 by experimental findings on its ability of penetrating skin and accumulating at high concentrations in the inflamed tissue [29]. The first controlled study with topical benzydamine used to treat patients presenting edema and post traumatic pain was published in 1971 [30].

In the NSAID family, the first in the class topical molecule with proven efficacy clearly had established oral/systemic efficacy.

2.1.6 Antivirals (1983)

As for antimicrobial agents, a clear historical starting point is difficult to set, as many treatments have been claimed to have antiviral properties. With iodoxuridine in the 60s the road towards effective treatments started. However, in the late 70s the discovery of the nucleoside analogue aciclovir represents a key milestone for antiviral treatments. Its oral efficacy against herpes simplex virus was first proven in 1982 in the treatment of genital herpes [31]. This was followed the following year by two small successful trials with topical acyclovir for the management of herpes simplex labialis [32, 33].

In the antiviral family, the first key molecule in the class with proven topical efficacy had clearly established oral/systemic efficacy prior to topical efficacy.

2.1.7 Vitamin D3 Derivatives (Late 1980s)

The third class of topical drugs relevant to psoriasis after the corticosteroids and retinoids is the vitamin D3 derivatives.

Dermatological interest in vitamin D3 and its active metabolites in the treatment of psoriasis started in 1985, when Morimoto et al. [34] described a patient with senile osteoporosis and psoriasis who benefited from oral administration of alphacalcidiol (a vitamin D3 metabolite) [1α(OH)D3]. In the following years, Morimoto et al. performed successful studies in larger group of psoriasis patients with alphacalcidiol and its hydroxylated metabolite calcitriol [1,25(OH)2D3] [35, 36]. In 1989, the first successful topical use of a vitamin D3 derivative is showed by Morimoto et al. They described good clinical results in chronic plaque psoriasis after topical application of 0.5 μg/g calcitriol ointment under occlusion [36].

Calcitriol, an endogenous compound that had showed oral efficacy was further tested successfully topically. The pragmatic approach described earlier applies for this drug class.

2.1.8 Immunosuppressors (1992)

One of the last major class of topical drugs that reached commercialisation is the immunosuppressors (or immunomodulators) that are indicated for atopic dermatitis treatment.

Their history is strictly linked with the development and use of the immunosuppressor drug cyclosporin, patented by Sandoz in 1978. Only a year later, the case for oral cyclosporin in psoriasis was made [37]. In order to avoid the immunosuppressive side effect of cyclosporin, topical cyclosporin was tested in five trials on psoriasis but all failed [38–42]. The use of oral cyclosporin in non-psoriatic dermatoses was established in 1987 [43, 44]. In two guinea pig allergic contact dermatitis model studies, topical cyclosporin delivered benefits. However these animal model results did not translate well to a human use of topical cyclosporin as its benefits is either small [45] or absent [46].

In 1986, tacrolimus a smaller and more potent immunosuppressor was synthesised by Fujisawa. Its immunosuppressive oral activity was demonstrated in transplant patients [47] and psoriasis patients [48]. The immunosuppressive activity being established, Lauerma et al. demonstrated clear topical efficacy of tacrolimus in contact allergic dermatitis [49] in man.

In this last topical class, the first molecule to show topical efficacy had a proven record of oral efficacy.

2.1.9 Summary

Table 2.1 below summarises the previous sections. Overall, it appears that for most of the topical drug classes, the first member of the class was developed pragmatically by applying topically a drug effective orally/systemically where the target was in the skin.

Developing a new drug has always been a long and costly operation. However, deciding to “try topically” a drug already developed for which the toxicity (the systemic one at least) is well established, sounds like a quicker and less costly operation than developing a totally new drug for a topical administration. As well, as shown in the table, such a simple approach appears to be successful: the beginning of most of the topical drug classes followed that development path.

It should, however, be noticed that if most of these “first” in their class drugs made it to a topical format via this approach, some failures or issues appeared for quite a few of these classes:

Table 2.1 First in their class topical drugs by year

Drug class	Drug	Year (oral/ systemic)	Year (topical)	Pragmatic approach
Anaesthetics	Cocaine	<Twentieth century	<Twentieth century	?
Corticosteroids	Hydrocortisone (active form of cortisone)	Endogenous 1949	1952	✓
Retinoids	Retinoic acid (vitamin A metabolite)	Endogenous 1925	1962	✓
Antifungals	Etonam	1969?	1967	✗
NSAIDs	Benzydamine	1965	1971	✓
Antivirals	Aciclovir	1982	1983	✓
Vitamin D3 derivatives	Calcitriol (vitamin D3 active metabolite)	Endogenous 1985–1989	1989	✓
Immuno-suppressors	Tacrolimus	1990	1992	✓

- For the corticosteroids, in 1951 cortisone, the first corticosteroid effective orally ever tried topically failed [8–10].
- If retinoic acid can be considered as first in its class, the topical use of retinol its prodrug failed to work in acne or psoriasis in earlier studies [16].
- Calcitriol was indeed effective topically in psoriasis under occlusion [36] but when tested without occlusion the 15 μg/g strength when applied on large body surface area lead to systemic exposure issue and its doses had to be limited to 3 μg/g [50].
- Among the anaesthetics, benzocaine an older molecule than lidocaine or tetracaine is not indicated for use on uncompromised skin (indicated for mosquito bites or on mucosal membranes).
- In the family of immunosuppressors, before tacrolimus was tried topically, cyclosporin A had been tried in several trials: all of psoriasis trials failed [38–42], and two atopic dermatitis trials had either limited benefit [51] or no benefit [46].

This simple process has proven its value but has shown as well its limits. Limits of this development approach are primarily unpredictable efficacy.

2.2 Moving towards Improved Topical Drug Candidate Selection Processes: Use of In Vivo Models

2.2.1 The Particular Case of Corticosteroids: Use of Human Models (Early 1960s)

Soon after the first success of topical hydrocortisone in 1952, new corticosteroids were synthesised and studied in inflamed skin conditions topically. The unpredictive outcome in patients as seen with the failure of topical cortisone, triggered the

need to search for a model that would predict the efficacy of these new corticosteroids in the clinic. The vasoconstrictor nature of such compounds was soon discovered and used as a surrogate marker of topical efficacy for this class of drugs: The corticosteroid blanching assay was born [52, 53].

The key advantages of this technique are:

- A one-day experiment is sufficient to assess efficacy of a new drug.
- There is no need to use patients with inflamed skin disease as simple healthy human volunteers will respond to blanching.
- Several compounds/formulations can be tested in the same volunteer.
- There is no requirement for complicated method of assessment as a trained panel is able to assess the blanching score.
- The small local area treated allows the development of new chemical entities with only a limited toxicological package.

This technique for its simplicity, ease of use and reliability, therefore became the gold standard and key decision tool to develop the subsequent corticosteroids and their formulations.

In the following decade, other types of human models were used to test topical corticosteroids. One is the use of induced inflammation model like the croton oil model [54] derived from the animal model, or, the UV erythema test [55]; another one is the use of microplaque disease models like the microplaque assay for psoriasis [56] or the poison ivy test for contact dermatitis [57].

Although these human models, especially the corticosteroid pharmacological blanching assay, greatly facilitated the expansion of dermatology as a therapeutic and commercial area they bypassed consideration of dermal pharmacokinetics, especially the rate of drug absorption. As a result, dosing strategies for topical products applied to the skin are poorly defined and developed.

2.2.2 Topical Rodent Models (1960s)

Although the blanching assay was successful for the development of corticosteroids, it did not help to develop new classes of drugs, as vasoconstrictor properties are not common for other classes of compounds. However, the principle of the blanching assay was recycled in an animal model. In the blanching assay, the end point measurement is a change of colour "pink to white." In the animal, a colour change was also used as the end point. This time, by causing irritation erythema to skin of the animal, the skin color would turn towards a reddish color, then the topical application of an effective anti-inflammatory drug would return the animal skin color towards normality [58–60]. As well as the induced inflamed models, the pharmacological antiproliferative effect of corticosteroids was used in various models [61–63].

The induced inflamed animal models as well as the antiproliferative animal models, offered a platform of models that could be used for further new classes of topical drugs. Indeed, for the two major dermatologic conditions—atopic dermatitis and

psoriasis—inflammation (for both dermatoses) and keratinocyte proliferation (for psoriasis only) represent the two main pharmacological targets.

For practical reasons the animals used in these models would be small animals: rodents. This choice of the animal was helped by the fact that classically, rodents are the pharmacological animal models of choice used in the pharmaceutical industry.

2.2.3 *Combined Use of Topical Models and Systemic Rodent Models (1980s)*

Efficacy has always been the primary end point for GO/NO GO decisions in topical drug development. With the development of very potent corticosteroids however, the issue of systemic exposure became more critical.

In the early 80s, new topical corticosteroids were developed (mainly designed for pulmonary delivery) with a lower potential to induce systemic exposure. The new synthesised drugs were called "soft drugs." The term "soft" conveys the principle that this new generation of drugs would be cleared more quickly in the body or would be less absorbed systemically than the previous generation. To design such new drugs, the corticosteroids were tested topically in a rodent/human model as well as systemically in a rodent model [64]. A good "soft" drug candidate would then be a drug that would be active topically at a low dose while a large systemic dose would be required to deliver the immunosuppressive effect.

This concept of designing drugs acting topically and not systemically was used to develop the latest corticosteroids.

2.2.4 *Use of Topical Pig Models (1990s)*

An important issue with the rodent inflamed skin model is the fact that it largely overpredicts the efficacy observed in human as shown in Table 2.3 [65]. This naturally leads to failures when the topical drug reaches the clinical stages. Little is published on that subject but it is believed that in the pharmaceutical industry a large number of such drug development failures exist.

There are two potential main hypothesis for this overprediction.

1. Poor translation of the pharmacology from the animal model to the human disease.
2. Difference in pharmacokinetics in between the animal model and human.

In the topical pharmacokinetic literature, the knowledge that rodent skin is more permeable than human skin is well established.

Brain et al. [66] review the data available in the ranking of skin permeability among animal species vs. human skin and they conclude:

1. Animal skin with high follicular density is poorly representative of human skin [67, 68].
2. Rat and rabbit do not give reliable estimation of human penetration [69–71].
3. Pig and rhesus monkey reasonably approximate absorption of several compounds in human [69, 72–76].
4. Shaving or depilation of hairy skin may alter the barrier function [77, 78].

Differences observed among species is not small as suggested by Table 2.2 [79]:

Some groups therefore investigated whether drug delivery could be involved in this overprediction of topical efficacy. In 1992, Meingassner and Stutz [80] set up a new inflamed skin model, using a pig as the animal model. The concept behind this choice was that skin permeability in pig is comparable to the human one.

In 1998, Mollison et al. [65] proved that the drug delivery hypothesis was correct by showing that the amount of drug to get efficacy in the pig model was equivalent to the human one while much lower doses, absorbed with much greater efficiency, were required in the rodent model (Table 2.3).

This approach has been followed by at least two pharmaceutical companies to develop new topical immunosuppressors: Novartis [81] and Abbot [65]. Such a development approach led to the development of pimecrolimus, a novel immunosuppressor drug that received FDA approval in 2001.

Table 2.2 Difference in topical pharmacokinetics in between species

Species	Type	Permeability coefficient ($cm^2/h \times 10^{-5}$) Paraquat	Animal/human ratio for Paraquat
Man		0.73	1
Rat	Wistar Alpk/AP	27	40
Mouse	Alpk/AP	97	135
Guinea pig	Dunkin-Hartley	196	270
Rabbit	NZ white	80	110

Table 2.3 Difference in topical dose strength to show efficacy: rat vs. pig vs. human

Compound	Rat ED50 (%)	Pig ED50 (%)	Human clinical dose (%)	Rat/human potency ratio	Pig/human potency ratio
FK506 (Tacrolimus)	0.0037	0.27	0.3	0.01	0.9
Clobetasol-17-propionate	0.0001	0.033	0.05	0.002	0.7
Hydrocortisone	0.006	>1.0	2.5	0.002	<2.5
Cyclosporin	0.034	>3.0	>3.0	<0.01	Inactive/inactive

2.3 Historical Topical Drug Candidate Selection Summary

The previous two sections suggest that topical drug classes have over the past 60 years largely been developed in the same way into two distinct stages:

The first stage is a quick and opportunistic approach as it is very much a matter of putting an existing drug in a topical format and testing it in patients. One could say that much is left to chance and that seems true when it is realised how often the first tested drug in a class failed for efficacy reasons (cortisone, retinol palmitate, cyclosporin) or had a difficult development path because of safety reasons (calcitriol).

The second stage as opposed to the first does usually involve some pre-clinical tests. This is a natural way to approach that stage as the aim of the populating stage should be to design superior new drugs compared to the existing ones in the class (Fig. 2.1).

Topical rodent models are often used as a way to test the efficacy of candidate molecules in vivo and for that reason they represent a helpful step towards discharging risk for progressing a molecule. A candidate molecule failing in such an assay that is supposed to overpredict efficacy could be a good reason to terminate a molecule. However, a positive outcome in a rodent model can lead to failure in the clinic as shown with cyclosporin because of the difference in between rodent and human skin permeability. This limits the added value of topical rodent models.

Pig models have proved good translation of efficacy with immunosuppressors and could be viewed as a good way to improve candidate selection process. There are, however, only a limited number of pig models. Moreover pig models are difficult models to set up and manage. The industry is used to small rodent models and few pharmaceutical companies investigating new topicals have switched to the use of pig models.

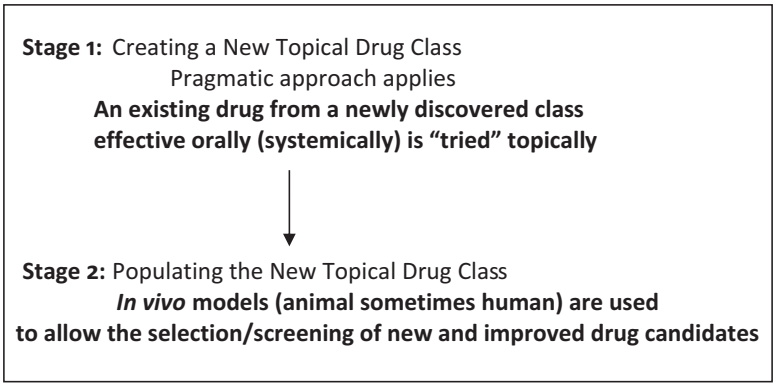

Fig. 2.1 Building up a new topical drug class

Overall, progress in selecting topical candidates have been made over the years, but the use of current animal models have limitations that likely prevent the industry for an effective risk discharge effort when selecting a candidate molecule.

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Chapter 3
Key Factors Affecting the Efficacy of a Topical Drug Candidate: Learnings from Past Topical Drug Development

This chapter focuses on lessons learned from the success and failure of topical drug development over the last 60 years. First, the skin barrier quality for a particular skin disease will be compared to the easiness of topical drug development. The importance of the candidate molecule potency will be considered as well in comparison to its clinical efficacy.

3.1 Skin Barrier Condition vs. "Easiness" of Topical Drug Development

As noted in the previous chapter topical drugs are proven more effective in rodent animal models than in human, and this difference in effectiveness seems to be linked with a difference in topical drug delivery. To investigate further the effect of drug delivery on the effectiveness of a topical drug, the impact of the skin barrier properties for a specific disease on the likely efficacy of a topical drug is discussed.

3.1.1 Skin and Its Barrier

Skin can be divided in four layers: The stratum corneum, the viable epidermis, the dermis and the subcutaneous tissue (Figs. 3.1 and 3.2). Of these four layers, the thin stratum corneum (10–20 μm) has been recognised for a century of being the impermeable barrier layer [1, 2]. Barrier properties of the stratum corneum are attributed to the highly organised layers of flattened, polygonal corneocytes and specialised intercellular lipids. Removing the full stratum corneum will translate into substantial increase in skin permeation, especially for poor permeants. In fact, once a molecule has crossed this layer, it is considered that it will keep travelling and diffusing into the lower part of skin and eventually, and unavoidably, reach the systemic circulation.

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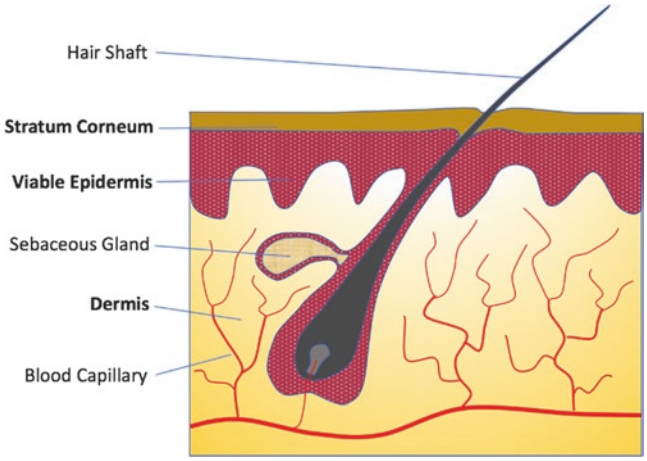

Fig. 3.1 Skin: stratum corneum, viable epidermis and dermis

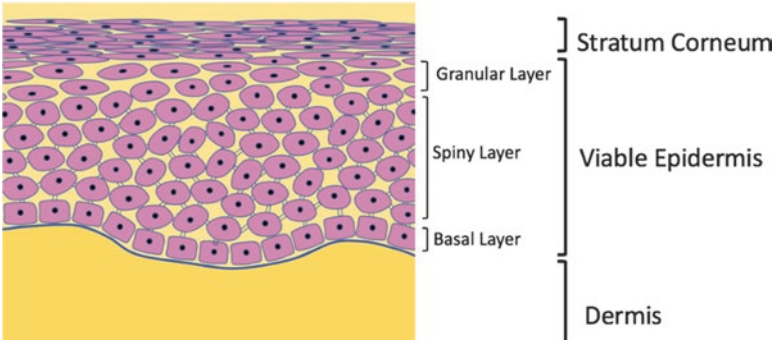

Fig. 3.2 Skin: epidermis

3.1.2 Skin Disease, Target Site in Skin and Skin Barrier Properties

Skin diseases have different causes, different target sites and the barrier properties of each of them may or may not be impacted by the disease as can be seen in Table 3.1.

Table 3.1 Skin disease, target site in skin and skin barrier properties

Disease	Target site	Skin barrier
Fungal infection	Stratum corneum	Not damaged and higher barrier[a]
Herpes simplex labialis	Bottom epidermis	Severely damaged[b]
Psoriasis	Epidermis/dermis	Not damaged[c]
Atopic dermatitis	Epidermis/dermis	Partly damaged = lower barrier[d]
Acne	Sebocyte/dermis	Not damaged and lower barrier[e]

[a]There is no clear literature evidence suggesting that the permeability of a skin site infected by a fungus is more permeable. However, the foot is the most common skin fungal infection site. Feldmann and Maibach [3] reported a lower permeability from the sole compared to the rest of the body

[b]Herpes Simplex Labialis open up (ulcer) by day two of an episode [4]

[c]Barrier property of psoriatic plaque compared to normal skin has been studied with hydrocortisone in vivo [5], concluding that the barrier property of psoriasis plaque skin was comparable to normal skin

[d]Effect of atopic dermatitis on skin barrier property of the skin has been studied [6–14]. Review of these papers suggests that unless in the case of patients with erythroderma -where the skin barrier has virtually disappeared- the skin barrier is decreased by about 10 fold in patients with severe atopic dermatitis and by about 2 fold in patients with mild atopic dermatitis

[e]There is no clear evidence suggesting that the permeability of acne skin is impaired. However, the most important skin location for a patient suffering from acne is the face. Feldmann and Maibach [3] reported a higher permeability from the face compared to rest of body

Table 3.2 Success rate of oral drug developed topically and first in their class topical drugs

Drug class	Success	Mixed results (positive but limited results or issues)	Failure	References
Antifungals	Etonam Ketoconazole Terbinafine			[15–18]
Antivirals	Aciclovir Penciclovir			[19–24]
Retinoids			Vitamin A (psoriasis)	[25]
Vitamin D3 derivatives		Calcitriol (effective but systemic side effect at high doses)		[26, 27]
Immuno-modulators	Tacrolimus (eczema, facial psoriasis)		Cyclosporin A—Tacrolimus (psoriasis)	[28–39]
Corticosteroids		Hydrocortisone (eczema)	Cortisone	[40–43]

3.1.3 Success Rate of First in Class Topical Drugs

Review of the success rate of oral drugs developed as topical drugs is of interest as it provides some ideas of elements that may influence, positively or negatively, the successful development of a topical drug (Table 3.2).

Drug classes discussed above can be summarised into two categories:

1. Easy Development Drug Class, defined as a class in which all oral drugs tried topically were successfully developed
2. Difficult Development Drug Class, defined as a class in which some oral drugs tried topically failed or were only partially successful.

3.1.3.1 Easy Development Drug Class

The antivirals (aciclovir and penciclovir both oral compounds successful topically) and the antifungals (etonam (1st azole): effective—ketoconazole (oral = > topical): effective—terbinafine (1st allyl): effective].

3.1.3.2 Difficult Development Drug Class

The retinoids (vitamin A: ineffective in Psoriasis), the vitamin D3 derivatives (Calcitriol: systemic exposure issue at high doses), the immunosuppressors (cyclosporin: ineffective—tacrolimus developed later: effective in atopic dermatitis but not or poorly in psoriasis), the corticosteroids (cortisone: ineffective—hydrocortisone: effective in atopic dermatitis but poorly effective in psoriasis).

3.1.4 Summary of Impact of Skin Disease, Its Target Site, Its Barrier and Success Rate of Topical Drug Development

Learnings of the previous sections can be represented in Table 3.3

This table suggests that developing easily (or not) a topical depends on two things:

Table 3.3 Barrier condition of skin diseases and success rate of topical drug development

Drug class	Disease	Target site	Skin barrier	Easiness of topical drug development[a]
Antifungals	Fungal infection	Stratum corneum	Not damaged	+
Antivirals	Coldsore	Bottom epidermis	Severely damaged	+
Corticosteroids	1. A.D. 2. Psoriasis	Dermis epidermis/ dermis	Partly damaged Not damaged	–[b] —[b]
Retinoids	1. Psoriasis 2. Acne	Epidermis/dermis Sebocyte	Not damaged Not damaged	– –
Vitamin D3 derivatives	Psoriasis	Epidermis/dermis	Not damaged	–
ImmunoModulators	1. A.D. 2. Psoriasis	Dermis Dermis	Partly damaged Not damaged	– —

[a]+ for easy, – for difficult, — for very difficult topical drug development

[b]Mild or moderately potent corticoids have poor clinical scores in Psoriasis while they do better in AD

1. If target site is in the stratum corneum (= top of the skin) = > easy development, but if target site is deeper, development is more difficult.
2. If skin is severely damaged = > easy development, but if skin is however not damaged development is more difficult.

Note that in atopic dermatitis (A.D.) where the skin barrier is partly compromised, the condition seems to be treated more easily than psoriasis. One could reasonably argue that it is the pharmacology of the disease responsible for the difference but it could well be argued that drug delivery could play a major role.

Location of the target site for a skin disease as well as the influence of this disease on the skin barrier properties appear to be critically important for the successful development of a topical drug. Likely due to these factors, some skin diseases appear to be, indeed, more easily treated (fungal infections and possibly cold sores) than others (atopic dermatitis, psoriasis or acne).

It is possible to explain these findings by schematically describing qualitatively the concentration reached in the different tissues in intact vs. damaged skin. After topical application and because of the passive diffusion transport of drugs through skin, a concentration gradient exists through the three skin compartments. Using the mean concentration in each skin compartment, skin concentration with skin depth can be represented as followed in Fig. 3.3.

Stratum corneum being at the surface of skin (and because of favourable drug partitioning into stratum corneum lipids for most drugs), drug concentration is higher than in the deeper tissues, hence a higher rate of success for drugs targeting this tissue.

As well, as represented on Fig. 3.3, with damaged skin, local concentrations are higher for the same target tissue hence a higher success rate for drugs targeting a skin disease where the barrier is impaired.

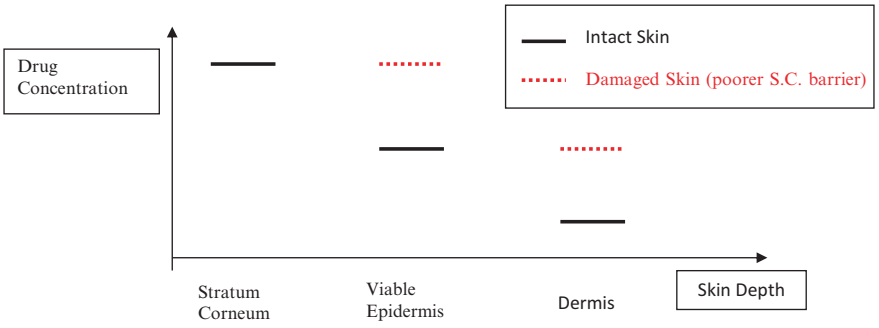

Fig. 3.3 Schematic Skin Concentration in Intact and Damaged Skin.

3.2 Drug Potency and Clinical Efficacy

Drug potency is another key element that can be learned from past topical drug development experience as being critical in the efficacy of a topical drug. Examples of three drug classes are given in Tables 3.4, 3.5, and 3.6. The reported potency data in Table 3.4 are, for most of them, the average (geometric mean) of at least two data sets.

Learnings from these three examples suggest that the drug potency can have a substantial impact on the topical efficacy of a topical drug candidate.

Table 3.4 In vitro potency of some anaesthetics, corticosteroids and immunosuppressors

Target class	Drug	Potency (nM)	References
Anaesthetics	Benzocaine	910,000	[44]
	Lidocaine	155,000	[44, 45]
	Prilocaine	125,000	[44, 45]
	Tetracaine (amethocaine)	3,500	[44, 45]
Corticosteroids	Hydrocortisone	14	[46–51]
	Bethametasone valerate	0.2	[46–51]
Immunosuppressors	Cyclosporin A	11	Oral dose + PK [52–55]
	Tacrolimus	0.17	Oral dose + PK [54, 56, 57]

Table 3.5 Clinical efficacy comparison of some anaesthetics, corticosteroids and immunossupressors

Target class	Clinical comparison
Anaesthetics	In a pinprick model [58], Ametop (tetracaine) is compared with EMLA (lidocaine + prilocaine) showing superiority of Ametop. In another study with the same model [59], saturated solution of tetracaine, lidocaine and benzocaine are compared showing that tetracaine is superior to lidocaine which is superior to benzocaine
Corticosteroids	Hydrocortisone is classified as “mild” in the topical corticosteroids while betamethasone valerate is classified as “potent” [60]
Immunossupressors	Topical tacrolimus is effective in the treatment of atopic dermatitis [61] while cyclosporin A has shown limited or no activity in atopic dermatitis [33, 34]

Table 3.6 In vitro potency vs. Clinical efficacy ranking of anaesthetics, corticosteroids and immunossupressors

Target class	In vitro potency ranking	Clinical efficacy ranking
Anaesthetics	Tetracaine > prilocaine ~ lidocaine > benzocaine	Tetracaine > prilocaine + lidocaine > benzocaine
Corticosteroids	Bethametasone valerate > hydrocortisone	Bethametasone valerate > hydrocortisone
Immunossupressors	Tacrolimus > cyclosporin A	Tacrolimus > cyclosporin A

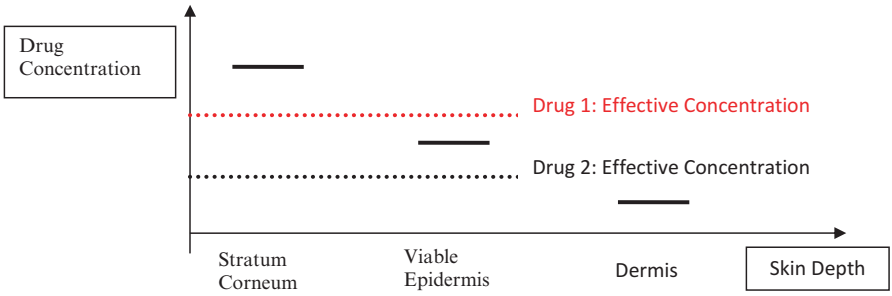

Fig. 3.4 Schematic representation of drug potency effect with regards to efficacy

To further picture this observation, one can conceptually plot concentration versus potency versus skin compartment.

Figure 3.4 represents the concentration profile of two imaginary drugs. Drug 1 and 2 are hypothesised to have the same concentration profile in skin but both have a different potency (Drug 2 is more potent). For Drug 2, its viable epidermis concentration after topical application exceeds its effective concentration and therefore, a pharmacological effect of Drug 2 is expected in the epidermis. However, for Drug 1 as the epidermis concentration is inferior to its effective concentration, no pharmacological effect is expected in the epidermis.

In summary, knowledge and use of both, drug concentration in skin (quantitatively), as well as, drug potency, appears to be key if one wants to rationalise the selection of a topical drug candidate.

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Chapter 4
Topical Versus Oral/Systemic Drug Discovery

4.1 Drug Discovery Evolution

Over the past decades, the drug discovery process of the pharmaceutical industry has vastly improved.

Up to the 90s, poor understanding of pharmacokinetics was a substantial cause of attrition in clinical phases (see Fig. 1.11 in Chap. 1). Thanks to the introduction of various *in vitro* and *in vivo* DMPK assays in the 90s, this risk was substantially decreased. During the same period, use of *in vitro* biology data combined with DMPK data allowed better ranking of molecules being tested in *in vivo* pharmacology models. It is in the 90s too, that high throughput screening assay were developed to improve the chance of success to find leads to start lead optimization programs on new targets.

Since 2000s large efforts have been utilized to obtain proof of target engagement earlier in the clinical phases. Thanks to use of biomarkers in clinical Phase 1 studies, an increased confidence that the mechanism could be engaged was brought forward before clinical Phase 2 studies. Similarly more care on the assessment of desired target plasma exposure to explore the mechanism (i.e., to define potential for viable dose and viable therapeutic index) is being used in the lead optimization phase before candidate selection occurs. Finally more resources and the use of cheminformatics are being applied at the target selection stage. The aim of that last initiative is to reduce picking poor targets (either due to target related toxicity or lack of translation of the mechanism into the desired disease in man).

When looking back at the progress made, one can see that the drug discovery process:

1. Became more efficient (to increase chances to find and develop a drug candidate).
2. Is discharging risks earlier (to reject the weaker molecules, candidates, targets earlier in the process).

As will be seen later on, both of these two drivers have been minimally looked after in the drug discovery of dermal drugs.

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4.2 Oral/Systemic Drug Discovery

Typically, for each program aiming to find a drug for an oral or a systemic (intravenous, subcutaneous…) administration, 200,000 to over a million compounds might be screened initially and during the following lead optimization, 100s of compounds will be synthesized and screened to eventually identify one or two candidate molecules, usually from different chemical series [1]. Four to five years will be required from the initiation of a research program to the selection of the candidate molecule [2].

From target selection to the proof of concept, risks will be discharged, with always the aim to discharge the big risks as early as possible. The lead optimization phase will contribute to discharge substantial risks. Most other risks, despite the efforts described earlier to improve the drug discovery process, will be discharged during the proof of concept study (Fig. 4.1).

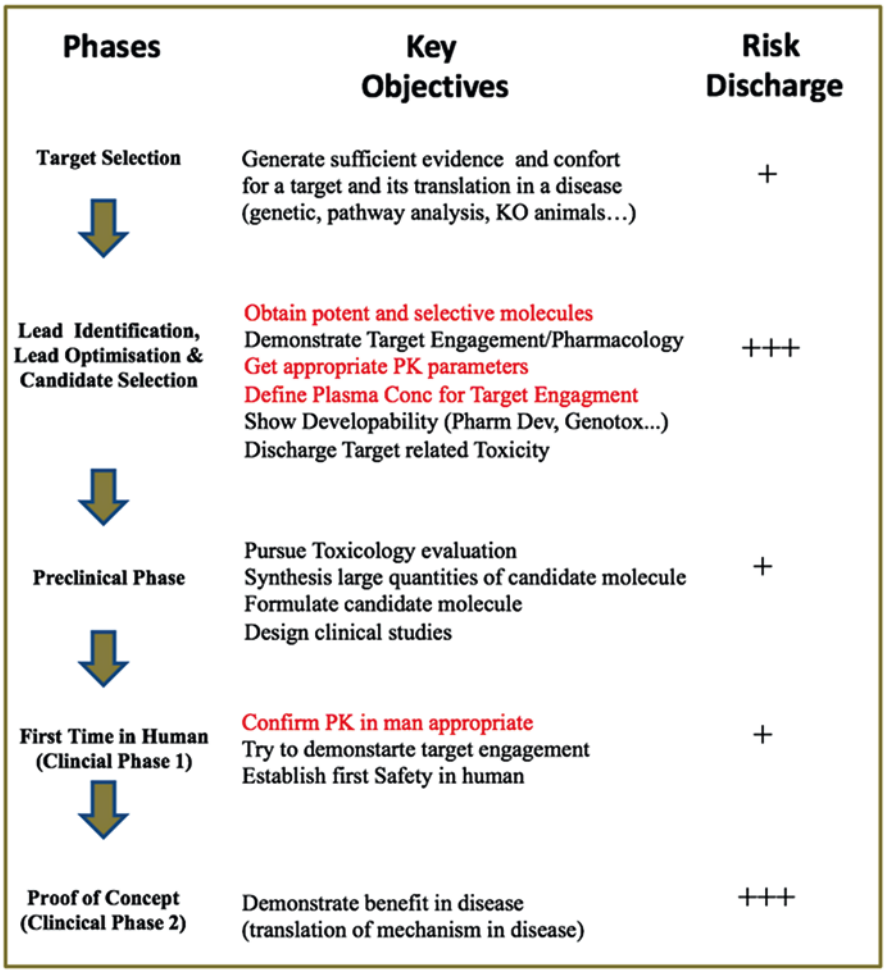

Fig. 4.1 Oral/systemic drug discovery objectives and risk discharge

4.3 Topical Drug Discovery

There are two main types of topical drug discovery programs. The most used one by non-specialised dermal pharma is the pragmatic approach which consists in pushing a single compound into a topical formulation (Fig. 4.2). The objective is to get the compound in the clinic and to give the compound a maximum chance of success. As can be seen, some elements present in the lead optimization phase are absent or different compared to what is done to develop an oral/systemic candidate which considerably limit the risk discharge.

In other instances a full lead optimization program or a full chemical series will be screened against various assays to try to rank and select the best topical candidate (Fig. 4.3). With several compounds (or even a full lead optimization program) to

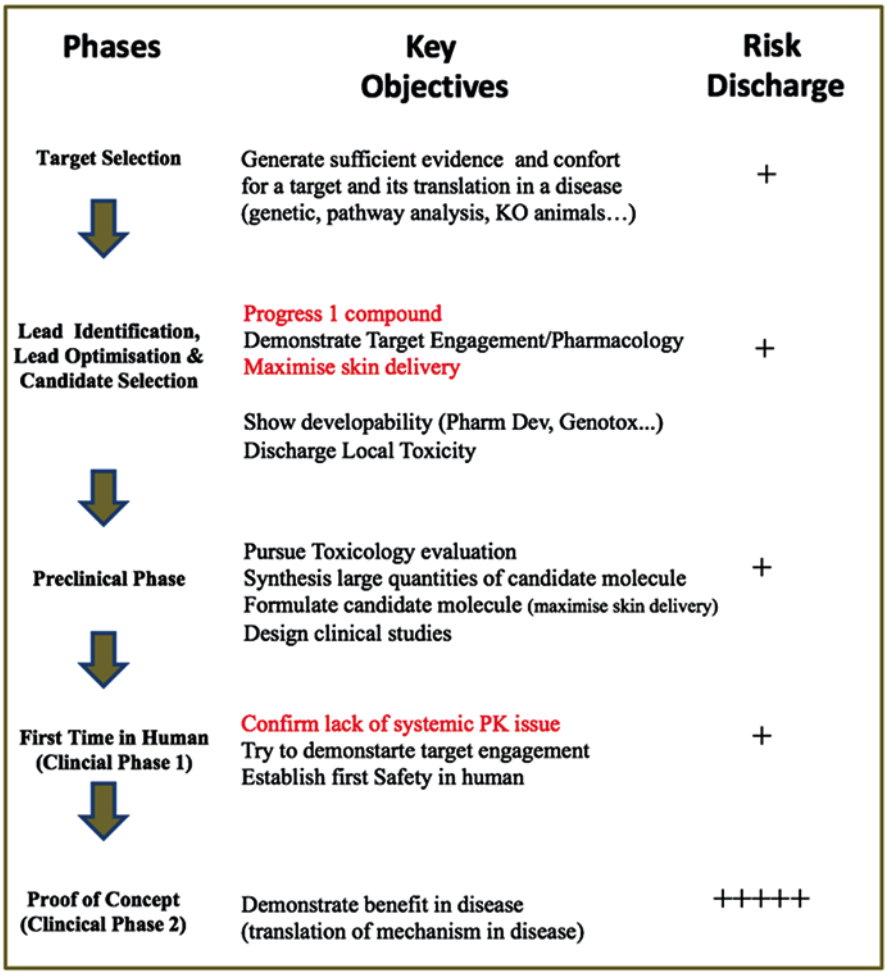

Fig. 4.2 Topical (one compound) drug discovery objectives and risk discharge

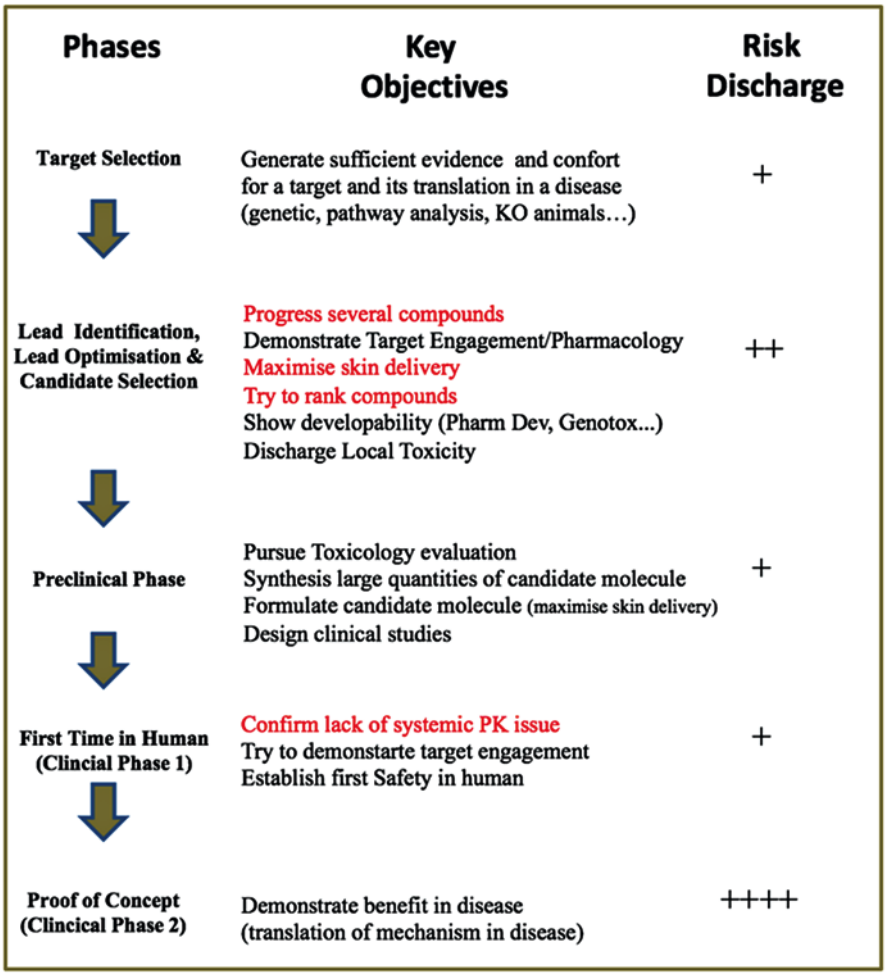

Fig. 4.3 Topical (several compounds) drug discovery objectives and risk discharge

start with instead of a single compound, the chances to get a winner will, from a statistical perspective, be higher. Having said that, the best compound selected may still be far away from being able to engage the target as screening methods before candidate selection may not be sufficient to predict target engagement in man. If, as often, rodent models are used (without factoring in the difference in skin permeability with human), a positive results in such a model could still mean a negative Proof of Concept as proven with cyclosporin (see Table 2.3 in Chap. 2).

Information in Phase 1 studies that only a limited systemic exposure is achieved (usually the case) does help to reassure the program team about the lack of systemic safety issue but not that the candidate molecule will engage the target. With an oral/systemic candidate, knowledge of the plasmatic exposure (without adverse findings)

will help confirm the likely target engagement and the safety window. Till the Proof of Concept stage, not much risk is, therefore, discharge with regards to the likelyhood of engaging the target with a topical candidate. This is unfortunate when one recognises that skin is an impermeable membrane and that the vast majority of compounds have poor delivery properties through skin. The chances to engage the target is therefore pretty low for most of the potential dermal drug candidates.

Contrary to the classic drug discovery program, two key elements are missing during the lead optimization phase: (1) there is no target exposure to reach in skin to aim for as defining skin concentration or skin target engagement is poorly understood or addressed as will be seen in future chapters and (2) there is no guidance for what would be good PK for a topical. For these reasons, large efforts will be put to maximise the capacity of the formulation to deliver the candidate compound through skin even if such efforts, as will be seen in Chap. 8 do not offer much gain.

Topical drug discovery is, therefore, somewhat different compared to classic oral/systemic drug discovery as most often the process does not allow the critical risks to be discharged until the proof of concept study in human.

4.4 Two Key Differences in Discharging Risk in Between the Oral/Systemic and Topical Drug Discovery Processes

4.4.1 Defining Target Tissue (Skin) Concentration

In the oral/systemic drug discovery process, one key role of the lead optimization phase is to define the target plasma concentration required to get the desired pharmacological response in the animal model. This concentration will indeed become a target concentration to reach in the Clinical Phases 1 and 2. The aim for the Clinical Phase 1 stage is then to escalate the dose given to healthy volunteers up to a dose that will give similar plasma concentration (more precisely, similar unbound plasma concentration) as the one observed in the animal that showed the pharmacological response. If such doses can be administered safely to human volunteers, such doses can be given then to patients with reasonable confidence that at this dose the drug administered should exhibit its pharmacological activity.

In the topical development process, this target concentration is absent, as there are no established ways to measure reliably drug levels in the skin tissue or to link plasma drug levels with skin tissue levels (as will be seen in Chap. 5). The consequence is that there are undischarged risks at the candidate selection stage. This means, as well, that the Proof of Concept study has to answer two questions: (1) Is the pharmacology correct? and (2) Is there enough drug at the target site? A negative outcome in the Proof of Concept study is, therefore, difficult to interpret [3, 4]. If the pharmacology is blamed while the true problem was a drug delivery one, this can have as a consequence the abandoning of a pharmacological target that could have been proven useful if the correct compound had been first selected.

4.4.2 Checking that Pharmacokinetic Parameters Are Appropriate

In the oral drug development process, a drug candidate must meet the two following criteria to pass pre-clinical pharmacokinetics selection:

- Sufficient Bioavailability & Rate of Delivery.
- Appropriate "Half-life" that permits reasonable dosage regimen (e.g., once daily).

4.4.2.1 Bioavailability and Delivery Rate

While selecting an oral drug candidate, two criteria are examined regarding the crossing of the gastrointestinal membrane: (1) Will it be possible to get a sufficiently high bioavailability such that subject to subject plasma level variation is small? and (2) Will it be possible to deliver enough drug to reach the pharmacologically effective drug plasma level?

To answer to these questions researchers have sought to understand the physicochemical properties that favour intestinal absorption [5–8]. The so-called "rule-of-5" has proved popular as a rapid screen for compounds likely to be poorly absorbed [9]. Various other analysis have followed [10–14].

However, these rules are not used on their own. The "triad of potency, solubility and permeability" has to be considered. For example, solubility guidelines to the Pfizer's chemists suggest a minimum solubility of 50 μg/ml for a compound that has a mid-range permeability and an average potency of 1.0 mg/kg [9].

This set of rules and guidelines allows to predict early which drug candidates would or would not be able to be delivered in sufficient quantity via the GI tract for their potency.

Interestingly, in topical drug development this approach is largely incomplete. Indeed, if there are tools to predict the rate at which a molecule can cross the skin membrane as reviewed by Pugh et al. [15], these tools do not define whether the rate (flux) for a particular molecule is sufficient or not to deliver the required concentration. There should be some link with the drug potency as shown by Lipinsky [16], with the "triad of potency, solubility and permeability"; but the lack of the knowledge of the drug concentration in the skin tissue prevents such rules to be established. Bad drug candidates cannot, therefore, be discontinued from further development with that method. The only tool remains the use of existing animal models with the caveat of large differences in skin permeability cross species [17] (see Table 2.2 in Chap. 2).

4.4.2.2 Concept of "Half-Life" in Topical Therapy

When developing an oral/systemic therapy, for a mechanism of action where the active compound has to be present constantly above a certain threshold (= the most classic case for a drug) a program team would not consider progressing into the

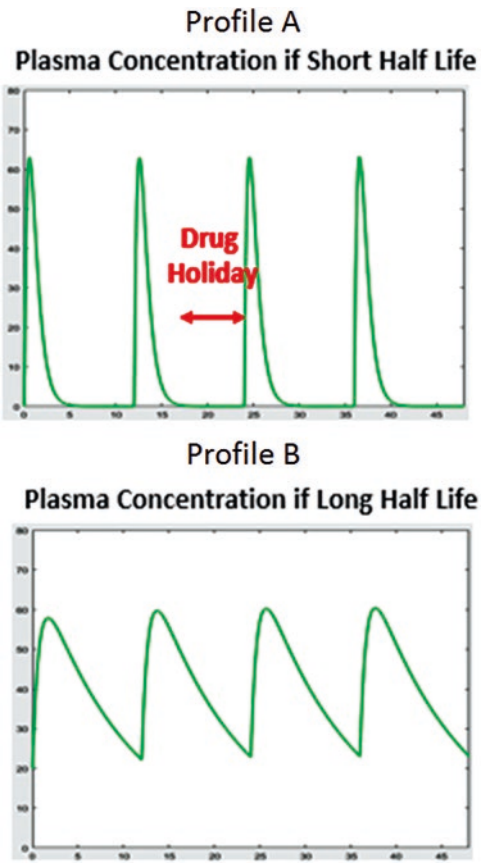

Fig. 4.4 Half-life and "Drug Holiday"

clinic a compound with "drug holiday" period (such as profile A in Fig. 4.4) and would aim to select a candidate with constant target engagement (such as profile B in Fig. 4.4).

With topicals, selecting a drug with profile A is done often not purposely but because of lack of knowledge on the pharmacokinetic in skin.

The half-life concept, sadly, therefore, just does not exist yet in topical therapy!

Classically when a clinical trial for a new topical candidate is designed, the clinical protocol most often states that the topical should be administered "twice a day." This is more an historical heritage and the likely maximum dose regimen that patients will likely accept, than a rationale reason for "a twice a day" dosing.

With some topical preparations after having been registered as "twice a day," further clinical work has been sometimes conducted and has shown that reduced dosing regimen can give similar efficacy: This is the case for example of Temovate® (clobetasol propionate) or Cutivate® (fluticasone propionate) where once daily can be equivalent to a twice a day dosage regimen. The case of the antifungal Lamisil® (terbinafine) is spectacular as a single dose has shown to be as effective as a once a day treatment for 1 week [18], though in this case the mechanism of action (fungicidal) can explain the dose regimen.

Later in paragraph "In silico" PK/PD approaches" in Chap. 6, use of PK/PD modelling will bring the half-life concept back and show how it can be used to improve or predict pharmacology and become a critical attribute to consider for the future topical drug candidate.

4.5 Consequences for Preclinical Stage: "Maximising Percutaneous Flux"

Knowledge that rodent animal models overpredict the topical efficacy in human, as well as the knowledge that a poor drug candidate from a skin permeability point of view cannot currently be screened out, have a logical consequence on what should be done at the pharmaceutical development stage of a topical drug:

"The percutaneous flux of the drug candidate must be maximised in order to limit the risk of not delivering enough drug".

This requirement pushes the topical drug development program team to impose to the pharmaceutics team involved in the formulation of the candidate to go for a percutaneous penetration enhancement program. An iterative process then follows which aims to maximise percutaneous permeation for the compound candidate. This process can be summarised in Fig. 4.5 below:

Consequences of this development approach are:

- Cost in resource.
- Cost in development time.

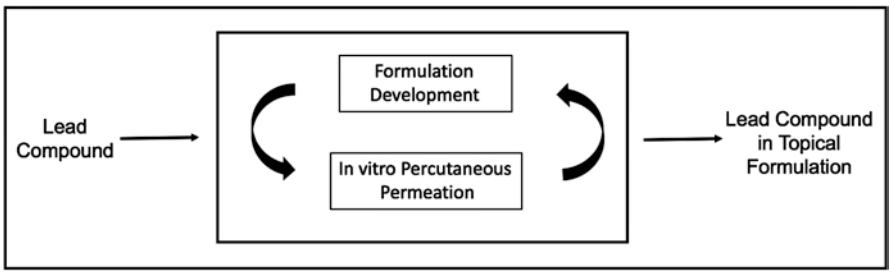

Fig. 4.5 Classic topical preclinical phase

– Uncertainty on the irritancy outcome as the penetration enhancers used often have potential irritancy associated with them.
– Uncertainty on the patient acceptability of the topical formulation developed as the presence of penetration enhancers can have negative effect on the aesthetics of the formulation, so will have the move from a cream to an ointment presentation.

4.6 Learnings from the Oral Drug Development Process

The previous section shows the consequences of lacking a skin concentration target in the lead optimization stage. The best solution that the pharmaceutical industry has been able to use, is to push as much drug as possible through the skin.

It is however "*missing the point"* as such an approach will have three potential consequences:

1. Topical treatment is effective and does not cause systemic side effect.
2. Topical treatment is effective but does cause systemic side effect (over dosing).
3. Topical treatment is not effective (still not enough drug at the target site).

Case N°1 is ideal as it delivers the required treatment.

Case N°2 is generally spotted in the human clinical Phase 1 in volunteers and requires the percutaneous penetration to be reduced which can be done easily by reducing drug concentration in the formulation.

Unfortunately, however, case N° 3 will most often occur. In such circumstances the topical drug development program team could consider that the percutaneous penetration of the drug candidate could have been further improved. Drug candidate could go back then to the preclinical phase. Such an iterative approach is rarely successful, as the percutaneous penetration of a molecule can be increased up to a point but not further. This is illustrated for example in the iterative failed clinical trials that have investigated the use of topical cyclosporin in psoriasis [19–23].

In summary, the true solution to these problems is likely to lie in transforming the current lead optimization phase of the topical drug discovery process into a process that would be equivalent to the oral drug development process, by:

– Defining skin concentration to aim for to achieve target engagement.
– Demonstrating such a concentration is reachable in human skin with the studied candidate compound.
– Defining and measuring the skin "half-life" to select the most appropriate candidate molecule and adapt the dose regimen in man.

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Chapter 5
Assessing Drug Concentration in Skin: Direct and Indirect Methods

This chapter reviews the most commonly used topical pharmacokinetic techniques. Numerous other techniques (e.g., the non-invasive spectroscopic techniques like confocal, fluorescence techniques as well as the NMR technique) are not described here as they will have one or more of the following characteristics: very specific for a drug or disease, possibly impractical, possibly not quantitative, possibly lacking sensitivity or possibly at a too early stage of development. They cannot, therefore, be applicable as versatile techniques for studying topical pharmacokinetics.

Two types of methods will be considered. To start, direct methods, where a skin tissue concentration can be directly obtained will be described. Then, indirect methods, where a skin tissue concentration will need to be derived following some interpretation, will be considered.

5.1 Direct Methods

5.1.1 Tape Stripping (Vitro/Vivo)

5.1.1.1 Description + Use of Method

This method is widely used. It can be used either *in vitro* or *in vivo* and aims at determining the concentration in the stratum corneum of a drug applied topically. There have been guidances for a period by the FDA as well as a method for defining bioequivalence between two topical formulations. It is performed as follows: (1) drug is applied to the skin surface for a fixed time period; (2) drug remaining on the skin surface is removed by wiping or washing; (3) a succession of stratum corneum layers are removed by sequential tape strips using adhesive tape; (4) drug content of the tape strips is determined [1] (Fig. 5.1).

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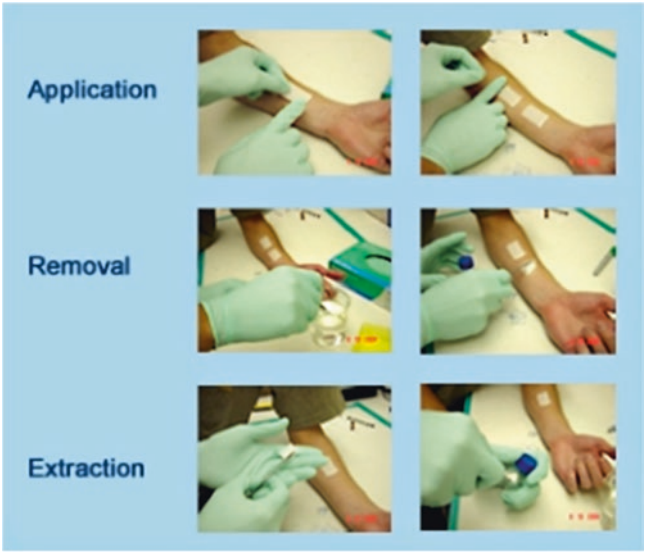

Fig. 5.1 The tape-stripping method: application, removal and extraction. From [2]. https://connect.niehs.nih.gov/srp/researchbriefs/view.cfm?Brief_ID=166

5.1.1.2 Pros

Location of the stratum corneum makes it easy to sample and the concentration within this first skin layer are high which does not generally cause issues regarding analytical detection limits.

The method can be used *in vivo* and is relatively non-invasive.

The method has been improved over the years as the quantification of the amount of stratum corneum removed greatly improves the quality of the data generated [3].

5.1.1.3 Cons

Stratum corneum is not a skin tissue of much interest for the development of topical treatment, as it is only the target site of antifungals or sunscreens.

In this technique the controversial issue of the washing procedure and the accounting or not of the first tape strip is present. This issue could be summarised as the "skin surface contamination issue." As it will be seen later for most of the other skin pharmacokinetic sampling methods, the "skin surface contamination issue" is an important factor.

In the case of the stratum corneum tape stripping technique, the first tape is, depending on the protocol, counted or not, which could be viewed as the recognition of the presence of the potential "contamination issue" described above.

There is as well some evidence in the literature of discrepancy in bioequivalence in the tape stripping approach which questions the validity of the data generated by this approach. One of them is the FDA removal in 2002 of the draft guidance it issued in 1998 following contradictory results from two expert laboratories (Pershing and Franz) on tretinoin formulations bioequivalence [4, 5].

There are as well other evidence such as comparison of the tape stripping technique with other techniques such as microdialysis which led to different conclusion for bioequivalence [6, 7]. It will be seen later that if microdialysis is rather a cumbersome technique with some limitations, the contamination issue should not be present and results from such a technique should be considered as of good quality.

5.1.2 Skin Biopsy

5.1.2.1 Description + Use of Method

This is the most invasive technique of the methods described in this section. It consists, after removal (optional) of the stratum corneum by an appropriate tape stripping method, of cutting deep into the skin. The punch biopsy will contain parts of the subcutaneous tissues, dermis and epidermis while the shave biopsy will contain epidermis and some dermis. Parts of the stratum corneum may remain depending on the method used for stratum corneum removal. The biopsy can be frozen which allows subsequent cryo-sectioning [8] (Fig. 5.2).

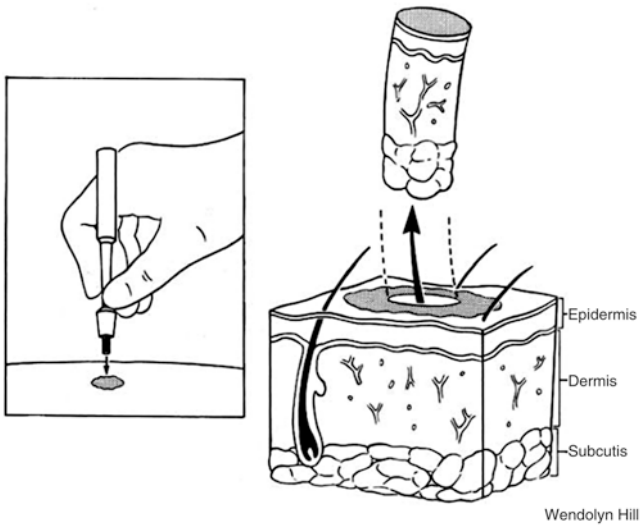

Fig. 5.2 Skin biopsy procedure. From https://www.healthtap.com/user_questions/482429

5.1.2.2 Pros

This technique provides *in vivo* drug concentration in all skin tissues.

5.1.2.3 Cons

This is an invasive technique. Volunteers can have a small scar usually for the rest of their life on every sampling point of the punch biopsy. Risk of scaring for shave biopsy is decreased, as some of the dermis is not sampled.

The "skin surface contamination issue" is present here, as the tool used to cut into the skin may carry some drug (unremoved during the surface washing procedure) from the surface into the deep layers of the skin. Some inconsistency in some data obtained and the potential for interlaminate drug contamination is pointed out by Surber et al. [9] when discussing the skin biopsy methodology.

The skin concentration obtained represents the bound + unbound drug fractions, while only the unbound concentration is of interest (only unbound drugs will be able to cross cell membranes or/and be presented to a receptor) [10].

5.1.3 In Vitro *Percutaneous Studies: Skin Tissue Concentration*

5.1.3.1 Description + Use of Method

The method consists of determining drug concentration in the different skin tissues after topical drug application *in vitro*. The methodology is the same as the Percutanous Flux method that is reviewed later on. Classically, after removal of the studied topical formulation from the skin surface, the stratum corneum is tape-stripped, the epidermis and dermis are then separated. Concentration in the three different tissues is then determined (Fig. 5.3).

5.1.3.2 Pros

This is an easily performed *in vitro* technique.

This technique provides *in vitro* drug concentration in all skin tissues.

5.1.3.3 Cons

This is an *in vitro* technique.

The "skin surface contamination issue" is present here, as the cutting tool used to recover the skin tissue will carry some drug (unremoved during the surface washing procedure) from the surface in the deep layer skin.

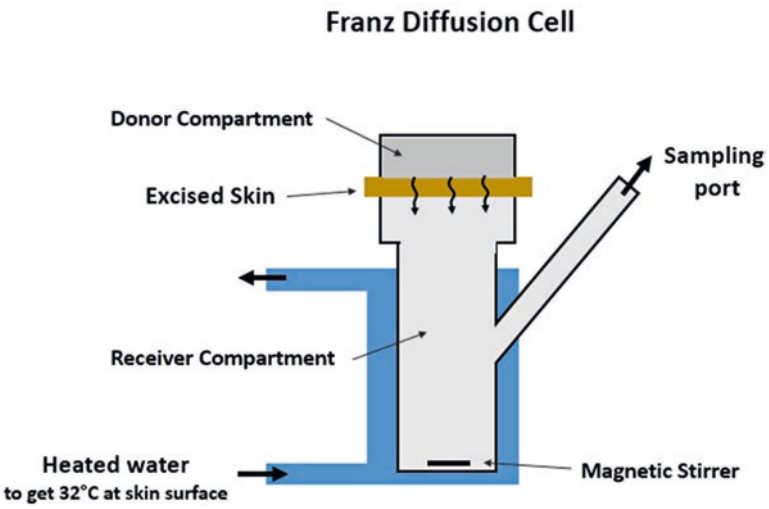

Fig. 5.3 Schematic drawing of excised skin mounted in a Franz diffusion cell

Skin concentration obtained represents the bound + unbound drug fractions, while only the unbound concentration is of interest.

5.1.4 Suction Blister

5.1.4.1 Description + Use of Method

The method consists in separating the epidermis from the dermis by the use of a special dome shaped Dermovac cap as described by Kiistala et al. [11, 12]. A suction of about 200 mm Hg (2.66 Pa) below atmospheric pressure is employed for a 2–3 h period after which 50–150 µl blister fluid and small corneum-epidermal sheet can be harvested. Blister fluid corresponds roughly to interstitial fluid. Protein content of suction blisters is about 60–70% of the corresponding serum value [13]. The aim of the method is to measure interstitial fluid concentration at the epidermal/dermal junction. The method has been used after topical application of different molecules [14–18] (Fig. 5.4).

5.1.4.2 Pros

The sample collected is sampled from the viable epidermis/dermis junction and a large number of the skin pharmacological targets are situated either side of this junction.

The sample collected is a liquid that will make the analysis easier than for a solid.

The method is used *in vivo* and is relatively non-invasive.

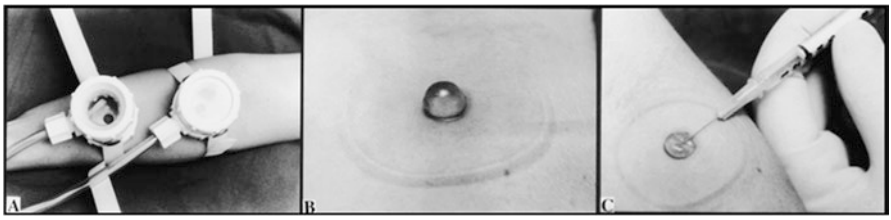

Fig. 5.4 Formation and sampling of blisters. (**a**) A suction chamber is placed on the forearm and a constant vaccum is applied. (**b**) Blisters are formed in 2–3 h. (**c**) Blister fluid is aspirated after a defined equilibration time. From [19]

5.1.4.3 Cons

The proportionality factor in between the drug concentration in the blister liquid and the drug concentration in the epidermis or dermis is not known, especially as the large volume of fluid created in the blister is likely to dilute the concentration truly present in the interstitial fluid at the epidermal-dermal junction.

The "skin surface contamination issue" is present here as well. While inserting the needle to collect the blister liquid the needle will transport from the surface some drug (unremoved during the washing procedure). However, the small surface area of the needle makes this issue less extensive than in other skin PK sampling direct methods.

5.1.5 Skin Surface Contamination Issue

The "skin surface contamination issue" is caused by the following situation: while applying to the skin surface a topical formulation, the amount of the drug applied will be several orders of magnitude higher than the amount of drug present in the skin tissue. As a consequence, the washing procedure used to remove the drug applied has to be extremely effective and should be in theory equal to 100%. At least, if the amount of drug sampled in the skin tissue is 100 times inferior to the amount of drug applied, then the washing procedure recovery should be superior to 99%. That task is in theory achievable on a surface that is smooth, tough and impermeable, but less so on the skin surface that is rough, soft and permeable. The task is more complicated by the fact that classically a small amount of the topical formulation is applied that will dry over the time course of the experiment.

In the example below only 0.24% of the dose crossed the skin. The washing procedure would, therefore, need to be very effective to obtain confidence in the dose recovered within the skin tissue (Table 5.1).

Table 5.1 Example of percentage of dose crossing the skin

Drug concentration in formulation (% w:w)	1
Formulation applied (mg/cm^2)	10
Dose applied (µg/cm^2)	100
Average percutaneous flux over 24 h (ng/cm^2/h)	10
Permeated cmpd in 24 h/cm^2 (µg)	0.24
Dose permeated vs dose applied (%)	0.24

The difficulty is that it is not possible to validate the washing procedure protocol as validation of the protocol can either occur at time t0 (time of formulation application = option 1) or at time t (time of skin tissue tissue sampling = option 2) as can be seen in Fig. 5.5 below.

With option 1, the formulation is still a semi-solid so it is reasonably easy to sample and remove. This option to validate the washing procedure does not account for the difficulty one would have had if sampling had been done once the formulation had dried into a thin matrix stuck to the stratum corneum.

With option 2, at the time of sampling, some drug material will have penetrated into the skin and will not be in the vehicle any more. It will then not be possible to make a calculation of the dose recovered as some will be missing.

This makes any validation, strictly speaking, impossible to perform.

The consequence of the "skin surface contamination issue" is that most often an overestimated amount of drug is present in the sample compared to what was really in the skin tissue before sample collection.

In order to limit this contamination, one can envisage not to count the stratum corneum. This can be achieved by tape stripping as this should remove the drug stuck on the skin surface. The difficulty in that approach is that it is not homogeneously removing the skin layers. It is not possible to count the number of tapes to know whether all the stratum corneum has been removed or not. It is considered that the tape strips have reached the viable part of the epidermis once a glistening layer is visible. This is reasonably well observable *in vivo*, but more difficult to observe *in vitro*. Furthermore once the glistening layer is reached, it is not reached homogeneously as shown on the diagram below where part of the stratum corneum could still be present which could overestimate viable epidermis concentration (Fig. 5.6).

Overall surface contamination and tissue separation make reliable measurements of skin concentration following topical application difficult to interpret.

Surface contamination for concentration determination is not the sole problem of skin pharmacokinetics. It is a shared problem of all pharmacokinetic studies when one wants to sample a local tissue which is in direct contact with the site of administration: alveola concentration after lung delivery, enterocyte concentration after oral delivery and nail concentration after application of local nail treatment.

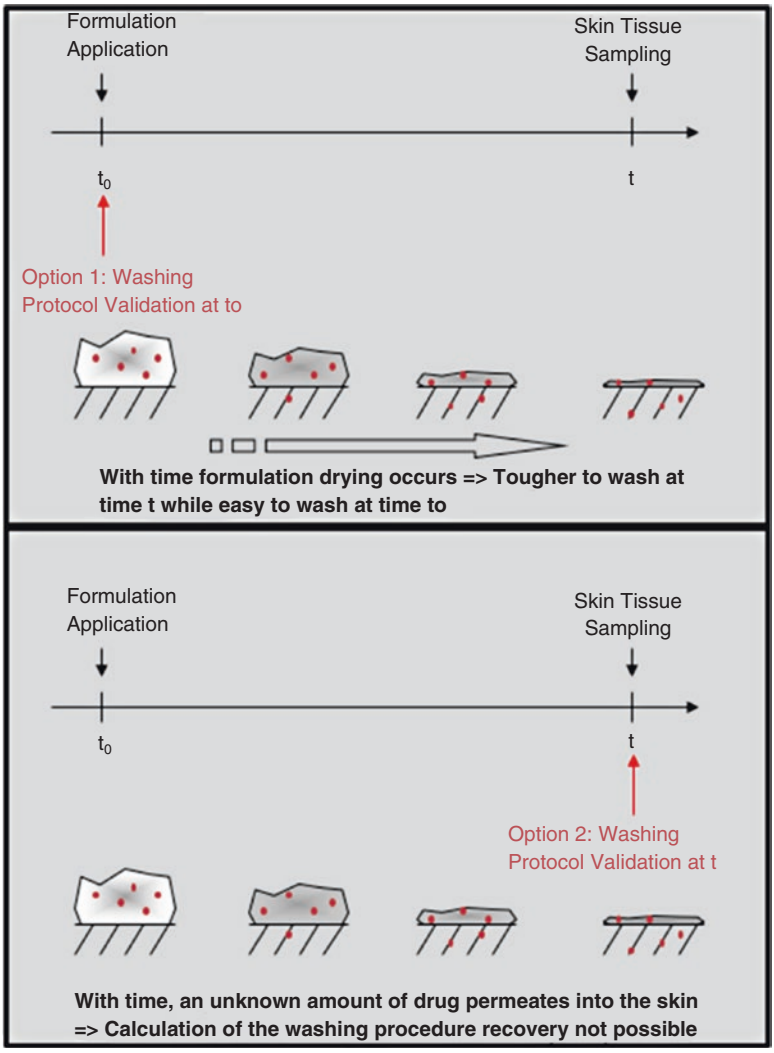

Fig. 5.5 Attempts to validate the washing procedure

Interestingly, nail pharmacokinetic studies also use Franz diffusion cells. The noticeable difference with skin is that nail is a hard tissue and over the years a trick has been found to get by the surface contamination issue. The concept consists in drilling—with a small dremel—the site in contact with the treatment (the dorsal side) and the side not in contact with the treament (the ventral side) [20].

If it is difficult to prove the extent of the contamination issue in skin pharmacokinetics as the issue has not been solved. However one can get a feel of it

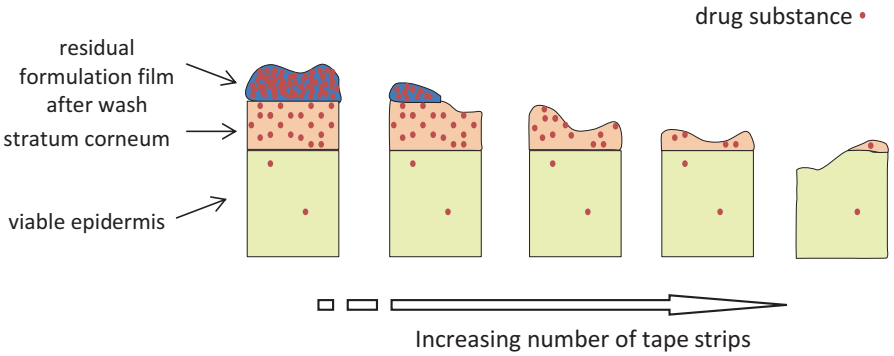

Fig. 5.6 Tape stripping of the stratum corneum

Table 5.2 Penetration results of four oxaboroles into the nail plate, compared to their physicochemical parameters with differentiation of dorsal and ventral sides

	Absolute amount in the nail plate after single dose left for 3 days	
Compound	Ventral/intermediate layer (μg/mg nail)	Dermal/intermediate layer (μg/mg nail)
AN2690	2.5 ± 3.8	2.1 ± 0.8
1	0.78 ± 0.63	2.3 ± 1.7
2	0.43 ± 0.67	2.0 ± 1.0
3	0.00 ± 0.00	1.9 ± 1.6
Ciclopirox	0.00 ± 0.01	1.5 ± 0.3

Each number represents the mean ± SD of three samples

when looking at nail pharmacokinetics for which a solution exists as described above. In the table the authors have compared the nail dorsal concentration (in contact with dose administered) and the nail ventral side (not in contact with the dose administered). As can be seen, on the dorsal side, all compounds appear to be delivered to the same extent. However on the ventral side (the side that should not be contaminated by the applied dose) very substantial differences exist [21] (see Table 5.2).

With regards to identifying or suspecting a contamination issue, another element can be looked at: the proportionality in between the percutaneous flux and the skin concentration obtained. As will be seen later (in paragraph "retention in skin" in Chap. 8), accumulation or retention in the viable epidermis and dermis due to the vehicle is not possible. Therefore proportionality should exist in between flux and skin concentration. When this does not occur, a strong suspicion should point towards a contamination of the skin tissue sampled.

5.2 Indirect Methods

5.2.1 Introduction

Indirect methods may appear less convenient to consider than direct methods. Indeed they often need more sensitive bioanalysis techniques and the data generated need to be interpreted and transformed to give information on the skin tissue concentration itself. This adds some uncomfort and some time lack of trust in such data and methods due to the difficulty in their interpretation. If they are more difficult to interprete, they do not have the skin surface contamination issue and therefore are more trustable data than the one from the direct methods. As well, the concentration derived from such data are free concentration while in the direct methods only total tissue concentration is obtained.

5.2.2 Plasma Collection

5.2.2.1 Description + Use of Method

This technique consists in collecting plasma samples or (and) excreta samples. If the samples collected are only plasma samples, flux through human skin can be calculated providing one knows the total systemic clearance of the drug studied [22]. If only excreta samples are used, the applied drug needs to be radiolabelled (or a large proportion of the drug needs to be excreted unchanged and this proportion needs to be well defined), the total bioavailability of the drug topically applied can be estimated.

5.2.2.2 Pros

These techniques are the standard pharmacokinetic techniques used for the development of oral drugs.

There is no "contamination issue".

The method is used *in vivo* and is relatively non-invasive.

5.2.2.3 Cons

For a drug applied topically, the proportionality factor in between the drug concentration in the plasma or excreta and the drug concentration in the different skin tissue is not known.

The concentration of the samples is generally extremely low, especially if the topical formulation was applied on a small body surface area. Measurement of such low concentrations will normally require the use of very sensitive analytical techniques.

Note: In preclinical studies, especially in rodent, it is difficult to perform such studies for two reasons: (1) the applied dose could get on the site where the blood samples will be collected from, therefore, contaminating the blood sample and (2) rodents spend much time grooming and this often lead to some oral ingestion of part of the topically applied dose which could be substantial.

5.2.3 Microdialysis

5.2.3.1 Description + Use of Method

Cutaneous microdialysis allows the measurement of drug concentration in the extra cellular space of the dermis. The technique consists in inserting a microdialysis fibre below the skin surface into the dermis and back. The dialysis fibre is then perfused with a physiological fluid that can collect the small molecules present in the area around the fibre. Due to the small pores of the microdialysis fibre, only small molecules can diffuse across the fibres, the sample therefore recovered is protein-free. After a defined period of time, which is used to let the inflammation caused by the insertion of the fibre to decrease, the topical drug is then applied above the area where the fibre has been inserted. A small sample size can then be collected over time [23]. A good description of the technique is given by Holmgaard et al. [24] (Fig. 5.7).

Two approaches can be used:

Case 1: Simple measurements of the dialysate are made. The concentration is proportional to the dermis free concentration. The "microdialysis fibre's recovery factor" (= the proportionality constant) needs to be defined separately so that true extra cellular dermal concentration can be estimated.

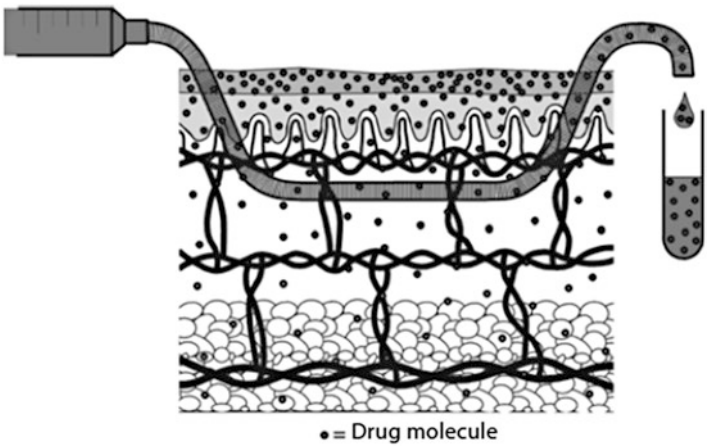

Fig. 5.7 Illustration of the microdialysis probe placed in the dermis, sampling increasing dermal concentration following topical drug penetration. From [25]

Case 2: The point of No Net Flux method (NNF) is used. It consists in infusing in 4–6 fibres a range of concentrations that are believed to cover the actual dermis drug concentration. The dermis concentration corresponds to the concentration infused in the fibre where no change was observed between the concentration infused in and the recovered sample.

5.2.3.2 Pros

The method can be used *in vivo*. There is no "contamination issue" providing the points of entry/exit of the fibre in/out of the skin are well isolated from area where the topical drug is applied.

It uses a small surface area which can be helpful to limit exposure and therefore could potentially be looked at with a small toxicology package.

Case 1: A concentration, which is proportional to the dermis free concentration *in vivo*, is generated which is the right information in an important pharmacological target skin tissue.

Case 2: The free concentration in the dermis is determined which is the right type of information wanted in a relevant skin tissue. There is no need to worry about a potential "microdialysis fibre's recovery factor" issue.

5.2.3.3 Cons

This is a relatively invasive method and difficult method to set up.

The drug concentration in the samples is generally low especially with lipophilic permeants. Measurement of such low concentrations will require normally the use of very sensitive analytical techniques.

Case 1: Validity of the concentration defined is dependent on the "microdialysis fibre's recovery factor" used and this factor determined outside of the *in vivo* condition is often poorly estimated [26]. It should be added however that the retrodialysis method when used *in vivo* as described by Stahle et al. [26], is recognised as a good method for estimating *in vivo* recovery and is used by a growing number of microdialysis groups as an abbreviated method of the NNF method as it does not require equilibration [27].

Case 2: It requires long equilibration time and reliable microdialysis fibres (that do not block over time). It assumes as well that the concentration to be measured is approximately known to "bracket" the different concentrations to be infused.

Overall an interesting technique that has a strong potential for bioequivalence studies, but likely some limitation at a drug discovery stage.

5.2.4 In Vitro *Percutaneous Studies: Percutaneous Flux*

5.2.4.1 Description + Use of Method

The method consists of studying the percutaneous flux of a topical drug. It uses the same set up as the skin tissue concentration method. Figure 5.3 gives a description of the technique. Skin samples are mounted on a diffusion cell that consists of two compartments. Donor compartment is where the topical drug is applied. Receptor compartment is filled with a fluid that will collect the drug diffusing from the donor chamber through the skin membrane. Receptor medium samples are collected over time and a flux profile is generated.

5.2.4.2 Pros

This is an *in vitro* technique and, therefore, easy to perform.

There is no "contamination issue," as the collected receptor sample has no direct contact with the skin surface.

5.2.4.3 Cons

This is an *in vitro* technique (the *in vivo* equivalent would be the plasma collection seen earlier).

The proportionality factor between the percutaneous flux and the drug concentrations in the different skin tissue is not known.

The drug concentration in the samples is generally low. Measurement of such low concentrations will normally require the use of very sensitive analytical techniques.

5.3 Potential Use of the Skin PharmacoKinetic Sampling Methods, Comparisons of Methods and Consequences

Table 5.3 summarises the Pros and Cons of the different skin pharmacokinetics techniques reviewed earlier.

From the quality and relevance of the data given, the microdialysis technique appears like the most attractive technique as it does give the information wanted. However, the practicality issues added to the tough analytical issues does not make microdialysis a suitable technique to form part of the topical drug development process, especially at the drug discovery stage, as pointed out by Simonsen from Leo Pharmaceuticals [28].

Table 5.3 Comparison of the different PK sampling techniques regarding the determination of skin tissue concentration

Techniques	*In vitro*/*In vivo*	Information given	Issues	Feasibility (1 ≥ 4) (easy to hard)
Tape stripping	*In vitro* or *in vivo*	Concentration in stratum corneum	Surface contamination + only stratum corneum + bound drug	2
Blister suction	*In vivo*	Pseudo tissue concentration (epidermal/dermal junction)	Surface contamination + not true tissue concentration	3
Skin biopsy	*In vivo*	Concentration in all tissues	Surface contamination + bound drug	3
Plasma or excreta collection	*In vivo*	Input (flux)	Detection limit + no tissue concentration information	3
Microdialysis	*In vivo*			
Case 1		1. Dialysate concentration	1. *In vivo* fibre's recovery factor difficult to define + detection limit	3–4
Case 2		2. Dermis free concentration	2. Long time for equilibration + detection limit	4
In vitro percutaneous permeation	*In vitro*	Percutaneous flux	Not tissue concentration	1
In vitro percutaneous skin tissue concentration	*In vitro*	Concentration in all tissues	Surface contamination + bound drug + *in vitro* only	2

All the other techniques that give skin tissue concentration information have the surface contamination issues coupled with the fact that the concentration measured is the total drug concentration (bound + unbound fraction). This last comment is not true for blister suction as the level of protein can be measured [13].

The only other techniques apart from microdialysis that do not have the issue of surface contamination are the techniques that measure flux either *in vivo* (plasma/excreta collection) or *in vitro* (*in vitro* percutaneous studies: flux determination). The problem is that the link between flux or plasma concentration and skin tissue concentration is not known.

Overall, it appears that no currently available techniques would be satisfactory to estimate drug concentration in skin tissue after topical application. They are either flawed because of surface contamination coupled with a concentration determination which is unsatisfactory as the total (bound + unbound) concentration is generated

(and not the unbound concentration as desired); or they are too complex to be used effectively as a key tool at the drug discovery stage; or they don't measure drug concentration in skin tissue per se.

When looking back at the importance given to pharmacokinetics to drive the selection of oral drug candidates and bearing in mind the vast skin permeation differences across compounds, the lack of reliable topical pharmacokinetics methods makes the selection of a good topical candidate challenging.

5.4 Using Percutaneous Flux or Plasma Concentration as Surrogate Measurement of Skin Concentration

The percutaneous flux can be obtained from *in vitro* studies and it can be also derived from the *in vivo* studies using the plasma concentration of the test molecule following its topical application by the classic pharmacokinetic equation:

$$\text{Plasma Concentration}\left(\mu g/L\right)=\frac{\text{Input Dose}\left(\mu g/h\right)}{\text{Systemic Plasma Clearance}\left(L/h\right)} \quad (5.1)$$

Using the percutaneous flux and surface area covered by the topical application:

$$\text{Plasma Concentration}\left(\mu g/L\right)=\frac{\text{Flux}\left(\mu g/cm^2/h\right)^{*}\ \text{Surface Area}\left(cm^2\right)}{\text{Systemic Plasma Clearance}\left(L/h\right)} \quad (5.2)$$

Therefore:

$$\text{Flux}\left(\mu g/cm^2/h\right)=\frac{\text{Plasma Concentration}\left(\mu g/L\right)^{*}\ \text{Systemic Plasma Clearance}\left(L/h\right)}{\text{Surface Area}\left(cm^2\right)} \quad (5.3)$$

Equations linking flux and skin tissue concentration have been established since the seventies and eighties [29, 30]. One difficulty with past mathematical models is that some of the input data were not practically measurable data.

Higuchi and co workers [31] paved the way to a simpler approach linking the free basal epidermis concentration to the percutaneous flux and to the permeability coefficient of the permeant in the dermis.

More recently the same type of equations, obtained by different approaches, all using Fick's law of diffusion is now being described in the literature which uses measurable data [32–34].

$$C_{\text{free}}\ \text{viable skin tissue}\left(\text{at depth x}\right)=\frac{\text{Flux}^{*}}{D}\ h^{*}\left(1-\frac{x}{h}\right) \quad (5.4)$$

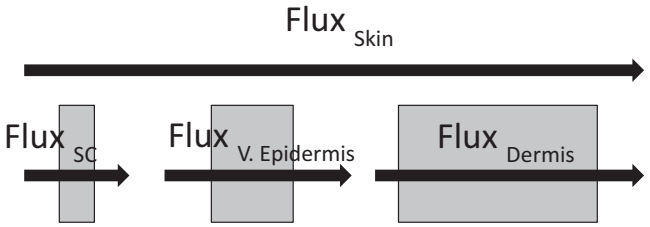

Fig. 5.8 Fluxes in the different skin tissue at steady state

Where
Flux = percutaneous flux (ng/cm^2/h).
D = diffusion coefficient in the tissue (cm^2/h).
C = free drug concentration (ng/cm^3).
x = viable membrane depth (cm).
h = total thickness of the viable membrane (cm).

Note that this concentration corresponds to a free concentration as only the diffusing molecules are taken into account. Bound molecules to protein would travel much less readily because of a much larger diffusion coefficient and would contribute only marginally to the percutaneous flux measured.

This equation is derived from Fick's first law of diffusion through membranes which says:

$$Flux = J = -D^* \frac{dC}{dx} \tag{5.5}$$

Indeed, at steady state: Flux through stratum corneum = Flux through viable epidermis = Flux through dermis = Flux through skin (Fig. 5.8).

At steady state because dC/dx = constant, by integrating Eq. (5.5), one would get Eq. (5.4).

At half thickness (x = h/2) Eq. (5.6) is obtained which corresponds to the average concentration in the membrane:

$$C_{free}(\text{mean}) = \frac{\text{Flux}^*}{D} \frac{h}{2} \tag{5.6}$$

If one wants to get further and define more precisely what the free concentration would look like knowing the percutaneous flux of a given molecule, it is then required to define D and h.

To know or estimate the diffusion coefficient in the viable epidermis Bunge and Cleek [35] suggest using.

$$\text{Diffusion Coefficient in viable epidermis} = \frac{7.1\ 10^{-6}}{\sqrt{\text{MW}}}\ \text{cm}^2/\text{s}$$

where MW = molecular weight.

This would lead a Diffusion Coefficient of $0.4.10^{-6}$ cm²/s for a molecule of 300 Da.

Trottet [34] reports diffusion coefficient in dermis ranging from 0.95×10^{-6} to 1.6×10^{-6} cm²/s for three substrates (MW from 166 to 477 Da). Ibrahim and Kasting [36] reports a diffusion coefficient of diclofenac (MW = 296 Da) through dermis of 1.1×10^{-6} cm²/s.

The thickness has to correspond with the part of the tissue considered and with the portion of the tissue from which the flux is measured. Most often the *in vitro* percutaneous studies use split thickness skin with a total thickness of 500–600 µm, so about 400 µm of dermis.

Using Eq. (5.6), with a dermis diffusion coefficient of 10^{-6} cm²/s and a thickness of 400 µm would lead to:

$$C_{\text{free top dermis in vitro}}\left(\text{ng/mL}\right) = \text{Flux}\ \left(\text{ng/cm}^2/\text{h}\right)^*\ 5\ \left(\text{h/cm}\right) \tag{5.7}$$

This equation links the concentration obtained in the top dermis *in vitro* with flux assuming no active capillary clearance and no specific skin disease characteristics.

Trottet [34] suggested adjustments to this equation with various hypothesis and literature data to account for the skin target sites, skin disease conditions and capillary clearance.

$$C_{\text{free skin target site in vivo}}\left(\text{ng/mL}\right) = \text{Flux}\ \left(\text{ng/cm}^2/\text{h}\right)^*\ \text{X}\ \left(\text{h/cm}\right) \tag{5.8}$$

In Table 5.4, one notices a difference for the X value in between atopic dermatitis and psoriasis suggesting that it may be easier to treat atopic dermatitis than psoriasis. The reason for the difference is due to the higher permeability through atopic

Table 5.4 Link in between flux and free concentration in the different skin compartments for various skin diseases

	Free concentration (ng/mL) = Flux (ng/cm²/h) * X (h/cm) Where X = …				
	Stratum corneum	Bottom of epidermis	Top of dermis	Bottom of dermis	Sub-cutaneous
Atopic dermatitis			1.8		
Psoriasis		0.73	0.18		
Acne (face)			3	0.6	
Fungal infection (athlete's foot)	666				
Dermal anaesthesia			1.8	0.37	
Muscle pain					0.028

dermatitis involved skin than psoriatic involved skin as well as a higher blood flow (local clearance) in psoriasis compared to atopic dermatitis.

Such a table and values for X(cm/h) should, however, be taken with cautions as many hypothesis had to be used.

As a rough estimate, in order to simplify the table above, one could suggest that:

$$C_{\text{free bottom epidermis or top dermis in vivo}}\left(\text{ng/mL}\right) = Flux\ \left(\text{ng/cm}^2/\text{h}\right)^{*} 1\ \left(\text{h/cm}\right) \quad (5.9)$$

As the percutaneous flux is a measurement that can be obtained *in vitro* easily and that does not have the contamination issue associated with, despite the uncertainty around some hypothesis for X it is likely a better option to have some ideas of the skin pharmacokinetics of the molecule rather than no data or untrustable data.

The measurement of flux as a surrogate of skin concentration could, therefore, help to guide a lead optimisation program team to make some judgment call on the risks taken in progressing a molecule towards candidate selection.

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Chapter 6
Assessing Topical Efficacy

6.1 Assessing Efficacy and Dose Prediction for a Systemic Target

As seen previously, a large part of the selection of a candidate process for an oral/systemic application relies on the use of plasma exposure and in vitro potency. This allows translating reachable plasma exposure (pharmacokinetics) into reachable in vivo pharmacodynamic effect: This is PharmacoKinetic/Pharmacodynamic (PK/PD) (Fig. 6.1).

Once it is established that a reasonable dose in man is predicted to translate into a pharmacokinetic profile that would lead to susbtantial pharmacodynamic effect, then, a large risk has been discharged for the candidate compound. Indeed, by then, it is predicted that a reasonable dose in man would allow the candidate compound to engage the target and that the pharmacology will be able to be explored [1]. The situation a program team does not want to get into is to push a candidate compound in the clinic without the option to fully explore the pharmacodynamic range of the target. If one is able to reach only 50% of target engagement while a 90% target engagement was required, the mechanism will not be tested fully and it will not be possible for the program team to claim the target is not valid [1].

The concept of sufficiently engaging the target is a key pitfall of dermal drug development. It is believed that many candidate compounds fail in topical proof of concept studies (Phase 2) because of not having been able to engage sufficiently their target. This can be often explained by the fact that PK/PD is most often not done during topical drug candidate selection because pharmacokinetic data are either not present, not reliable or not understood. Nowadays for a systemic drug development, it would not be thinkable to progress a candidate compound in the clinic without a systemic concentration to aim for.

L. Trottet, H. Maibach, *Dermal Drug Selection and Development*,
DOI 10.1007/978-3-319-59504-7_6

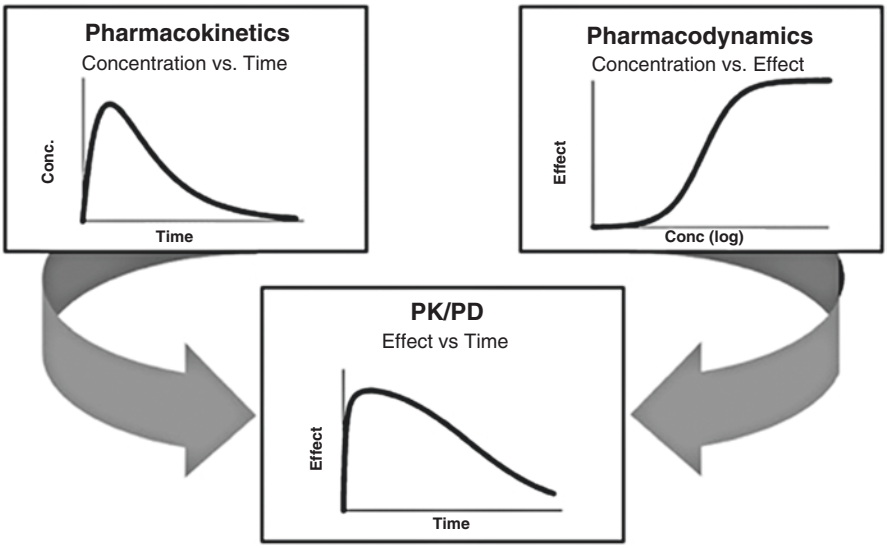

Fig. 6.1 Pharmacokinetic/pharmacodynamic modelling

6.2 PharmacoDynamic Models

6.2.1 Rodents

As seen in the section "Moving towards improved topical drug candidate selection processes: Use of in vivo models" in Chap. 2, rodents have been used since the 60s for topical pharmacology testing. There are pros and cons to such models.

Pros

- Rodent are the model of choice of the industry: small, inexpensive, easy to handle (skills and facility), small compound quantity required.
- Many skin disease model exists (though translation to the human disease condition as in every animal model is not necessarily robust).
- Many transgenic or KO mice models are available.

Cons

- Rodent skin is much more permeable than human skin (overestimate of delivery and therefore of efficacy).
- Topical application is complex: rodent will try to remove the topical dose applied (grooming, licking, scratching). It is not uncommon to see the animal absorbing large quantity of the dose applied which can lead to pharmacologically relevant systemic exposure (100 µL twice a day of a 1% w/w formulation applied on back of a mice (20 g) will be equivalent to a daily dose of 100 mg/kg). Protecting the site of application is complex as animals generally do not stand the protection considered and will do their best to remove it.

- Plasma PK measurement is complex too, as the animals run in the cage with substantial dose loaded on their skin. The dose is spread in the cage and then back on untreated skin sites on the animals. When sampling the animals for PK it is not uncommon to get spikes in some time points likely reflecting external contamination of the sample at time of sampling the animal.

Likely Best Use of Such Models

- Demonstrate topical efficacy. This can be done for example by using a three arms approach and measuring the plasma exposure in the three arms: (1) a topical arm, (2) a systemic arm (oral, intraperitoneal, subcutaneous, mini pump) with an effective dose, and (3) a systemic arm with a non effective dose. Once it has been demonstrated that the plasma exposure following topical application is inferior to the non effective systemic dose plasma exposure, topical efficacy is established.
- Rank candidate compounds: as above using for several compounds topical administration in parallel to systemic administration with effective and non effective dose and the corresponding plasma exposures.
- Translation to human of the likely topical target engagement: Due to the susbtantial higher permeability of rodent skin, the dose in the topical formulation tested in the rodent model would need to be dropped (as per the example with tacrolimus in Table 2.3 in Chap. 2), if one wanted to use the rodent model data as a mean of demonstrating target engagement in man. Theoretically the dose drop should be of the magnitude of percutaneous flux difference from the rodent model to human skin. To get the value of the required drop dose one could perform an in vitro flux comparison in between rodent and human skin for the compound of interest.

6.2.2 Minipigs

Minipig models have been used since the 90s in the assessment of efficacy of topical drug candidates.

Pros

- Similar skin permeability as human skin.
- Skin site more easily protected than rodent. Reliable topical PK can be determined. No risk of substantial oral ingestion leading to pharmacology relevant systemic concentration.
- Well recognised by regulatory bodies as an animal for toxicology testing during topical drug development.

Cons

- Large animals that the industry has difficult access to (cost, skillset, facility).
- Number of disease models limited.
- No transgenic or KO animals.

Likely Best Use of Such Models

- During lead optimization, this model (when the model exists) can be used for demonstrating topical efficacy, ranking compounds and predicting efficacy in man. All this can be done without paying much attention to PK as it is assumed that pig skin PK will be closed to human skin PK.

The program team using such a model will have to bear the initial decision and cost of settting up and running such a model.

6.2.3 Human Microplaque Assay

One advantage of topical drugs is that they can be applied to a small part of the body without exposing the whole body to the tested molecule. This can be proven very helpful for assessing the efficacy of a topical drug in a patient or an healthy subject providing a relevant biomarker is availabe.

This approach was first tested a century ago, just after world war I, while understanding mustard gas pharmacology using the "nail head" method consisting in applying, on a 3 mm diameter patch with a nail head, mustard gas on the skin of healthy volunteers [2].

This is as well thanks to this concept that the most succesfull topical drug classes, the corticosteroids, were developed from the 50s through the 70s using blanching (vasocontrictor properties of corticoids) as the biomarker.

Pros

- Can be performed directly in healthy subjects or patients (no translation question, no skin PK difference question).
- Smaller toxicology package than for a full proof of concept study.

Cons

- Clinical study. Access to heallty patient and/or patients is not as straightforward as access to an animal model. A minimum toxicology package will be required. Cost will be high. Timelines will be long.
- Only a limited number of skin disease can today be considered (the most common one being for psoriasis) because of the lack of relevant/reliable biomakers.
- Microplaque assays are often conducted with the skin site protected/occluded. This will lead to overdosing the site locally compared to a real life clinical situation. A positive outcome would not necessarily translate into a positive Proof of Concept in a real clinical setting. It will therefore be important to weigh the pros and cons of the loading dose and occlusion in the clinical protocol.

Likely Best Use of Such an Approach

- Derisking a mechanism of action (derisking a target). A candidate compound could be applied under occlusion with potentially a good delivery vehicle (high

solvent content for example) to maximise delivery and chance of engaging the target and therefore maximising the chance to explore the pharmacology.
- Derisking a candidate compound for which ability to engage the target is a strong risk.

In future, with the progresses on identifying and measuring biomarkers by various analytical methods, program teams may envisage more readily such an approach for testing candidates even for ranking candidates. To get there, however, the program team will need to have a strong understanding of the regulatory requirements. Indeed such an approach can be viewed favourably only if the time, cost and efforts are substantially more attractive than the full classic drug development.

6.2.4 In Vitro *PharmacoDynamic Models*

With the difficulties described earlier for the in vivo PharmacoDynamic models to assess efficacy, some in vitro cell culture models have been engineered into the Franz diffusion cells (the same system as the one described earlier in Fig. 5.3. in Chap. 5) using human skin biopsies. The use of Franz cells allow obtaining a 3D model with a relevant skin barrier. The key challenge for this attractive approach is to find a relevant biomarker for the mechanism of action tested.

An obvious approach would be to take the skin sample out of the Franz cell and do an ex vivo bioassay. For example an ex vivo bioassay would consist in incubating the removed sample with a substrate of the target and look for the disappearance of this substrate or appearance of the product of reaction of this substrate with the target. This approach works well with most tissues sampled following systemic application as the drug is well distributed within the body without substantial difference in drug concentration from tissue to tissue. However for a topical application the "surface contamination issue" described earlier will be well present. Large quantity of compound that would not have penetrated into the skin tissue could be taken with the sample and this compound will disolve into the incubation medium and interfere with the substrate enzyme reaction and give a false positive signal. It is, therefore, not straightforward to find such a biomarker as it should be already present in the skin tissue or receiver fluid at the time the skin sample/receiver fluid is taken. Sensitivity will be a clear hurdle. Specificity of the susbtrate or product of reaction will be another one.

Pros

- Can be done in vitro.
- Use relevant skin barrier.
- Use human skin.
- No need to pay attention to contamination (if no incubation is required post skin sample recovery for the biomarker assayed).

Cons

- Difficult to find the biomarker.
- The studied biomarker should not be based on an incubation post skin tissue removal (contamination from skin surface could lead to false positive).
- New area and approach where little to no information is yet found in literature.

Likely Best Use of Such an Approach

- Proof of target engagement before Candidate Selection.
- Ranking compounds during lead optimization.
- Selecting the candidate.

The program team using such an approach will have to bear the initial decision and cost of looking for the relevant biomarker which can be challenging unless it is described in the literature.

In future, with the progresses on identifying and measuring biomarkers by various analytical methods, program teams may envisage more readily this approach for ranking candidates and demonstrating target engagment. This step could as well become a stepping stone before the First Time in Human phase (Phase 1) in which demonstration of target engagement will be looked for. It could be as well the natural step to take before advancing into a microplaque assay study in man.

6.2.5 "In Silico" PK/PD Approaches

6.2.5.1 Ratio Percutaneous Flux/In Vitro Potency

When performing PK/PD analysis, the first approach that tends to be used especially in lead optimization is to link the free concentration (i.e., the pharmacologically relevant concentration) in plasma with the relevant in vitro potency (e.g., the IC50). If the free concentration in plasma is superior to the IC50 then it is expected that 50% of the target is engaged which could translate in starting to observe some in vivo efficacy. This varies however from target to target as for an antagonist most often a larger target engagement is required while for an agonist a smaller target engagement is usually required.

In the previous chapter, it has been seen that a rough estimate of the free concentration in the top dermis/bottom epidermis could be given by Eq. 5.9 in Chap. 5:

$$C_{\text{free bottom epidermis or top dermis in vivo}}\left(\text{ng/mL}\right) = \text{Flux}\ \left(\text{ng/cm}^2\text{/h}\right)^{*} 1\ \left(\text{h/cm}\right)$$

Therefore one would expect that if the Flux (using ng/cm^2/h as the unit) is superior to the in vitro potency (using ng/mL as the unit), then the local skin free concentration should be superior to the in vitro potency and the target should start to be engaged. Therefore a ratio flux/in vitro potency equal to one could be a delimitation of efficacy and non efficacy.

By studying the five topical main drug classes acting in the epidermis/dermis and their respective flux and in vitro potency, Trottet [3] has demonstrated that indeed a ratio flux/in vitro potency equal to one could be a target to estimate efficacy potential in the clinic. Literature, however, lacks much examples of non efficacy of topical molecules (only two described: cyclosporin and benzocaine (for intact skin)) which would increase the strength of the trend observed. The pharmaceutical industry has many of such topical program failures but such compounds with their percutaneous flux and in vitro potency are however not described in the literature.

In Table 6.1 is summarised the various reported percutaneous flux and in vitro potency by Trottet [3].

Notes

- Reported data are for most the average (geometric mean) of at least two data for both flux and in vitro potency.
- When the flux of different formulations existed for a single drug, the geometric mean was determined to give a single value.
- Corticosteroids have vasoconstricting properties, therefore they reduce local clearance of the drug and therefore this property increases their skin concentration, therefore a correction factor of three for the flux/in vitro potency was used to take into account for such properties.

Figure 6.2 overviews the link in between clinical efficacy and the ratio percutaneous flux/in vitro potency.

This summary figure suggests that the cut off value of "1" for "flux/in vitro potency" (i.e., Eq. 5.9 in Chap. 5 being true) could be a guiding element for separating effective and non effective topical molecules.

$$\frac{Flux\left(\mathrm{ng/cm^2/h}\right)}{EC50\left(\mu g/\mathrm{L}\right)} > 1\left(\mathrm{mL/cm^2/h}\right) \tag{6.1}$$

Looking more carefully at the ratios, one can as well observe that within corticoids the least potent (hydrocortisone) has the lowest ratio, while the most potent corticoid (clobetasol propionate) has the highest one.

To refine the likely efficacy one could look more carefully at the disease modification aspect to get a more accurate target skin tissue concentration as described earlier in Eq. 5.8 in Chap. 5 and Table 5.4 in Chap. 5.

Pros

- Simple.
- Requires only easily accessible in vitro data.
- Use human skin.

Table 6.1 Percutaneous flux vs *in vitro* potency for 5 drug classes

Compound	Target class	Percutaneous flux (ng/cm²/h)	*In vitro* potency (nM)	Flux (ng/cm²/h)/ potency (ng/mL)	References used for flux, *in vitro* potency and clinical assessment
Tetracaine	Anaesthetics	30,000	3500	32.5	[4–14]
Lidocaine	Anaesthetics	44,000	155,000	1.2	
Prilocaine	Anaesthetics	50,000	125,000	1.8	
Benzocaine	Anaesthetics	8000	910,000	0.1	
Tretinoin	Retinoids	0.2	0.56	1.2	[15–24]
Clobetasol propionate	Corticosteroids	0.37	0.29	8.2	[3, 25–40]
Betamethasone di-propionate	Corticosteroids	0.26	0.79	2.1	
Fluticasone propionate	Corticosteroids	0.16	0.1	9.7	
Fluocinolone Acetonide	Corticosteroids	0.043	0.3	1.0	
Clobetasol butyrate	Corticosteroids	0.059	0.32	1.2	
Hydrocortisone	Corticosteroids	0.29	14.4	0.2	
Calcitriol	Vitamin D3 derivatives	0.02	0.07	0.7	[41–50]
Calcipotriol	Vitamin D3 derivatives	0.04	0.1	1.0	
Tacalcitol	Vitamin D3 derivatives	0.01	0.03	0.8	
Tacrolimus	Immunosuppressors	1.25	0.17	9.1	[51–66]
Pimecrolimus	Immunosuppressors	0.65	0.23	3.5	
Cyclosporin A	Immunosuppressors	1.25	11	0.1	

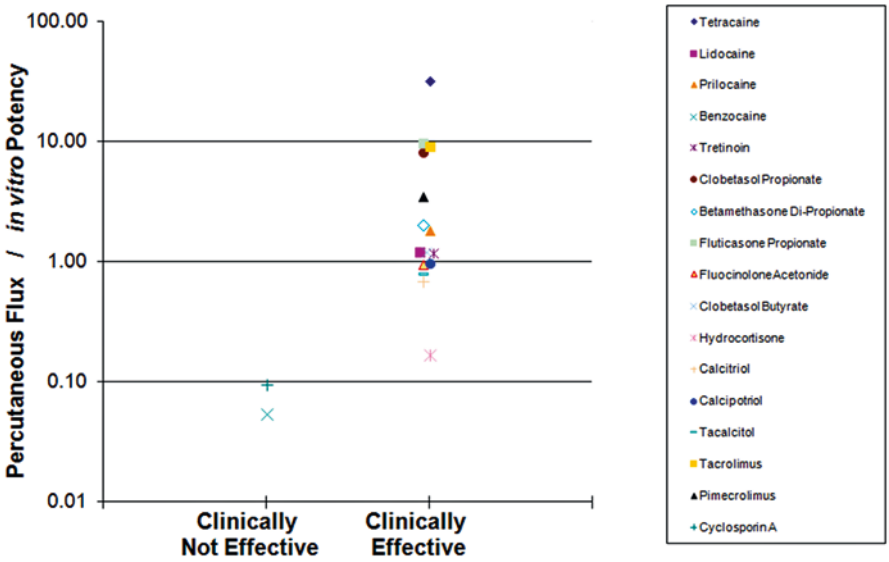

Fig. 6.2 Clinical efficacy vs percutaneous flux/in vitro potency

Cons

- Only in silico no pharmacology data following topical application are being generated.

Likely Best Use of Such an Approach

- Easy step to do early to gain confidence in a specific compound before investing more into it.
- Tool to screen out and to rank compounds.
- Guiding tool during a topical lead optimization program.

6.2.5.2 Modelling to Get Full Prediction with Local Target Engagement, Systemic Target Engagement and Therapeutic Window

The previous in silico approach offers some guidance towards predicting efficacy. One may however want to go further to predict efficacy as well as systemic exposure.

Predicting efficacy with only flux and in vitro potency does not guide the clinical program with regards to the dose regimen. During a lead optimization program of a systemically administered drug, the dose regimen will be substantially studied in order to make sure the target is constantly engaged and that the pill burden will be low for the patient. Many compounds will be screened out because of unappropriate PK properties. The half-life will be the driving element that will define the dose regimen.

With a topical, as previously discussed, the half-life concept is still not or poorly considered as for most topical program the first dose regimen that will be considered

in the proof of concept study will be "Twice a day." This is not driven by a specific topical pharmacokinetic parameters of the molecule but by what the patient will be likely to accept. Therefore attempting, even theoretically, to model what the target engagement could be over a treatment time course can be helpful to maximise the benefit from the topical drug by avoiding/limitting "drug holiday" periods.

Predicting systemic exposure and, therefore, systemic target engagement can be particularly interesting to assess the systemic therapeutic window. It is, as well, interesting as it can help a lead optimization team to focus or not on target specificity. For a systemically developed drug, getting specificity is a must as if one does not get specificity, then off-target effects are expected. For a topically applied drug, this is somewhat different as unless the other targets are present in skin where the concentration will be high, the plasma level may be so low that it does not become a problem any more. Having this is mind can speed up a lead optimization effort as such specificity is not a must for the attributes of the candidate drug.

Many software packages can be used to make modelling and many models can be build depending on the requirement. In the next pages, a relatively simple model is described (Fig. 6.3). The model was built with SimBiology® a toolbox using MATLAB® language.

The PK(PharamcoKinetics) (Fig. 6.4) and PD (PharmacoDynamics) (Fig. 6.5) obtained below are imaginary examples and have the following input parameters:

Target mechanism = inhibition.

pIC50 = 7 (IC50 = 100 nM)—hill coefficient = 1.

Target location = middle of viable epidermis (Ep3).

100% of body surface area is treated.

Topical PK: ka = 1/h, flux (0–24 h) = 17 ng/cm^2/h (if BID dosing), SC crossing time = 4 h.

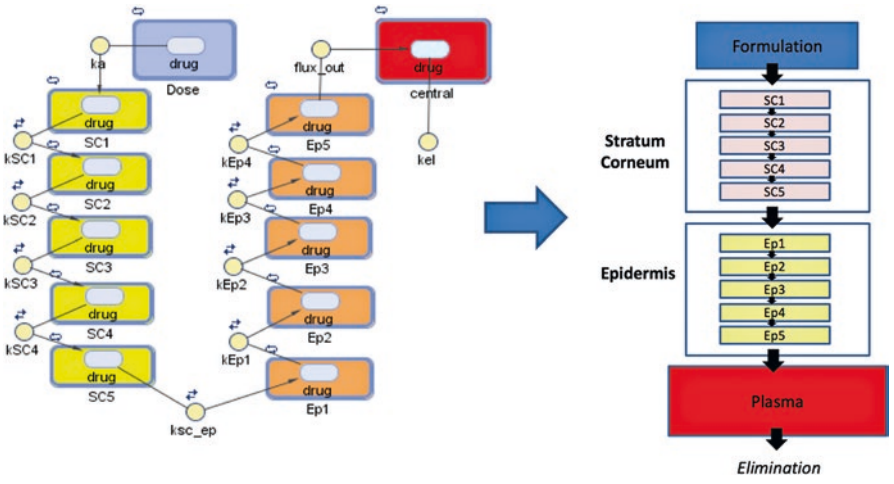

Fig. 6.3 Skin model mimicking release from formulation, passive diffusion through the stratum corneum down to the plasma compartment

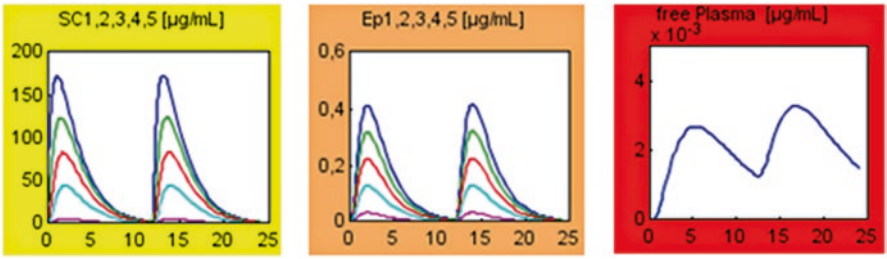

Fig. 6.4 PK: free concentration profiles in the compartments of the stratum corneum, viable epidermis and in the plasma over 24 h

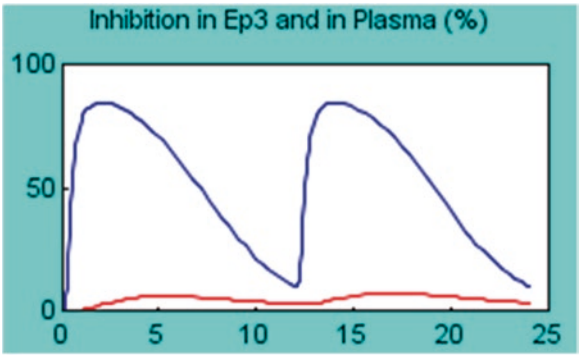

Fig. 6.5 PD: inhibition in the middle compartment of the viable epidermis (blue) and in plasma (red) over 24 h

Systemic PK: t1/2 = 4 h, Vd = 1 L/kg, CL = 12 L/h, Plasma protein binding = 90%.

In this example with the input parameters used, one can observe that despite the large body surface area treated, the target is not engaged systemically while it is in the viable epidermis.

Using the same model, examples in Fig. 6.6 show the impact of twice a day and once a day dosing as well as the impact of "skin crossing time" on target engagement. In particular, the example shows the large "drug holiday" period for the fast skin crossing time compound in the once a day dosing regimen.

6.2.5.3 Case Study: The Lidocaine/Tetracaine Patch

The previous examples are virtual examples, the lidocaine/tetracaine patch is of interest as PK data [67] and PD data [68, 69] exist for this topical formulation. The case of this patch starts to demonstrate how the use of PK information especially skin crossing time could be translated in the onset and the duration of action which is so poorly studied with topical drugs.

The lidocaine plasma concentration profile from the lidocaine/tetracaine patch is shown in Fig. 6.2 of Marriott et al. paper [67] and summarized in Table 6.2. It shows well how heat can decrease diffusion time. Its impact on anaesthesia onset time

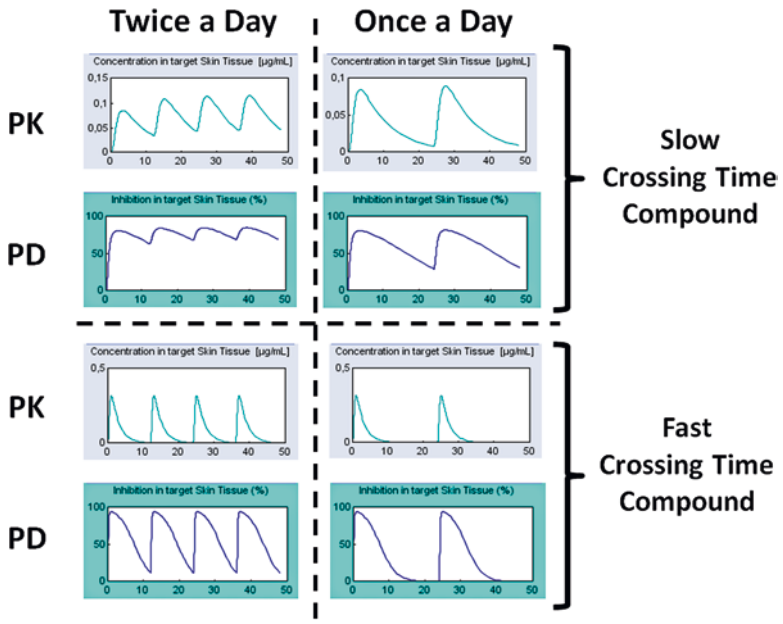

Fig. 6.6 Comparison of PK and PD target engagement if twice or once a day dosing and if fast or slow skin crossing time compound

Table 6.2 Lidocaine plasma concentration after 4 h application of heated or unheated tetracaine/lidocaine patch

	Lidocaine plasma concentration (ng/mL)	
	Unheated patch	Heated patch
30 min	1.1	5.5
1 h	7.3	17.7
4 h	24.2	25.7
8 h	~10	~10

versus Lidocaine/Prilocaine cream is documented [68] and shows a more rapid onset time for the heated lidocaine/tetracain patch than the lidocaine/prilocaine cream. Direct comparison is not strictly possible as the plasma concentration profile of both tetracaine and prilocaine are not available due to their extremely short half-life, as well, tetracaine has been showed to be more potent [4, 5] and to act more quickly than lidocaine/prilocaine [6]. The PK data can only, therefore, be suggestive of a beneficial effect on the onset time due to more rapid penetration.

More interesting, though, is the duration of action which for both lidocaine/tetracaine patch and lidocaine/prilocaine cream is known to be short after patch or cream removal (1–2 h for lidocaine/prilocaine cream and at least 100 min for lidocaine/tetracaine patch [69, 70])).

In order to predict the duration of anaesthesia, one can use the lidocaine plasma concentration, coupled with the potency of lidocaine and a mathematical model such as the one described in Fig. 6.3. The heated effect being transient and not maintained, the PK of the unheated patch is therefore more representative of the lidocaine skin crossing time.

The lidocaine/tetracaine patch has an active diffusion area of 10 cm^2 [71]. Using a half-life of 1.8 h and Vd of 1.2 L/kg for lidocaine [72], the model predicts that the percutaneous flux of lidocaine is 110 µg/cm^2/h (which is closed to the reported literature value of around 45 µg/cm^2/h [8, 11, 13]) in order to reach a plasma Cmax of about 24 µg/mL in 4 h with a diffusional arear of 10 cm^2. Figure 6.2 in Morimoto's paper [13] suggests that the lag time (i.e., skin crossing time) of lidocaine is 1.5 h. These various input data allow to obtaining all the PK parameters required to get the model (described in Fig. 6.3) to generate the profiles as shown in Fig. 6.7.

Using the in vitro IC50 potency of lidocaine which is around 155 µM [4, 5], this leads to the inhibition profile showed in Fig. 6.8.

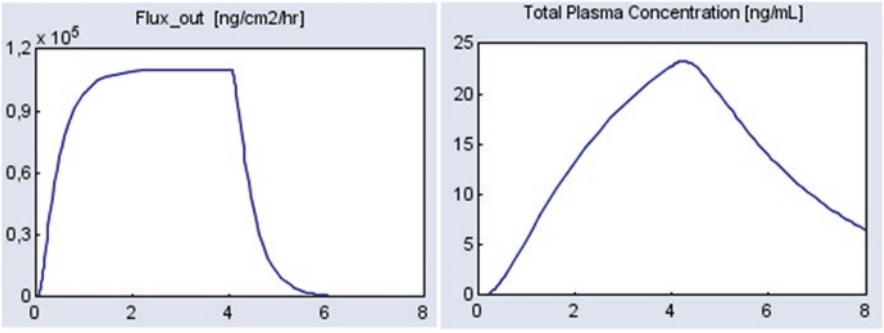

Fig. 6.7 Predicted instantaneous percutaneous flux profile as well as plasma concentration profile following the application of lidocaine over 10 cm^2 for 4 h

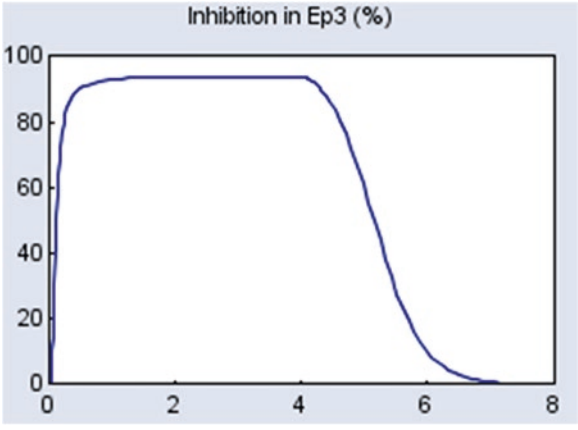

Fig. 6.8 Inhibition profile in the viable epidermis following 4 h application of a lidocaine patch

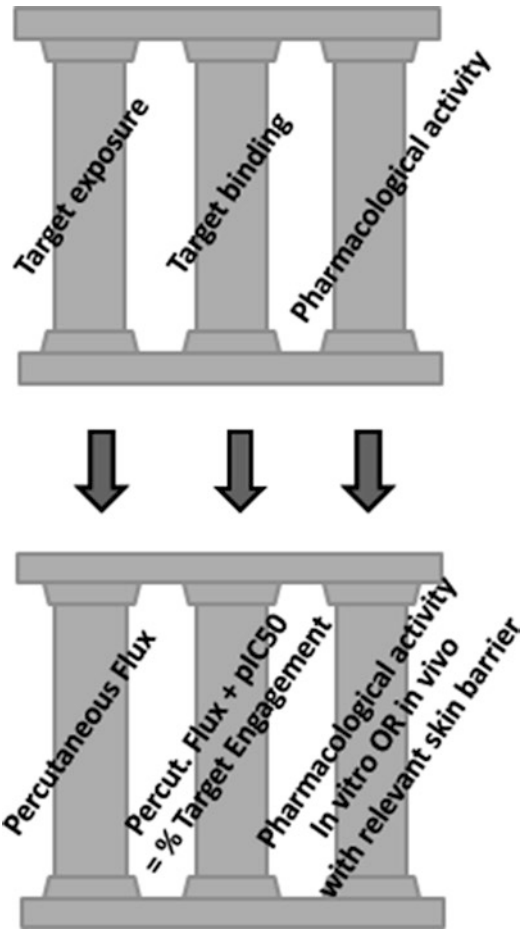

Fig. 6.9 Three pillars approach for a topical drug candidate

Interestingly the short duration anaesthesia (less than 2 h after patch removal) predicted by the PK and PD modeling in Fig. 6.8 appears to fit reasonably well with what is observed clinically [69, 70].

6.3 Conclusion

Many approaches exist to assess topical efficacy. Some are more straightforward than others. All have pros and cons. The likely best approach is the approach that will answer the questions one has with the risk at stake at the stage of development.

If a program team has a single asset to investigate, chosing a heavy approach such as minipig or microplaque assay could be an option though the team may want to derisk it earlier with a more simple approach.

If a program team is in a lead optimization program or has many compounds to choose from a terminated lead optimization program that is being repurposed, there

will be the need to have ways to rank the many compounds available. In which case using flux and in vitro potency could be an effective way to achieve such a ranking exercise and a key decision tool to select the candidate molecule.

The various approaches described above to define topical efficacy have all in common the need to use a relevant barrier property (or account for it) to predict efficacy in man.

Combination of some of these approaches would fit in the three pillars validation discussed earlier [1]. Percutaneous flux would be used for assessing "target exposure," a composite of pIC50 and percutaneous flux would be used for assessing "target binding" and finally an in vitro or in vivo pharmacology model would be used for assessing "pharmacological activity" (Fig. 6.9). If the three pillars concept could be done before pushing the compound in the clinic, this would decrease substantially the risk for the POC (proof of concept) and allow to better answer the question whether the mechanism of action was tested for the skin disease or not.

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Chapter 7
Assessing Therapeutic Index

7.1 Introduction

One key advantage of a topical administration is the decreased risk of toxicological findings. This perceived element is generally the driving rationale for developing a topical medicine.

This advantage is well proven by key topical target classes such as corticosteroids, immunomodulators, retinoids and vitamin D3 derivatives which have side effects difficult to manage if given systemically for long period but which are well effective and mostly safe if given topically.

As mentioned before, the number of new mechanisms of action with target related toxicity has largely increased over the last decade because the pharmaceutical industry has focused its research efforts on new targets rather than known derisked targets. The result has been a large number of research programs failing to reach or to go beyond the candidate selection stage because of target related toxicity despite having succeeded in generating potent molecules against the desired target. This represents a large number of potential assets that could be repurposed in a topical indication.

A research project team looking for repurposing, as a dermal drug, an asset with target related toxicity will try to assess the risk with such a route of administration. The push to get some assessment will be particularly high if the toxicological findings are particularly of concerns.

When the compound is administered directly onto the skin, a steep concentration gradient will exist from the upper skin layers down to the plasma compartment. On the contrary when delivering a compound systemically, assuming steady state equilibrium has been reached and no transporter are involved, the concentration (the free concentration) of the compound is expected to be similar in all tissues. In the example in the figure below (Fig. 7.1), the target tissue is the dermis, the therapeutic index will be the ratio of the concentration in dermis vs. the concentration in plasma. Such a ratio has been examplified by microdialysis with Diclofenac by Brunner et al. [1].

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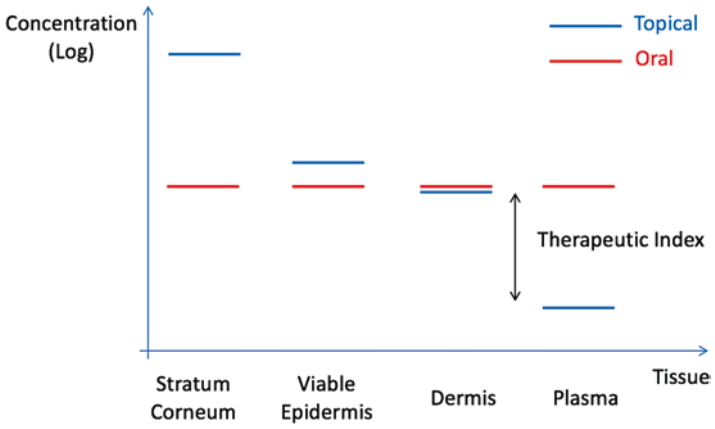

Fig. 7.1 Skin tissue concentration gradient after oral and topical administration

7.2 A "Crude" Approach: Comparing the Mass of Target Tissue with Total Body Mass

Paracelsus (1493–1541), a precursor of modern pharmacology, rightly pointed out that:

"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison." This is exactly that right dose that one has to define to assess the potential risk of systemic target engagement toxicology. Indeed another way to look at the therapeutic index for a topical in Fig. 7.1 is to compare the dose needed to exert a systemic pharmacological effect versus the dose needed to generate only a local skin pharmacological effect.

As will be seen later and as suggested by key topical drug classes, the general message is that it is usually safe from a systemic exposure point of view to envisage a topical administration for most disease with most compounds. Indeed the dose delivered topically to engage the target in skin is most often rather low compared to the dose that would be required to engage the target following systemic administration.

In order to get some early approximation of the type of therapeutic window that is achievable one can consider the mass of skin tissue being targeted versus the total body mass. As the dose will first cross the skin tissue before reaching the systemic circulation, the concentration in the skin will be substantially higher than in the systemic circulation. By analogy, this is like pouring a concentrated solution in a glass (the skin compartment) before transferring this solution into a bathtub (the systemic whole body compartment) (Fig. 7.2). A substantial dilution event occurs when transferring from the skin compartment to the systemic circulation compartment.

The dose delivered systemically depends on the surface area treated as the larger the surface area the larger the mass of skin tissue to treat.

If one assumes that the full epidermis and dermis are to be treated, this equates to a tissue thickness of about 2 mm. In Table 7.1 an approximative evaluation of the therapeutic index is calculated.

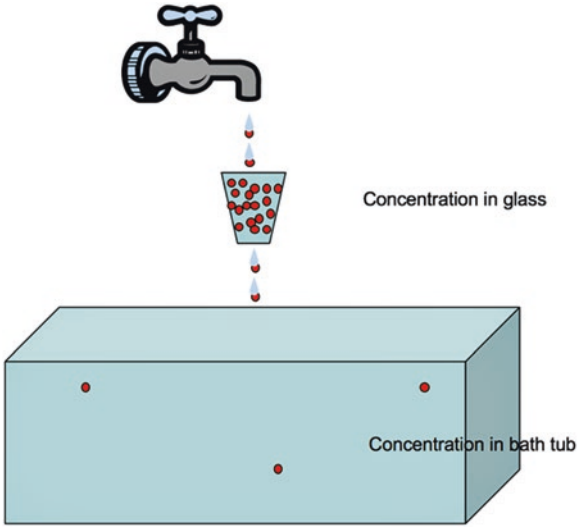

Fig. 7.2 Whole body dilution analogy

Table 7.1 Approximative therapeutic index evaluation

% of surface area treated	Surface area treated (cm^2)[a]	Volume of target tissue (cm^3)	Mass of target tissue (kg)	Approximative therapeutic index[b]
30	5400	1080	1.08	65
10	1800	360	0.36	194
3	540	108	0.108	648
1	180	36	0.036	1944
0.3	54	11	0.0108	6481
0.1	18	4	0.0036	19,444

[a]Assuming total skin area for 70 kg adult = 18,000 cm^2
[b]Ratio: 70 kg/mass of target tissue

The reality is somewhat more complicated as one has to take into account the gradient within the skin tissues, the residence time in the skin tissue vs. in plasma, as well as, the free concentration rather than the total concentration. This will be detailed in the next paragraph. However, what can be observed at this early stage is that even for large body surface area a good therapeutic index seems to exist.

7.3 Calculated Approach

In order to calculate more precisely the therapeutic index, one needs to calculate the ratio of target skin concentration versus plasma concentration following topical administration. More precisely one needs to compare the pharmacologically active concentrations [2] that is to say the free concentration in skin and free concentration in plasma [2].

In Eq. (5.8) in Chap. 5, the free concentration in skin has been calculated:

$$\text{Free Concentrat ion in Skin (ng/mL)} = \text{Flux } \left(\text{ng/cm}^2\text{/h}\right)^* \text{ X } \left(\text{h/cm}\right)$$

Where X (h/cm) is skin site dependant and disease dependant but mostly falls for disease of epidermis and dermis in the range 0.18–3 (in Table 5.4 in Chap. 5).

For simplicity of the following equations, it will be assumed that X = 1 (h/cm).

Classic pharmacokinetic Eq. (7.1) allows calculating steady state concentration in plasma based on input rate and systemic clearance.

$$\text{Total Plasma Concentration}_{\text{steady state}} \left(\mu\text{g/mL}\right) = \frac{\text{input rate}\left(\mu\text{g/h}\right)}{\text{clearance}\left(\text{mL/h}\right)} \tag{7.1}$$

Input rate for a dermal agent is dependant on body surface area and the input flux (percutaneous flux) (Eq. (7.2)):

$$\text{Input Rate}\left(\mu\text{g/h}\right) = \text{surface area } \left(\text{cm}^2\right)^* \text{ input flux } \left(\mu\text{g/cm}^2\text{/h}\right) \tag{7.2}$$

From Eqs. (7.1) and (7.2)

$$\text{Total Plasma Concentration}_{\text{steady state}} \left(\mu\text{g/mL}\right) = \frac{\text{surface area } \left(\text{cm}^2\right)^* \text{ input flux } \left(\mu\text{g/cm}^2\text{/h}\right)}{\text{clearance } \left(\text{mL/h}\right)} \tag{7.3}$$

Transforming total plasma concentration into free plasma concentration from Eq. (7.3)

$$\text{Free Plasma Conc.}_{\text{steady state}} \left(\mu\text{g/mL}\right) = \frac{\text{surface area } \left(\text{cm}^2\right)^* \text{ input flux } \left(\mu\text{g/cm}^2\text{/h}\right)^* \left(100\text{-plasma protein binding}\right)}{\text{clearance } \left(\text{mL/h}\right)^* \ 100} \tag{7.4}$$

Therapeutic index is the ratio of free skin concentration and free plasma concentration. This gives therefore:

Table 7.2 Example of calculated therapeutic index evaluation

% of surface area treated	Surface area treated (cm^2)[a]	Systemic clearance (L/h)	Plasma protein binding (%)	Therapeutic index[b]
30	5400	20	95	74
10	1800	20	95	222
3	540	20	95	741
1	180	20	95	2222
0.3	54	20	95	7407
0.1	18	20	95	22,222

[a]Assuming total skin area for 70 kg adult = 18,000 cm^2
[b]Assuming that in Eq. (5.8) in Chap. 5, X = 1 (h/cm)—for range of X refer to Table 5.4 in Chap. 5.

$$\text{Therapeutic Index} = \frac{\text{input flux}\left(\mu g/cm^2/h\right)^* \; 1\left(h/cm\right)^*}{\text{clearance}\left(mL/h\right)^* \; 100} \cdot \text{surface area}\left(cm^2\right)^* \text{input flux}\left(\mu g/cm^2/h\right)^* \left(100\text{-plasma protein binding}\right)$$

$$\text{Therapeutic Index} = \frac{1\left(h/cm\right)^* \; \text{clearance}\left(mL/h\right)^* \; 100}{\text{surface area}\left(cm^2\right)^* \left(100\text{-plasma protein binding}\right)} \tag{7.5}$$

Assuming a compound with a systemic clearance of 25% the human hepatic blood flow (20 L/h) and a relatively low protein binding of 95%, using Eq. (7.5), this would translate into a calculated therapeutic index given in Table 7.2.

The therapeutic index for the same surface area would increase if clearance and plasma protein binding were to increase, while it would decrease if clearance and plasma protein binding were to decrease.

As well, on the example above X (h/cm) was taken as equal to one. If X is higher than one then the therapeutic index would increase and vice-versa.

If the percutaneous flux was to be tenfold higher than required (i.e., over dosing), then the value of the therapeutic index would decrease by tenfold.

From the approximative approach and a more rigorous approach, even topical application on 30% body surface area would appear to offer a reasonable safety window.

For compounds overdosed or for compounds with low clearance combined with low plasma protein binding the window would however shrink.

7.4 Comparative Approach

A comparative approach on the potential risk of systemic exposure can be particularly helpful in a repurpose exercise with a set of compounds or in a lead optimization effort to select a topical candidate, if systemic safety is an important concern.

The calculated approach described previously can be challenged because of the various hypothesis taken for defining X (h/cm). However, the concept that C free skin is proportional to Flux (C_{free} skin = A * Flux) (where A is a constant independent from the compound) is less prone to challenge because it has been suggested by several authors [3–5].

Using this proportionality as well as Eq. (7.4) lead to the following equation for the therapeutic index:

$$\begin{aligned}\text{Therapeutic Index} &= \frac{\text{C free skin}}{\text{C free plasma}} \\ &= \frac{\text{A}^{*}\ \text{Clearance}\ \left(\text{mL/h}\right)^{*}\ 100}{\text{Surface Area}\ \left(\text{cm}^{2}\right)^{*}\ \left(100\text{-plasma protein binding}\right)}\end{aligned} \tag{7.6}$$

For a given skin disease, the surface area to treat would be the same.

$$\begin{aligned}\text{Therapeutic Index} &= \frac{\text{C free skin}}{\text{C free plasma}} \\ &= \text{Constant}^{*}\ \frac{\text{Clearance}\ \left(\text{mL/h}\right)^{*}\ 100}{\left(100\text{-plasma protein binding}\right)}\end{aligned} \tag{7.7}$$

Using Eq. (7.7), one could then compare the potential safety window of a set of molecules as showed below on six imaginary compounds. Out of these molecules, Compound F would be the one with the lowest systemic exposure risk (Table 7.3).

Table 7.3 Compound ranking for their topical therapeutic index

	Systemic clearance (L/h)	Plasma protein binding (%)	Topical therapeutic index
Compound A	20	95	Constant × 400
Compound B	2	95	Constant × 40
Compound C	80	95	Constant × 1600
Compound D	20	50	Constant × 40
Compound E	20	98	Constant × 1000
Compound F	20	99.5	Constant × 4000

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Chapter 8
Topical Vehicle Selection: Myths and Reality

8.1 Introduction

During the development of a dermal drug, much efforts tend to be placed on improving its delivery through skin. These efforts are driven by the known risk of not engaging the target. Indeed to increase comfort that the target will be engaged one need to try fullfill as best as it can evidence of (1) sufficient compound on board for a desired time (i.e., PK within skin) and (2) demonstration of pharmacological activity [1].

As seen previously, reliable PK within skin is not available unless flux data are interpreted to predict a translated skin tissue concentration, or, unless microdialysis data are available but either of the two being available is rarely the case.

Demonstration of pharmacological activity can be available but often it will be based on rodent topical pharmacology studies where it is known that the permeation through rodent skin is much higher than through human skin [2]. Rodent pharmacology after topical administration can therefore give false positive results [3]. Ideally, as seen previously, one would require preclinical data using either in vivo, a minipig pharmacology model [4] or in vitro, a target engagement model in franz cell using human skin. If such data were available, confidence in engaging the mechanism would be largely increased, unfortunately most of the time such data are not available.

The consequence is a major risk being carried forward after candidate selection. To try to limit such a risk, it is quite logical that the project team will attempt to maximise drug delivery of the chosen compound. One difficulty is that the team has no defined objective in terms of enhancement needed. Another risk is that such an approach does not necessarily lead to a decrease of the overall risks for the project, as penetration enhancement is often limited, local irritation can be increased and the aesthetics of the formulation is impaired.

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8.2 Skin Penetration Enhancement

Large efforts in the 70s–90s have been made to improve topical drug delivery. The way to improve topical drug delivery can be divided into four categories, all of them aiming to impact the crossing of the stratum corneum:

1. Using physico-mechanical approaches to overcome the stratum corneum barrier.
2. Improving solubility of permeant into the stratum corneum.
3. Interacting with the lipid bilayer structure of the stratum corneum to increase the permeability in the stratum corneum.
4. Using thermodynamic activity in the vehicle to increase penetration in the first layers of the stratum corneum.

The first category though the most successful one will not be discussed here, as it can be performed only on small skin surface (therefore helpfull for transdermal delivery) as such approaches are too skin disruptive and not practical (use of devices) for large skin surface area. They include the use of ultrasound devices (sonophoresis, sonoporation, acoustic ablation), electrical devices (iontophoresis, electroporation), high pressure devices (liquid and powder injections), microneedles as well as thermal and optical devices [5].

The second strategy aims at using the good solvent properties as well as the good skin penetration properties of some solvents (ethanol and other alcohols, propylene glycol and other glycols, urea, DMSO…). By penetrating into the stratum corneum they increase the solubilising capabilities of the stratum corneum. Therefore a permeant will be able to reach higher concentration in the stratum corneum which will increase its capacity to cross it.

The third approach consists in increasing the diffusion of drug molecules through the lipid bilayers. Some excipients (azone, fatty acids and esters, surfactants…) interact with the bilayers of the stratum corneum by disordering the hydrophobic tails of lipids or the polar head groups of the lipids. The consequence is an increased diffusivity of solutes which translate into an increased skin penetration.

Excipients used on both approaches, unfortunately, often have some irritancy issues (ethanol, fatty acids and esters, azone, surfactants) or aesthetics issues (greasiness for some fatty excipients, odor for DMSO).

Some papers show some impressive penetration enhancement which could suggest that chemical penetration enhancement is the way forward to solve the difficult delivery of drug candidates through skin.

However strong caution should be applied when analysing the skin penetration enhancement literature. Indeed one needs to be careful with the amount of formulation applied in such in vitro settings as it has been suggested that the penetration enhancement benefit is proportional to the amount of formulation applied [6]. For skin diseases involving reasonably large body surface area, Surber and Davis [7] have reviewed the field related to the dose applied with topical formulations and they have showed that the amount applied vary from 0.7 to 4 mg/cm^2. In the vast majority of papers describing substantial penetration enhancement benefits, much

higher volume of formulation were applied. The real clinical benefits of chemical penetration enhancers is, therefore, substantially lower than the large benefit that some papers suggest.

This lower than expected penetration enhancement benefit combined with often some irritancy and sometimes poor aesthetic properties of such excipients, make the chemical enhancement route (approaches 2 and 3) much less attractive than it first appeared.

The fourth way to improve skin delivery consists in using thermodynamics in the vehicle. Molecule transport through membrane is driven by the saturated state of the molecule in its vehicle [8]. Following topical application, the vehicle will dry and its composition will change with time up to complete dryness over the skin. The thermodynamic activity of the drug molecule dissolved in the original formulation will change as the vehicle composition changes upon drying. Indeed as the composition of the vehicle changes the saturated solubility of the drug molecule will change. Most often supersaturation will occur at least briefly during the drying process as less vehicle volume will be available for the permeant to disolve in. Sometimes the supersaturation will be stable for long periods while sometimes the drug molecule will precipitate straight away. In theory loosing the good solvent excipients (by evaporation or skin penetration) before loosing the poor solvent excipients will create supersaturation more quickly than loosing the poor solvent first. However this does not translate necessarily in an improved skin delivery as precipitation may occur more quickly. Some polymers can be used to stabilize the super saturation state and avoid rapid precipitation [9] which could potentially translate into improve skin drug delivery.

In any case in order to maximise skin permeation the classic strategy for the formulator consists in maximising solubility into the formulation. By doing so, more drug molecules are available to enter into the stratum corneum. At the same time the formulator will try to formulate near or above saturation in order to be at a thermodynamic activity closed or equal to one not to loose on thermodynamic. While trying to maximise solubility some aesthetics elements should be considered by the formulator, as most often the best solubilisation formulations have poor aesthetics properties (this will be discussed in more detail later in this chapter).

8.3 Retention in Skin

It is not uncommon to find claims of the potential for some formulations or excipients to increase drug concentration into viable epidermis or dermis.

These claims are largely based upon studies where the measurement of drug concentration in these viable tissues has been performed. Unfortunately reliable techniques to measure drug concentration in such tissues after topical application are still difficult to put in place as (1) drug contamination from the surface can occur and (2) tissue separation is not easy (see the paragraph dedicated to the surface contamination issue in Chap. 5).

If technically it is difficult to validate the potential for formulations or excipients to drive drug retention in skin, one can look at the theoretical viability of such an hypothesis.

In Chap. 5, the link in between skin concentration and flux has been established with Eqs. 5.5 and 5.6.

$$C_{free}\left(mean\right) = \frac{Flux^{*}h}{D^{*}2} \quad Flux = J = -D^{*}\frac{dC}{dx}$$

Where

D is the diffusion coefficient of the drug in the medium.

C is the drug concentration.

h is a distance (thickness of the diffusion membrane).

These equations can be graphically represented as follows (Fig. 8.1):

Equation 6 in Chap. 5, shows that, flux and skin concentration are linked and proportional. In order to lose this proportionality, as h cannot be modified, the only way is to modify the diffusion coefficient of the diffusing molecule.

To decrease the diffusion coefficient (which would then increase local concentration for the same flux) the foreseeable way is to get the tissue looking more like a solid. Bringing either new proteins or polymers in these viable tissues are the most probable options to achieve a more solid state membrane (because of the biological nature of viable epidermis and dermis, and because of the nature of the excipients used in topical formulations).

The large size of proteins or polymers suggests, however, that a flux larger than 1 ng/cm^2/h. cannot be reached for such permeants (use of the Potts and Guy equation [10] = Eq. 8.1).

$$\log kp\left(\mathrm{cm/h}\right) = -2.72 + 0.71\log Koct - 0.0061\mathrm{MW}$$

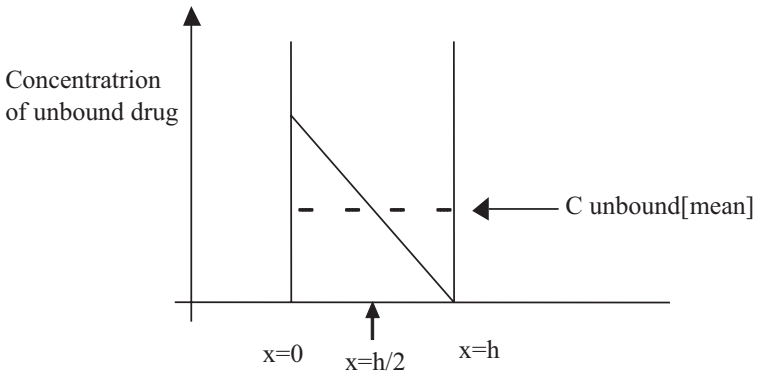

Fig. 8.1 Graphical representation of Eqs. 5.5 and 5.6 in Chap. 5

Equation 8.1 Potts and Guy Equation to Predict Drug Permeability Through Skin

To calculate the flux of the permeant, the permeability value (kp) has to be multiplied by the saturated solubility of the permeant (S) in water.

$$Flux\left(\mathrm{ng/cm^2/h}\right) = kp\left(\mathrm{cm/h}\right)^{*} S\left(\mathrm{ng/cm^3}\right)$$

Equation 8.2 Flux vs. Permeability Coefficient vs. Water Saturated Solubility

Concentration of polymer or protein in the dermis are then expected to be less than 0.0000005% (use of Eq. 5.6 in Chap. 5 with: Thickness ~400 μm (top part only of dermis being considered) and using a Diffusion Coefficient in the Dermis of 10^{-6} cm^2/s) and more likely inferior to 0.00005% (if using a Diffusion Coefficient in the dermis of 10^{-8} cm^2/s as these are extremely large molecules—Diffusion coefficient of proteins in water are 10 to 50-fold lower than for small solutes [11]).

The same approach can be used for the viable epidermis. If one assumes that the viable epidermis diffusion coefficient is about tenfold inferior to the dermis one: = > Concentration of polymer or protein in the viable epidermis are then expected to be less than 0.002% (thickness ~150 μm—using a Diffusion Coefficient in the viable epidermis of 10^{-9} cm^2/s).

At such low concentrations (0.002%) it seems unlikely that a polymer/protein would have a substantial effect on the diffusion coefficient of a drug in the viable epidermis or dermis.

The same conclusion is not made for the stratum corneum, as it is known that some excipients do affect the diffusion coefficient of molecules into that membrane (thanks to much higher concentration achievable in the stratum corneum). It is to note that known examples of excipients affecting the stratum corneum diffusion only demonstrate an increase of diffusion not a decrease in diffusion.

The above discussion can be transcripted schematically in Fig. 8.2.

Overall this demonstration suggests that theoretically compound retention in the skin viable tissue due to the vehicle cannot be supported. Therefore, claims of potential skin retention thanks to the use of some special formulations should be investigated with high caution.

8.4 For Each Compound, A Specific Formulation: A Must?

Formulations for oral, inhaled, ocular or parenteral administration use a limited number of excipients and are quite standard and simple and tend to use “off the shelf” formulations. Topical formulations have generally a larger number of excipients and will be quite different in aspect from one to another.

People tend to defend the idea that there is a need to develop one specific formulation for every compound as opposed to a universal “off the shelf” formulation. The need

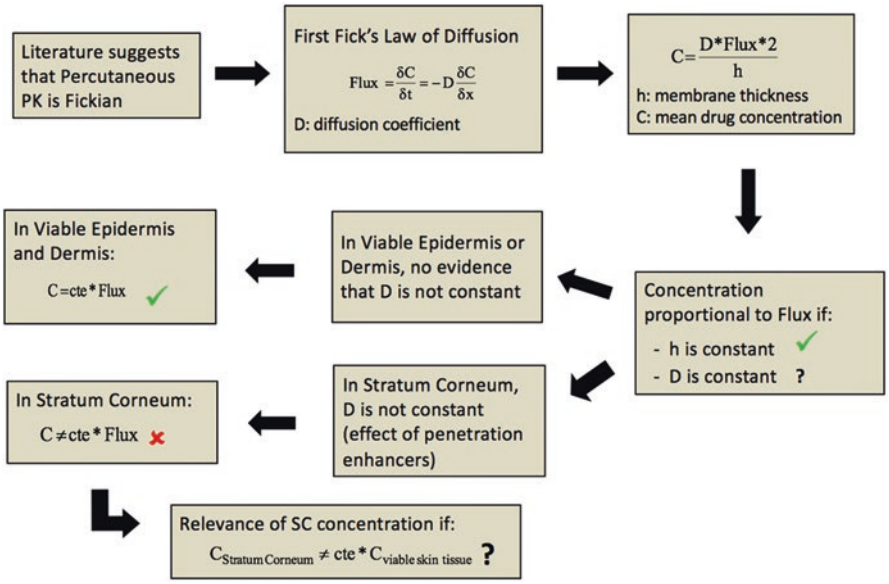

Fig. 8.2 Assessment of the change in drug retention in skin

to maximise drug delivery pushes the screening of various solvents to increase solubility of the compound. Formulation composition will be driven to some extent by the results from the solvent screen. Following that, compatibility (stability) of the compound with the potential best solvents will be required solvent by solvent. Then the physical and chemical stability of prototype formulations will be performed. An in vitro skin penetration study or/and an in vivo/in vitro pharmacology study will be done too. In parallel or sequentially, an irritation study will be conducted preclinically. This will lead to choice of the final formulation (Fig. 8.3).

This suggests that for every compound, one should develop a specific formulation. That may be true. On the other end one could argue that, say for a cream, the cream is an emulsion consisting of a surfactant, an oil phase and an aqueous phase where the drug molecule is dissolved. One could then envisage a standard cream with a given oil phase (e.g., paraffin wax and liquid paraffin), a given surfactant system (non ionic surfactant system) and an aqueous phase containing water with some solvent and a pH adapted for the stability and solubility for the drug candidate. Most marketed topical corticoid creams have such a simple approach, where the solvent added to water is propylene glycol.

Using a standard unique simple cream formulation at a screening stage when selecting the candidate compound among a set of compounds maybe an option for the project team. This removes the need to perform formulation development stage to evaluate the compound. As well, as it is a real formulation and with a large number of exemplified marketed case, it should give a fair evaluation for the skin delivery potential of the test compound.

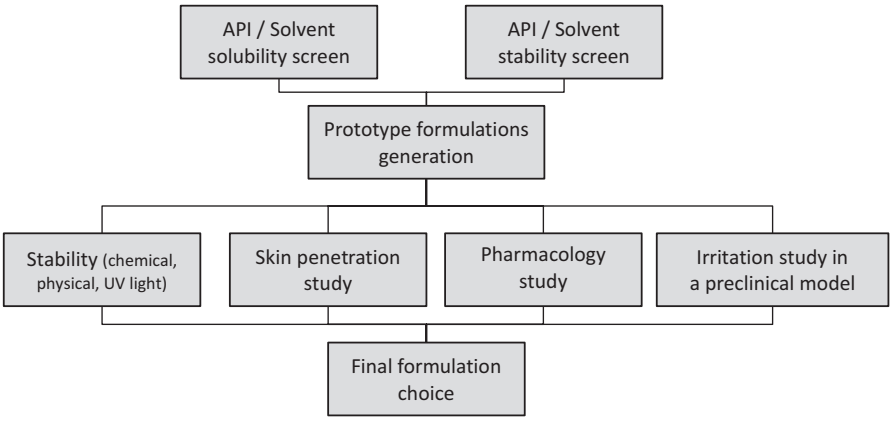

Fig. 8.3 Example of topical formulation development cascade. *API* active pharmaceutical ingredient (the drug or drug candidate)

Studying early for each compound the best formulation is another option, but this could be resource consuming, and as a consequence, could limit the number of compounds tested before the candidate is selected.

A third alternative to studying (1) only a single formulation or (2) lots of potential formulations could consist in examining a few predefined and well established residual phases (i.e., remaining formulation after evaporation) to compare the candidate molecules.

Prior to the selection of the candidate (or to the selection of a small set of potential candidates), the right balance should be chosen in between a formulation effort and the other assays required to select the candidate, especially as post candidate selection a formulation effort will occur to define the final formulation.

8.5 Vehicle Aesthetics

While looking for improved drug delivery in order to improve efficacy, the derived vehicles from such enhancement programs often offer poor aesthetics properties. Aesthetics properties of a topical drives compliance and, therefore, efficacy.

A good example of this phenomenon can be seen below with the comparison of long term use of fluticasone propionate cream vs. ointment [12]. In the vasoconstrictor assay [13], the ointment is considered more potent than the cream, so one would expect that its efficacy should be superior. It is likely true on a short term basis if compliance follows but real life experience after long term treatment suggests compliance, likely due to the vehicle aesthetics of the ointment, is altering its efficacy. In the end after long term use, the cream, despite a lower potency but better aesthetics than the ointment, delivers higher efficacy than the ointment [12] as showed in Table 8.1.

Table 8.1 Effect of twice weekly fluticasone propionate cream or ointment vs its placebo on relapse in atopic dermatitis patients over 16 weeks

	Group using cream		Group using ointment	
	Daily emolient + twice weekly fluticasone propionate ($n = 70$)	Daily emolient + twice weekly base (placebo) ($n = 84$)	Daily emolient + twice weekly fluticasone propionate ($n = 68$)	Daily emolient + twice weekly base (placebo) ($n = 73$)
% of patients having a relapse	19	64	40	56
Probability of a relapse occurring at any time point in the study, on placebo vs fluticasone treatment	5.8		1.9	

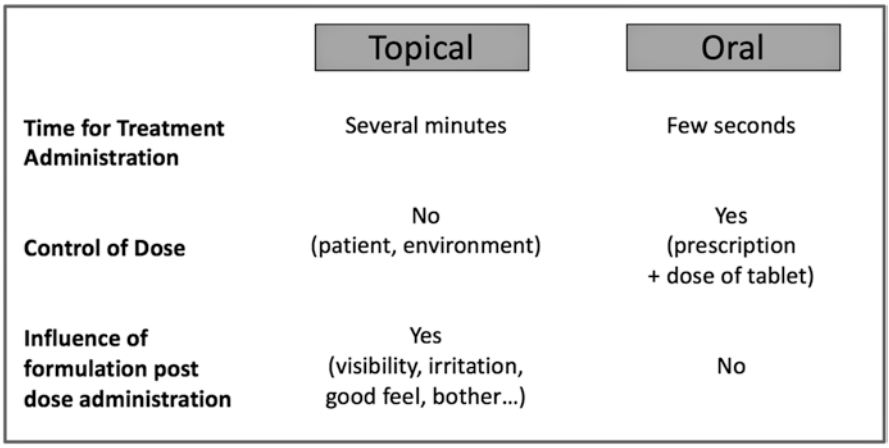

Fig. 8.4 Comparison of oral vs topical drug administration for the patients

Mugglestone et al. [14] generalise these findings when explaining that the occlusive properties of ointments should theoretically translate into more effective delivery of the active to the skin [15]. But at the same time, they note that patients find ointments greasy to use and creams are more popular with patients in the management of skin conditions such as psoriasis and eczema [16, 17]. Other authors [18–20] come to the same conclusion, especially with the good case of clobetasol propionate and its large variety of vehicles which revealed that ointments had comparable, rather than superior efficacy.

Patient compliance is a known problem for any medication whatever the route of administration. Extent of the compliance issue with topicals is, however, likely superior than for an oral medication.

As can be seen in Fig. 8.4, three elements make the use of topicals more cumbersome.

Table 8.2 Thickness of sunscreen applied under normal practice to the face and forearm measured in 23 subjects

	Thickness of sun screen applied (mg/cm^2)	
	Face	Forearm
Individual maximum	1.75	1.74
Population average	1.17	1.22
Individual minimum	0.27	0.42

Time for treatment administration is probably a big element pushing for poor compliance with topicals. Applying a topical medication, especially on large body surface area, will take substantial time. The patient will often need to remove his clothes to treat the area of interest, apply its medication and then wait that it dries, at least to some extent, before he can put his clothes back on.

Another element will be the lack of dose control with a topical. As can be seen with sunscreen in Table 8.2 the applied formulation thickness can vary substantially from subject to subject [21].

The higher the thickness, the higher the delivery [6] and higher the efficacy [21]. From patient to patient this will therefore create some difference in efficacy while this is not the case with an oral medicine. However at the same time, the more formulation is applied the longer it will take time to dry so compliance could be more problematic.

Finally after swallowing a pill not much effect for the patient can be noticed. For a topical, it is different as the medication can be visible, irritant, bothering or on the contrary soothing. A topical formulation aesthetics, like its greasiness or dryness could be viewed positively by patients for a skin disease while it will be perceived negatively for others. For example atopic dermatitis patients becaused of the dryness of their skin condition will favor rich and somewhat greasy medications while acne patients, who tend to have a greasy skin, will prefer light and non greasy topical formulations.

Overall the vehicle used in topicals plays a noticeable role in the compliance and efficacy of a topical medication and this should not be underestimated when designing a new topical medication.

Interestingly there is good evidence that the vehicle problem on compliance could become an advantage if looked after carefully. The cosmetic industry has demonstrated how to turn the quality of a formulation and its good sensory perception as a key selling proposition. The pharmaceutical industry has to a large extent failed on that. The likely reason is that the objective of the pharmaceutical industry is different to the cosmetic industry one as can be seen in Fig. 8.5.

The risk for a topical medicine is on the drug and the pharmaceutical industry most often does not want to take risk on the formulation vehicle if it means delivering less the active drug in it. The result is a focus on the delivery of the active moiety at the cost of poor aesthetics. The cosmetic industry largely drives the development of its product by putting the customer first and by having strong sensory requirements in the target product profile. The use of sensory panels and of customer testing is the rule in the cosmetic industry. It is largely absent for the development of a topical medicine.

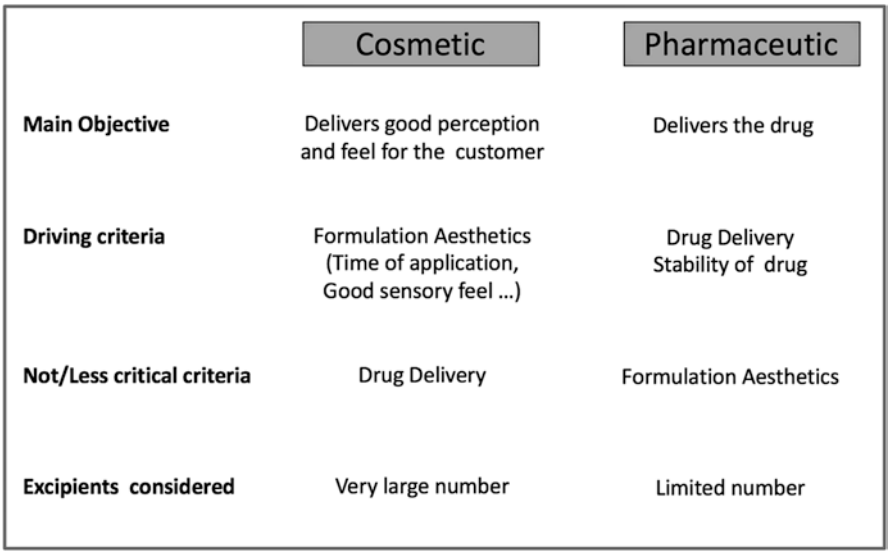

Fig. 8.5 Comparison of cosmetic and pharmaceutic topical formulation vehicles

In order to convince the pharmaceutical industry that efficacy and aesthetics are not incompatible, it is interesting to look at the development of corticosteroids and sunscreens.

For corticosteroids there is a vast choice and numbers of corticosteroids formulation formats: ointment, cream, lotion, gel, spray, foam and shampoo. What is particular about corticosteroids is that some of them are extremely potent, and it is among the most potent one such as clobetasol propionate that one finds the highest choice of formats. Less common and lighter format (e.g. lotion, gel, spray, foam, shampoo) may be inferior delivery vehicles but may offer more appropriate aesthetic properties. What is suggested here is that if a potent drug is able to engage fully its target in skin with a suboptimised delivery system, then it is possible to combine both good efficacy and good aesthetics which will deliver high compliance. Reviews of clobetasol propionate newer formulations suggest good efficacy from such vehicles [18, 20]. The key to that success is to have a powerfull drug. Hence the need to carefully select the topical drug candidate if one once to offer good aesthetic properties in the end product.

The development of sunscreens in the cosmetic industry is of particular interest too. In the early days of the sunscreens, the efficacy was not quite there nor was the aesthetic quality. However with the development of more effective chemical filters, the cosmetic industry has achieved exceptional aesthetic properties for their products: short application time, ease of application, short time to dryness, good feel after application. This is especially remarkable as full body surface area has to be treated and the children population is a key customer section too. The industry managed that success thanks to dedicated research initiative in the aesthetics properties of their formulations.

Such a success however would have been difficult without the use of effective chemical filters covering the full UVB + UVA2 spectrum. The use of such filters is now common as suggested by Diffey et al. [22] who, already in 2000, had showed that from the evaluation of 59 commercial products, 93% had a critical wavelength value greater than 340 nm—i.e., full cover of UVB + UVA2 and part cover of UVA1.

8.6 Drug Formulated as a Dispersion or as a Solution?

Historically, the pharmaceutical industry has been developing topical formulations with the drug in suspension (i.e., dispersion type formulation) (often with a large proportion in suspension). With a suspension, the active moiety is at saturation therefore in the best thermodynamic conditions to be delivered. Another advantage of suspensions is that a suspension offers increased shelf life as the part in suspension is protected from the potential degradation that can occur in solution.

However, nowadays, because of regulatory requirements to qualify more carefully dispersion type formulations by studying the part of the drug present in suspension (specifications + evolution during stability, in particular for: the particule size and the polymorphic form), formulators are trying their best to develop formulations with the drug in solution only, and avoid dispersion type formulations. Unfortunately this is done at the expense of some drug delivery.

The question dispersion versus solution should therefore be raised when developing the formulation and pros and cons considered.

8.7 Conclusion

Focusing on the vehicle is an important consideration for a dermal medicine as the aesthetic properties of the vehicle will help or not the patient to apply its medication. Without good compliance, a promising medicine will deliver less efficacy as the medicine will not be applied regularly leading to large period of “drug holiday” (without target engagement).

Unfortunately, too often the project team selects the vehicle for its delivery properties at the expenses of its aesthetic properties. This happens as there is always some doubts that not enough drug will be delivered to the target site and therefore, the program team may choose to limit this risk. Unfortunately the gain on the extra delivery are often small compared to the loss on the aesthetics side.

If, in the first place, a good candidate had been selected (high potency versus its permeation capacity) a good aesthetic vehicle could have been chosen. It is likely that a topical drug development project will be more successful if more time is spent on the selection of the drug candidate than on the penetration enhancement of the vehicle carrying the drug candidate.

Recently, when launching its Mirvaso gel for rosacea, Galderma may have followed that strategy when selecting and developing brimonidine as this small molecule (MW = 292) is extremely potent (EC50 = 0.45 nM [23]) and the gel vehicle appears to be light with good aesthetics properties for a facial application.

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Chapter 9
Dermal Drug Development Strategies

As seen in Chap. 1, the pharma industry nowadays works on more therapeutic targets than it used to do thanks to the advances in the understanding of the molecular basis of diseases as well as the push from payors to deliver better medicines compared to standard of care. This presents a strong opportunity for pharma companies who want to invest into dermal drug development projects as more assets and more therapeutic targets are becoming available.

Various approaches can be taken to develop a new topical drug. Some will be opportunistics with limited resources and efforts while other will involve full drug discovery program. Overall the approaches can be separated into four categories.

9.1 Option#1: Clinical Molecule Repurposing—Developed Drug for a Non Systemic Indication on a New Target Class

This first option is probably the most tested and tempting strategy for the Pharma industry. The mindset will often be the following one: "We have this good clinical drug molecule, there is a good rationale for the pharmacology for that skin disease, the target site is just there on our skin, we have plenty of this compound synthesised and a good toxicological package, let's put the molecule into a cream and get it tested in the clinic… That should work".

Drug repurposing is indeed becoming more and more popular within the industry and this is well described by the surge of published papers on that subject (Fig. 9.1).

Several factor accounts for that:

- Number of new targets explored in lead optimization programs has increased substantially,

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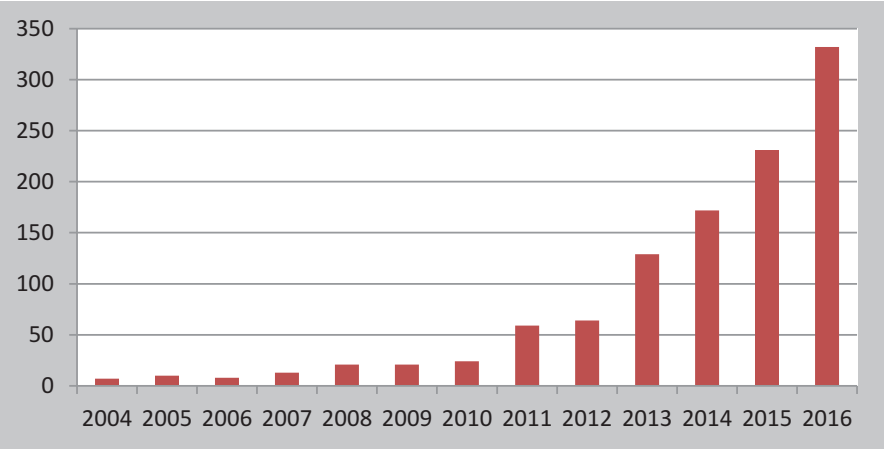

Fig. 9.1 Number of published papers about drug repurposing (published papers containing either 'drug repositioning,' 'drug repurposing,' 'drug reprofiling,' 'drug redirecting' or 'drug rediscovery' in title or abstract. Searched via PubMed)

- Advances in the understanding of the molecular basis of diseases coupled with the progress in chemoinformatics, and
- The pharma industry tries to maximise the value of their successful assets as well as of their failed assets.

In the dermatological field, as seen before, many of first in class drug were repurposed molecules from another indication. This is still true today as in 2013, the FDA approved topical brimonidine (Mirvaso), an old alpha2 adrenergic agonist first described in 1981 [1], for facial erythema or rosacea.

This can be the cheapest and most effective approach as the lead optimization effort has been done and the right molecule maybe available. The difficulty of this approach is to make sure the right criteria are used to select the molecule and accept No Go decision early if the criteria cannot be met.

Pros

- Low cost.
- Large amount of available new mechanism of action.

Cons

- Need to have good molecules.
- Accept No Go decision if criteria are not met.
- Intellectual Property can be problematic (old drug or NCE with short patent life).

9.2 Option#2: Full Lead Optimization—New Drug from a New Mechanism of Action for a Topical Application

This approach will likely have a high chance of success as it is a complete process. It will allow to apply and select the compounds using criteria for a topical candidate and not for a systemic one. However this is a costly and long one as a full lead optimization drug discovery program has to be applied. This will involve in particular a substantial medicinal chemistry effort.

Pros

- Total freedom to progress the desired chemistry.

Cons

- Cost and time.
- Risk on pharmacology.

An option could be to start from a known lead optimization program and make new molecules (this can shorten lead optimization effort and will reduce the cost).

9.3 Option#3: "Me Better"—Improved Drug for a Known Topical Target Class

Development of the corticosteroids and immunosuppresors class are good examples of such an approach.

It can come from knowledge base chemistry effort where a template exists and the medicinal chemistry effort can start from there. This would reduce cost and time.

Need to define what needs to be improved

- Short term efficacy (flux vs potency).
- Avoidance of drug holiday (Need to consider: (1) Stratum Corneum crossing time or/and (2) covalent approaches to benefit from small k_{off} of the drug candidate from its target).
- Aesthetics (improved drug to allow the use a less performing vehicle but with improved aesthetics properties).

Note: Combinations are not considered here, as it does not relate to a new drug candidate but combination of two drug candidates. It should be said though that this can be a successful development strategy for maintaining patent life on a topical asset (e.g., Dovobet (calcipotriol + betamethasone dipropionate)). A strategy to bring an NCE in combination with an old drug can be considered but clinical development as well as the toxicology package will likely be challenging.

Pros

- Chemistry template starting point exists (though the SAR may not be available).
- Pharmacology is proven.

Cons

- Still a drug discovery (lead optimization effort) = > cost and time though likely lower than Option#2.

9.4 Option#4: Chemical Series Repurposing—Advanced Lead Optimized Chemicals Series Screened Against for a Topical Indication

A potential alternative to these three strategies is to go open minded about not a single clinical asset but about the full chemical series that has been developed during a lead optimization program that may have lead to a clinical asset. This approach requires some screening and ranking to make sure the best molecule is selected but it does not require new chemical synthesis. The cost of such an approach is therefore much reduced and the chance of success to get a successful drug candidate is increased compared to pushing a single molecule. In order to embark on such a strategy the right selection cascade has to be in place.

Pros

- Reasonably low cost.
- Large amount of available new mechanism of action.
- Plenty of molecules to choose from for each mechanism of action.

Cons

- Need to have good molecules in the chemical series considered.
- Accept No Go decision if criteria are not met.
- Intellectual Property may be problematic (but less so than in Option#1).

In summary, the overall strategies can be summarized in Table 9.1.

Table 9.1 Pros and Cons of the different topical drug development strategies

	Cost and time	Intellectual property	Chance of success
Option#1: Clinical molecule repurposing	+++	+ (if old molecule)	+
Option#2: Full lead optimization	+	+++	++
Option#3: “Me better”	+	+++	++
Option#4: Chemical series repurposing	++	++	++

All options have their pros and cons. It very much depends on the position or strategy of the project team or Pharma sponsor of such an effort. On balance, Option#4 which has not been so commonly used by the Pharma Industry may offer a good overall return on investment and may fit well the current R&D Pharma environment where many chemical series assets may be available.

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Chapter 10
Topical Drug Candidate Selection Criteria and Cascade

10.1 General Principles: Discharging Risk

A key objective of the drug discovery project team is to discharge as much risk as possible for the selected candidate such that the best possible molecule can be progressed.

Protection against making the wrong selection is to do more experiments. If one takes all possible development paths in parallel, there will be a better protection against making the wrong selection but at the cost of generating many bits of data that were neither essential nor actionable, at least at the stage in the development process when they were acquired.

In a paper entitled "What is the most important approach in current drug discovery: doing the right things or doing things right?," Elebring et al. [1] state that effectiveness in drug discovery is far more important than efficiency. In their argumentation they refer to the following quote, 'There is nothing more wasteful than becoming highly efficient at doing the wrong thing' which in a drug discovery setting could translate into: 'There is nothing more wasteful than efficiently producing failing drug candidates'.

The key is therefore to choose the right studies/assays and sequential cascade of such assays to progress the chemical series in order to select the best possible molecule. This will save time, use resources optimally and help to take the right decisions throughout.

This is particularly challenging for the discovery effort of a topical drug candidate as knowledge and know-how is much less well established than for an oral drug candidate. Furthermore, risks are quite different compared to the risks taken for the development of an oral drug. Some risks are shared for both topical and oral while some are present in one and absent in the other.

In the following sections various elements and properties will be discussed.

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10.2 Medicinal Chemistry and Chemical Space

For a medicinal chemist, having parameters to follow in order to increase chance of success of a lead optimization program is always helpful. For oral drug development, often the parameters considered include MW and cLogP like in the Lipinsky rule of 5 [2].

When considering the topical dermatology pharmacopoeia of drug acting in the epidermis or dermis (anaesthetics, corticosteroids, retinoids, vitaminD3 derivatives and immunosuppressors), a large chemical space is covered as showed in Fig. 10.1 using cLogP and MW.

Considering solubility, does not look clearer either as retinoids and vitamin D3 derivatives have a solubility in water inferior to 1 μg/mL

Using empirical equations for skin delivery (i.e., to calculate the percutaneous flux) which often rely on LogP, MW and solubility [3] does not help to understand further the chemical space as the calculated flux vary enormously from compound to compound.

A likely reason for the lack of chemical space from a phys-chem point of view is that the intrinsic potency of compounds will influence dramatically the amount of drug to deliver.

Topical Drug Delivery: **Substantial differences cross target drug classes** (from Table 6.1 in Chap. 6)

Dovanex® (vitamin D3 derivative) Flux ~ 40pg/cm²/hr	→ x 1,000,000	EMLA® (anaesthetics) Flux ~ 50μg/cm²/hr

In vitro Drug Potency: Substantial differences cross target drug classes (from Table 6.1 in Chap. 6)

Dovanex® (vitamin D3 derivative) In vitro potency ~ 100pM	→ x 1,000,000	EMLA® (anaesthetics) In vitro potency ~ 140μM

Overall, contrary to oral drug development, a chemical space with some specific Phys-Chem parameters to consider does not exist. Potency plays such a critical balance in the PharmacoDynamic outcome that a compound with poor phys-chem properties but which is extremely potent, has the potential to become a topical drug (e.g., retinoids, vitamin D3 derivatives).

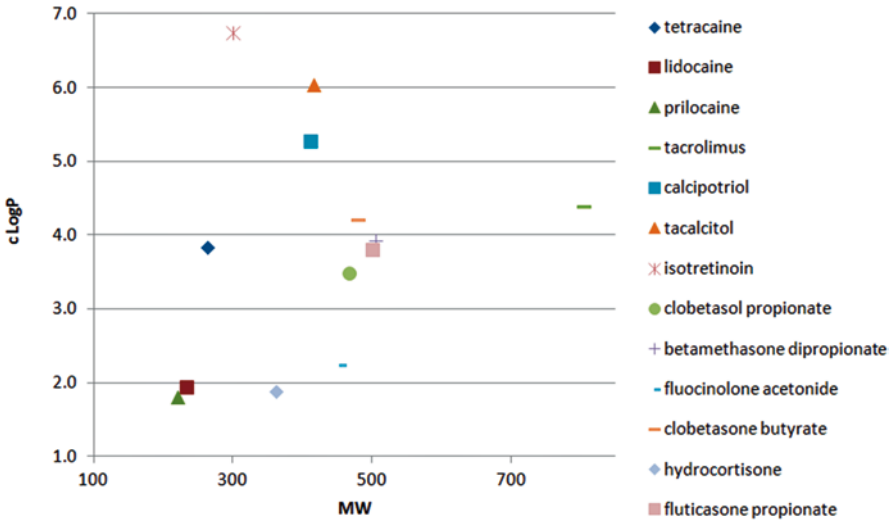

Fig. 10.1 Chemical space of some marketed topical drugs

10.3 Potency

As illustrated in the previous section, to compensate for a low skin delivery potential, potency can play a major role. As for any lead optimization program where medicinal chemists will optimize their chemical series on potency, the same will be true for a topical drug lead optimization effort.

However one should always keep an eye to the skin delivery potential of the compound. A not so potent molecule with excellent skin delivery properties could become a topical drug (as showed with anaesthetics in Table 6.1 in Chap. 6).

Using Eq. 5.9 in Chap. 5, one could obtain some guiding figures for the percutaneous flux to obtain for a given in vitro potency. For example to get 50% target engagement, the percutaneous Flux (ng/cm^2/h) would need to be equal to the IC50 (ng/mL) as showed in Table 10.1.

Optimizing on potency should therefore be a driving objective for the medicinal chemistry team. However potency optimization should not be done at all cost. It should not be done at the cost of skin drug delivery. Unfortunately, it is well known, that most often lead optimization programs generally end up with potent compounds because they have been made more greasy. The reason is a too strong emphasis on potency during lead optimization as well as hit selection. Potency gain is done at the detriment of phys-chem properties which impact pharmacokinetic properties such as absorption for an oral drug.

A trend however is emerging nowadays in medicinal chemistry efforts to keep good phys-chem properties. A good guiding tool that is being used more and more during a lead optimization effort is the Ligand Efficiency (LE) [4].

Table 10.1 Guiding flux requirement vs IC50 for topical target engagement

IC50 (ng/mL)	Required percutaneous flux (ng/cm²/h)
0.1	0.1
1	1
10	10
100	100
1000	1000
10,000	10,000

$$LE = 1.4 \frac{-\log IC_{50}}{N} \quad (10.1)$$

Where N = Number of non hydrogen atoms

Using LE during Lead Optimization will help the medicinal chemist effort to be focus not only on potency but on gain in potency not achieved through a larger molecule. The consequence should be increased potency without (or with limited) physicochemical properties loss.

Such a consideration of gaining potency without physicochemical loss is likely even more important with topicals than for orals as skin permeation is more dependant on physicochemistry than intestinal permeation due to the severe impermeability of the skin membrane.

Fragment based lead optimization which emerged more recently is becoming more popular in the strategies used in drug discovery [5–7]. It consists in starting optimization from small molecules (fragment) poorly potent and using crystalography to understand the binding of these molecules to focus on the key spots of the molecule that could lead to some good binding to the target. Starting with small molecules and focusing on LE helps to achieve candidate with good phys-chem properties.

Percutaneous flux being so dependant on the size of the molecule, one could expect that fragments in the early phase of a lead optimization program could have the right properties to be candidate topical molecules. Indeed a fragment can have high flux (>1 μg/cm²/h) and a potency of 1 μM, which would not be sufficient most often for an oral drug, could be sufficient for a topical as suggested by Table 10.1. Fragment based drug design for a topical program may therefore be an interesting strategy for a lead optimization program for a topical medicine.

10.4 Percutaneous Flux

Percutaneous studies aiming at determining the percutaneous flux is not an assay that would be generated during a systemic lead optimization program. Still, as largely described in Chaps. 5 and 6, the percutaneous flux is a critical data to have as this is likely the most valuable pharmacokinetic information one can have following the topical application of the test compound. As previously seen, the combined use of the compound potency and its percutaneous flux (Chap. 6 and in particular

the Fig. 6.2 in Chap. 6) could help to make prediction of the likeliness of target engagement and therefore should help the project team to decide whether the compound is worth progressing or not.

Because of some difficulties in performing in vitro percutaneous flux studies, it may be then tempting to consider the use of Reconstituted Human Epidermis instead of human skin as the membrane for the percutaneous study. Indeed this membrane is more easily obtainable, and running such studies is more affordable as they could potentially be set up internally rather than going externally in a Contract Research Organisation. However, this is to be avoided as such membranes are more permeable than human skin (overprediction of target engagement) (Table 10.2). Such an assay can sometimes be helpful for ranking of compounds (and formulations) but that has some strong limitations as the fold change in permeability vs. human skin from one compound to another may vary substantially (Table 10.2).

An alternative to performing in vitro percutaneous study in order to obtain topical pharmacokinetic information can be the use of in silico equations [3, 9, 10]. Such empirical equations can be helpful to predict early and quickly what would be bad candidate molecules. Indeed using these empirical equations would allow to get early a predicted ratio of percutaneous flux over in vitro potency (Fig. 6.2 in Chap. 6). A low value for this ratio (e.g., <0.01) would suggest that the chance of success for this molecule to engage its target following topical application is low and the considered molecule should not be progressed further. On the contrary, compounds showing a ratio closed or superior to one could be considered as interesting compounds worth progressing further.

This being said, one should be carefull not to put too much weight on such predicted flux as often the predicted flux are overestimated with these empirical equations. Indeed the datasets used [11, 12] to generate these equations are not that representative of molecules synthesised in today's lead optimization efforts. Since the mid 90's, molecules generated in drug discovery effort have on average, higher molecular weight, higher lipophilicity and have more functional groups than the one used in these datasets. It has been noticed since then that the in silico equations predicting flux from these data sets do not account so well for these changes of properties. The consequence is an overestimation of the potential for a molecule to be a good topical candidate. It would then be strongly advisable for a program team, after having assessed in silico the potential flux of their compounds, to run a real in vitro percutaneous study to know the true potential of their asset molecules.

Table 10.2 Comparison of the percutaneous flux of four drugs through reconstituted human epidermis, rat skin, minipig skin and human skin in vitro [8]

	Percutaneous flux (μg/cm²/h)[a]			
	Human reconstituted epidermis	Rat skin	Minipig skin	Human skin
Terbinafine	0.37	0.55	0.011	<0.01
Clotrimazole	18.8	0.055	0.02	0.02
Hydrocortisone	5.29	1.16	0.010	0.023
Salicylic acid	152.8	24.2	9.6	21.9

[a]Applied as 1% solution in propylene glycol

Obtaining a percutaneous flux data is not so easily done as this would most often be done externally in a Contract Research Organisation, with its associated cost and potential delays. As well, depending on the way such studies are run, they could use substantial quantity of the tested compound which may not be available. Therefore, finding a good way to perform such studies needs to be considered carefully.

The following points could be considered when performing an in vitro percutaneous study:

- Need to be close to the clinical condition to obtain a flux close to a real use.
  - Consider the use of human or pig skin versus other membranes (rodent skin, reconstituted human epidermis, synthetic membranes…) as such other membranes do not share the same permeability properties as human skin (they tend to be more permeable) (Table 2.2 in Chap. 2 and Table 10.2 in this Chapter).
  - Consider the use of a receiving media that is solvent free (in order to avoid penetration enhancement effect due to partitionning and migration of the solvent into the stratum corneum).
  - Consider the use of pharmaceutical like vehicle (not high containing solvent mix) in order to avoid unrealistic penetration enhancement effect due to the solvent on the stratum corneum or due to very high solubility in such a vehicle compared to what would be obtained in a more classic pharmaceutical vehicle.
  - Consider the use of finite dose volume of formulation: <10 mg/cm^2 (ideally close to 2 mg/cm^2) [13].
- Need to be cost effective.
  - Consider generating the saturated solubility of the test compound in the vehicle to know the level of saturation of the compound in the study AND to limit the concentration of the test compound in the vehicle. It is expected that a compound above saturation in its vehicle (i.e., part of the dose in suspension) will not deliver more than if at saturation. Therefore putting an excess of compound in suspension will not increase flux, while below saturation the flux obtained is proportional to the level of saturation.

    For example if the test formulation is an Oil/Water (33%/67%) emulsion where the test compound has no solubility in the oil phase and a saturated solubility of 1.5 mg/mL in the aqueous phase, a formulation of the test compound at 0.1% (w:w) will allow to have the compound at 100% saturation (0.67 (mL of aqueous phase in 1 mL of cream) × 1.5 (mg/mL) = 1 mg/mL). Therefore no need to consider formulating the compound at 1% w:w which would require 10 times higher quantity of compound.
  - Consider small batch of the vehicle + test compound in order to limit the amount of test compound required. To achieve that, there will be the need to adapt volume and tools to manafacture the test formulation.

For single phase vehicles such as gel, batch size inferior to 1 g are easily achievable.

For double phase vehicles such as Oil/Water emulsion (i.e., classic cream), a batch size of 5 g can be made without much difficulty.

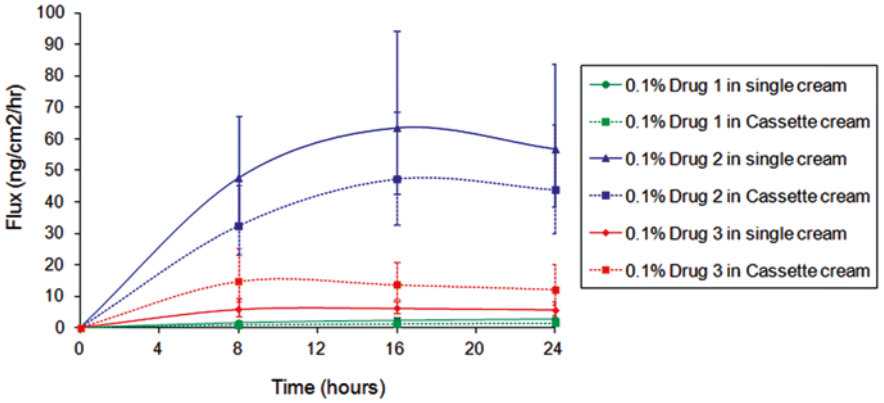

Fig. 10.2 Comparison of percutaneous flux of three drugs added in a cream with cassette dosing vs single dosing [14]

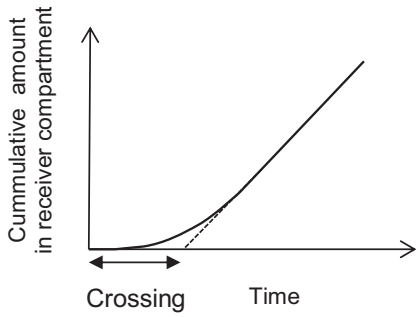

Fig. 10.3 Determination of crossing time in an in vitro percutaneous study

In the example above for a cream where a batch of 5 g is made and where 0.1% w:w allows to be at saturation in this cream, only 5 mg of the test compound would be required to manufacture the vehicle to perform the percutaneous study.

– Consider using the test compounds in cassette dosing. As percutaneous permeation is a passive transport mechanism, it is not expected that cassette dosing would cause a difference in skin permeation of each tested compounds. Therefore testing compounds in cassette dosing should lead to similar flux dosed either as cassette or individually as described in Fig. 10.2. This would allow to testing more compounds for the same cost as the same number of franz diffusion cells would be used.

It is noteworthy as well that from a percutaneous study, the skin crossing time can be obtained (Fig. 10.3).

As showed earlier in Fig. 6.6 in Chap. 6, such a data, that could be associated with the half-life of a compound for a systemic application, would be helpful too to

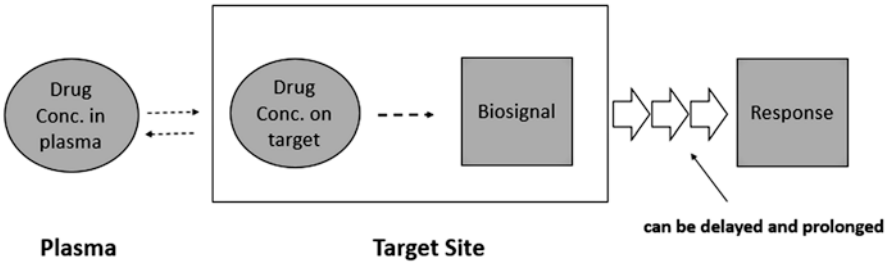

Fig. 10.4 Basic components of pharmacodynamic models of drug action

predict the dose regimen. Crossing time could, therefore, be another parameter the program team could draw from a percutaneous study and help the team to rank compounds further.

10.5 Pharmacological Kinetics Response

Duration of action, because of the potential short skin crossing time, can decrease substantially the effectiveness of a topical compound. Understanding the kinetic of the pharmacological response can therefore be helpful to estimate the duration of the clinical effect (to be done with the skin crossing time). In Fig. 6.6 in Chap. 6, the mathematical model to predict the PD assumes a direct effect but this depends (1) on the pharmacology of the target and (2) on the type of binding interaction of the molecule with its target.

The response to the presence of the tested compound on its targte site can be somewhat delayed and various models can account for that as described by Mager et al. [15] and summarised schematically on Fig. 10.4. Therefore the duration of the pharmacological response could sometime be prolonged despite the absence of compound on its target. The knowledge of such an information can be usefull if one wants to predict the duration of a clinical effect.

As well the nature of the binding of the test compound to its target can influence the kinetics of the response. Compounds that would slowly equilibrate with their target (as well named “tight binder” or “slowly reversible binder”) would have a longer residence time and therefore would prolong the duration of action. Even better if the compound was to behave as an “irreversible binder” the impact on the duration of action would be substantially impacted.

Knowing that, for the given target, a substantial delayed pharmacological response is expected or knowing that the test compound is a tight binder could help in the selection of the candidate molecule. It should however be mentioned that most of the time the pharmacological response is not delayed by much for most targets and that tight binders with relevant prolong duration of action are not common and designing such binders is difficult in practice.

10.6 Preclinical Proof of Concept

In Chap. 6 and in particular the Fig. 6.2 in Chap. 6, it has been seen that the combined use of the compound potency and its percutaneous flux could help to make prediction of the likeliness of target engagement and therefore could help a project team to decide whether the compound is worth progressing or not. However such an approach remains an in silico prediction and not well proven so far. The drive to generate "real data" could be high.

As seen in Chap. 2, in vivo Pharmacodynamic (PD) models exist, though such models may not be appropriate for the desired disease or target. Beyond this, as discussed in the same chapter, the rodent PD models often overestimate efficacy, therefore it would be advisable to strongly consider Pros and Cons of such models before using them to predict a likely target engagement in man. Such models could be considered more readily, to deselect uneffective compounds in such models or to rank compounds. One caution, however, is that, skin crossing time which can be short in rodent could suggest poor efficacy because of long "drug holiday" period and in this case underestimate the true potential of the tested compound (see Fig. 6.6 in Chap. 6 and consider that the same compound could have a short crossing time in rodent while a long crossing time in man). The minipig PD models could be more appropriate though access and cost to such models may be more challenging.

A potential alternative to the in vivo PD models would be the use of in vitro PD models as discussed in Chap. 6. Such models use human skin and are set up in Franz diffusion cells to control the transport of the topically applied compound. The development of such models are recent and not really described yet in the literature. They rely heavily on the access to a relevant biomaker that can be followed. Without a relevant biomarker described and accessible, developing such an assay could be quite risky, lead to delays and be expensive. If on the other end, a relevant biomarker described in the literature could be followed, such an approach should be considered by the program team.

Performing such an in vitro PD assay in diffusion cells and demonstrating proof of concept would bring high value to the developed compound as it would discharge the high risk of not engaging the target topically.

10.7 Solution Stability—Water Stability

Solution stability is not of much concern for an oral drug, but it is clearly one for a topical. The candidate compound will be totally dissolved or in part dissolved in the future topical formulation which will need to have a shelf life of 2 years.

A whole chemical series or a specific compound in a series can be unstable in water or in presence of another solvent/excipient. This is not a rare occurrence and should be addressed early not to progress/select a flawed asset or to know early that water or another solvent/excipients will not be part of the formulation.

Instability with another solvent/excipients than water can most often be managed later on as the problematic solvent/excipient can be removed or swapped with another one or with a purer one.

Water remains probably the key solvent to study as removing water from the formulation has consequences. One could say it has Cost of Goods consequences as water does not cost anything, but it is not the real reason. In a cream, gel or lotion, water will most often account for more than 50% of the formulation. It is a polar solvent that evaporates quickly. There are not that many volatile excipients available to choose from to replace water. Small chain alcohols like ethanol or propanol are an option, but the formulation may sting and such a formulation will not be usable on many skin conditions. Volatile silicones, such as cyclomethicone, are another option, but they partition in the oil phase of Oil in Water or Water in Oil system—not in the aqueous phase. Most often water will not be replaced by a volatile solvent but by a leave-on solvent which will result in poorer formulation aesthetics. As discussed in Chap. 8, poor aesthetics has important consequences on compliance and, therefore, efficacy.

In order to assess the risk of solution stability the candidate molecule can be put through a short stability study of a few weeks at elevated temperature (e.g., 40 or 50 °C) with LC-UV analysis to look for the molecule disappearance and as well for the appearance of new peaks.

Knowing the cause of the instability can be helpful. Hydrolysis vs oxydation are different problems that can be addressed or minimized by different approaches.

10.8 UV Absorption

UV absorption is a parameter looked at for oral drugs as a potential flag for the development of the candidate molecule. For a topical drug the consequences are stronger as the photo safety package is substantial and it will be impossible in most disease to take the medication while protecting the site from sunlight.

ICH guidelines—S10—Photosafety Evaluation of Pharmaceuticals [16] gives the cascade to follow for Photosafety evaluation. An interesting element is the fact that if the Molar Extinction Coefficient (MEC) is inferior to 1000 L mol^{-1} cm^{-1} for a peak or tail above 290 nm, there is no concern for phototoxicity and no more studies are requested.

Checking early for MEC above 290 nm is, therefore, an easy way to discriminate/rank compounds if a program team is in a lead optimization program or if the program team has many compounds to chose from a stopped lead optimization program that is being repurposed.

Another potential consequence of pushing a UV absorbing compound is that this compound maybe coloured, if so, cloth staining and aesthetics issues for the patient could be further problems to face.

10.9 Local Irritation

If systemic exposure is low following topical application, skin exposure is substantial, especially in the upper part of the epidermis (Fig. 7.1 in Chap. 7). Therefore observing local irritation following topical application is somewhat expected and should be known early in order to manage expectation and the risk associated with the candidate compound. An undesired local effect could be target related or unrelated and knowing this early could be helpful for the project team.

Various options can be considered to assess local irritation:

- In vitro: use of Reconstituted Human Epidermis following various biomarkers representative of irritation [17–19]. Such methods have even been shown to be superior (on specificity) to the in vivo irritation studies performed in rabbit [19].
- In vivo: Rabbits have been traditionally used as preclinical species to test the dermal irritation potential of chemical in humans. However, as rabbits tend to overpredict the irritation observed in humans [19–22], false-positive data may result in deselecting a potentially useful compound or formulation. Minipigs, morphologically and functionally similar to human skin, especially on skin absorption (Table 10.2), are increasingly replacing rabbits in such studies and have become an animal of choice for dermal safety assessments [23].

10.10 Systemic Effect (Clearance & Protein Binding)

In Chap. 7, it has been demonstrated via Eq. 7.5 in Chap. 7 that the higher the systemic clearance and higher the plasma protein binding, the lower the risk of a pharmacologically relevant systemic exposure. This is the complete reverse of the criteria that one would consider to develop a systemic candidate as in such cases one wants to maximise unbound plasma concentration. Clearance and plasma protein binding should, therefore, be considered when selecting a topical candidate. Plasma protein binding can be assessed via the in vitro rapid equilibrium device assay [24]. Clearance can be assessed either by performing in vivo PK studies in rat or/and other species and scaling the clearance observed to the one expected in man [25, 26]. Alternatively clearance can be assessed by determining the in vitro intrinsic clearance in human liver microsomes or in human hepatocytes [27].

10.11 Other Criteria Not that Important for a Topical Candidate

10.11.1 Skin Metabolism

The skin is not just a passive barrier to foreign compounds: it contains a wide range of enzymatic activities, including phase I functionalisation reactions (CYP450: oxidative, reductive, hydrolytic) and phase II conjugative reactions [28] that could

degrade a wide variety of compounds [29]. This local phenomenon can, therefore, theoretically have an effect on the pharmacological activity of a compound: reducing its activity or increasing it if the metabolite is more active than the parent molecule.

Various attempts have been made to compare skin and liver metabolism. They suggest that skin activities ranges from 0.1% to 50% of liver activities [29]. However, significant skin enzymatic activity has only been well established for esterase activity. Cutaneous esterase activity has been reported for corticosteroid esters [30], metronidazole esters [31], parabens [32], and salicylates [33]. Therefore, apart for the cases where esters would be considered as candidate, studying skin metabolisation for non-ester compounds is unlikely to bring added value to select the candidate molecule.

10.11.2 CYP 450 Inhibition/Induction and Drug Drug Interaction

As there is no significant CYP450 metabolism occuring in skin, the local skin pharmacokinetic of the topically applied compound will not be subject to the presence of CYP 450 perpetrator coadministred systemically.

As the plasma concentration of a topically applied test compound is extremely small (for the vast majority of compounds), the test compound is unlikely to be a CYP450 perpetrator for a compound coadministred systemically. Drug drug interaction via CYP450 inhibition or induction, as a victim or as a perpetrator, should therefore not be considered as a criteria to select a topical candidate.

Having said that, a P450 enzyme present in the skin could be the target of a dermally applied agent and therefore such a P450 inhibitor could have a local skin tissue pharmacological effect. This is for example the case with CYP26 inhibitors which can block retinoic acid metabolism and that could have a potential to prevent hyperkeratosis [34, 35].

10.12 Comparison of the Criteria Used to Select an Oral/Systemic Candidate and a Topical One

As seen in the previous paragraphs, parameters to select a topical candidate are somewhat different vs the one used for a sytemic/oral candidate. Table 10.3 gives a comparative summary of the criteria used.

The importance of each individual parameter is context dependant.

For example if one program team was repurposing a single molecule and it was found that this molecule was a strong UV absorber or had a strong adverse local effect or was unstable in water, a single of these criteria could potentially be a showstopper for the progression of the molecule.

Table 10.3 Criteria to consider to select a systemic/oral candidate vs a topical one

	Systemic/oral	Topical
In vitro potency (e.g., EC50)	+	+
Systemic clearance	+ (the lower)	+ (the higher)
Plasma protein	+ (the lower)	+ (the higher)
Percutaneous flux	−	+
Oral absorption	+	−
Systemic side effect	+	−
Local side effect	+ (GI tract)	+ (skin)
Aqueous stability	−	+
UV absorption	+	+
P450 inhibition/induction	+	−

In another example, if a specific part of a molecule shared by all the active molecules of a chemical series, that could not be changed, was giving a strong UV absorbance or a strong adverse local effect or unstability in water, such a criteria could become a show-stopper for the progression of the chemical series. However, when doing lead optimization, often molecules can be designed such that they would not share the same unwanted properties. Similarly if in a repurpose exercice, several chemical series are considered, it is unlikely that all chemical series will share the same unwanted properties (unless it is a local target related side effect).

As described in Chap. 6 and in particular the Fig. 6.2 in Chap. 6, potency and the percutaneous flux should be considered together as the ratio percutaneous flux/potency appears to be a predictor of topical efficacy. As such, this ratio could be an interesting guiding parameter in the selection of the candidate molecule. Importance of this ratio is, however, rarely known nor understood. For that reason, it is most often not considered. Interestingly, the equivalent criteria is used during the selection of a systemic candidate.

Indeed, when developing a systemic candidate molecule, the lead optimization will be driven by one key element: dropping the dose! Decreasing the dose helps to limit some toxicological issues, to limit the size of the tablet and some bioavailability issues (if oral administration), to limit the volume to inject and some solubility issues (if parenteral administration) and finally to limit the cost of goods to manufacture/synthesize the future medicine.

For a parenteral (systemic) administration, the required dose rate, is derived from the Clearance equation:

$$\frac{dose\ rate\ (\mu g/h)}{steady\ state\ Concentration\ plasma\ (\mu g/L)} = Clearance\ (L/h) \qquad (10.2)$$

Using the Effective concentration one can find the required dose rate to get the pharmacological effect

$$dose\ rate > Clearance^{*} Effective\ Concentration\ plasma \tag{10.3}$$

Thus

$$dose\ rate > Clearance^{*} \frac{free\ Effective\ Concentration\ plasma}{fu} \tag{10.4}$$

Where fu is the fraction unbound in plasma.
Assuming the free Effective Concentration is the EC50

$$dose\ rate > Clearance^{*} \frac{EC50}{fu} \tag{10.5}$$

And finally

$$\frac{dose\ rate\left(\mu g/h\right)}{EC50\left(\mu g/L\right)} > \frac{Clearance\left(L/h\right)}{fu} \tag{10.6}$$

Interestingly, percutaneous flux is a dose rate (per surface area). There is, therefore, a strong analogy in between parenteral and topical candidate with regards to predicting efficacy. They both need to meet the criteria where dose rate/potency is superior to a value to reach efficacy.

Parenteral candidate	**Topical candidate**
$\frac{dose\ rate\left(\mu g/h\right)}{EC50\left(\mu g/L\right)} > \frac{Clearance\left(L/h\right)}{fu}$	$\frac{flux\left(ng/cm^2/h\right)}{EC50\left(\mu g/L\right)} > 1\ \left(mL/cm^2/h\right)$
Eq. 10.6	Eq. (6.1) in Chap. 6

A note of caution though as, if Eq. 10.6 is derived from sound validated equations, Eq. 6.1 in Chap. 6 though derived from equations, there are several hypothesis behind it.

10.13 Example of Candidate Selection Cascade When Repurposing a Whole Chemical Series

In Chap. 9, four topical development strategies have been discussed. The last one, Chemical Series Repurposing maybe promising from a return on investment point of view for a pharmaceutical company; it requires a low investiment versus an

interesting likelyhood to select a good candidate molecule. The investment cost and the quality of the candidate molecule depends however highly on the way the selection is run.

The example below proposes a two steps approach to move rapidly with a low cost to a decision to select or not a topical candidate.

Step 1: In silico *selection of a small set of molecules*

- **Scope:** Look at all compounds synthesized for the target
- **Approach:**
  - Compounds efficiency: consider the ratio of skin permeability (percutaneous flux) vs in vitro potency. Potency data exists and skin permeability is predicted with in silico equations [3, 9, 10]
  - Minimizing exposure: consider ratio of clearance to plasma protein binding (when such data exists)
  - Solution stability: interrogate lead chemist, in charge of the lead optimization program of the target of interest, on potential observed major instability of the various chemical series
- **Deliverables:** define a set of structurally diverse compounds (10–15 cmpds) for further characterisation

Step 2: *Generation of key data for a topical candidate (in vitro and in vivo)*

- **Scope:** Generate key topical candidate data on the set of compounds defined on step 1 (*in vitro* percutaneous flux, solution stability, systemic clearance and plasma protein binding)
- **Approach:**

(a) **Part 1:** *On the whole set of compounds selected in Step 1*

- Compounds efficiency: in vitro percutaneous study performed using cassette dosing using a standard generic formulation
- Solution Stability: accelerated stability (40 °C or 50 °C for 2–4 weeks in an aqueous solution) at various pH (4, 6 and 8)
- Local irriation: use Reconstituted Human Epidermis model to assess the potential for a local undesired effect

(b) **Part 2:** *On the most interesting compounds obtained following Part 1 of Step 2*

- Minimizing exposure (Systemic Clearance and Plasma Protein Binding)
  - plasma protein binding in rat and human
  - intravenous pharmacokinetic study in rat
  - intrinsic clearance (microsomes or hepatocyte) in rat and human
- Target engagement in Franz diffusion cell using human skin (in vitro PD). Need to generate a condition which would allow to follow a biomarker in skin or in the receiving medium demonstrating target engagement.

Note: *Such a model of target engagement may not be available for the project team. It is, therefore, possible, that, this last element of the package, though highly desirable, may not be obtainable and therefore the decision to progress or not a molecule would need to be taken without it. Alternatively, an in vivo PD model could be considered but with carefull interpretations of the data generated as described in the paragraph "*in vivo *PD models" in Chap. 6.*

- **Deliverables:** recommendation for a candidate molecule
  OR recommendation to design new molecules
  OR recommendation not to pursue any of the compounds from the various chemical series

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Chapter 11
Selecting Dermal Drug Candidate: Some Useful Quotations and "Rules"

In the preceding chapters, several elements and concepts have emerged. In order to put in perspectives some of them in the industrial context, some quotations and rules are listed in this chapter. Extra comments met during the course of various topical drug development programs are added too. Overall these quotations and rules, sometimes considered provocative, may be found helpful for program teams developing a topical molecule.

11.1 "Manage Every One's Expectation on Chance of Success… Even If Skin Is Thin and the Target Site Less than 1 mm Down, Delivering through the Topical Route Is Challenging"

Some historical case studies of topical drug development described in Chap. 2 do exemplify the risk of not translating a successful oral drug into a topical one. Unpublished experiences from the industry would further confirm the substantial risk of failing to develop a topical molecule originally designed for the oral route. A strong focus, therefore, of the project team should be on the assessment of the likely target engagement in man.

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11.2 "Don't Believe the Molecule You Have Developed for a Systemic Route Is the Best One You Have from Your Lead Optimisation Effort… Look for a Better One"

Program teams often consider the repurposing of advanced molecules that may have failed for various reasons in the development path. Such molecules have a good safety package, they are potent and they have all the properties required to be oral or systemic candidate medicines. They could be good candidate topical molecules too… and maybe not. Clearance and protein binding properties would be opposite to what is required. Stability in water could be a problem. Very important too, its percutaneous flux vs. its potency may not be appropriate. The drive to develop the advanced molecule can be strong because part of the package is there already and large quantities of material may have been synthesised by then. It would, however, be advisable to assess the properties described in Chap. 10 for the advanced molecule and to compare such properties with other molecules developed during the lead optimization effort. Better molecules could then be discovered and the focus should be put on such molecules.

11.3 "Don't Be Scared of the Systemic Toxicological Findings Associated with the Target… It Is Most of the Time Not of Concern and Manageable"

Key advantage of a topical administration is the decreased risk of toxicological findings and this is generally the driving rationale for developing a topical medicine. Still, a program team could be concerned by the bad toxicological findings observed with the target considered. This could drive a decision not to go after the target topically even if the pharmacological rationale is strong.

Two elements should put program teams at ease with that potential concern. The first one is that it is well proven by the successful development and the systemic safety of key topical target classes such as corticosteroids, immunomodulators, retinoids and vitamin D3 derivatives which have side effects difficult to manage if given systemically for long period. The second one is that as seen in Chap. 7, one can estimate/quantify the risk and the therapeutic index. Eq. 7.5 in Chap. 7 gives a way to calculate the therapeutic index and the figures obtained from that equation in Table 7.2 in Chap. 7 show the large safety window that can exist.

11.4 "Expect a Substantial Toxcological Package to Develop a Topical NCE and a Long Development Time"

Developing a topical molecule requires the same safety assessment studies as for an oral/systemic molecule and as well some specific studies for the toxicological evaluation of the topical risks. Overall cost and time dedicated to the toxicological

assessment is therefore higher than for an oral/systemic drug. Similarly, due to the time dedicated to develop the formulation, timings are somewhat longer from the time the candidate molecule has been identified to the time it reaches the clinical phases.

11.5 "Prefer Minipig to Rodent for the Toxicological Package If You Don't Want to Stop Your Asset for a Wrong Reason: Exacerbated Local Tox that Would Not Translate in Human"

This is the direct consequence of what is described in the paragraph dedicated to "local irritation" in Chap. 10.

11.6 "For an In Vitro Skin Permeation, If Substantial Concentration Appears to Have Been Achieved in Skin While Nothing Is Found in the Receiving Fluid, this Is Bad News Not Good News"

A program team may decide to perform in vitro skin permeation work and collect skin to get a concentration in the skin layers. In the paragraph "The Skin Surface Contamination Issue" in Chap. 5, several elements are brought to the attention of the reader about the risk associated with the use of such data. Therefore, getting high concentration in skin as measured in a classic in vitro percutaneous assay may be highly misleading and ought not to be considered as a positive element if this is not associated with good percutaneous flux. On the other end, absence of quantifiable concentration of the compound in the receiving fluid (assuming a low limit of quantification was achieved in the bioanalytical method), strongly suggests that the compound is not penetrating well into and through the skin. Therefore its chance to engage the target in skin may be low.

11.7 "Don't Believe in Compound Retention in the Viable Epidermis or Dermis"

Once a molecule has crossed the stratum corneum it will diffuse passively into the lower tissue and into the receiving fluid, as the viable epidermis and dermis do not act as real barriers. The law of passive diffusion (Fick's law) prevails. Molecules will move from high concentration zone to low concentration zone. Similarly, the formulation itself will not provide the key to retention either as demonstrated in the paragraph "retention in skin" in Chap. 8.

11.8 "Don't Expect Miracles from the Formulation in Terms of Drug Delivery"

Unless ones uses mechanical or physical ways to deliver a molecule (holes, electroporation, iontophoresis…), the formulation will most often have a small impact on the delivery of the molecule. Some vehicles, though, should be avoided as they can impair the delivery of the molecule. A classic aqueous cream BP is already a good starting delivery vehicle. To the current public knowledge in the field it is unlikely that another formulation would be able to improve the percutaneous flux of a molecule more than tenfold compared to such a standard formulation (assuming similar aesthetics and a dose volume applied of 2 mg/cm^2). It is the molecule itself that will drive most of its delivery not the vehicle it is formulated in, hence the requirement to select well the candidate molecule. It will be, therefore, more effective to spend time and resources on the selection of the candidate than on the delivery improvement from the formulation.

11.9 "Don't Go with Fancy "Gunky" Vehicle… Think of the Patients and the Aesthetics Required for a Topical"

As described in Chap. 8, selecting a vehicle that meets the patient's requirements is an important consideration for a dermal medicine as the aesthetic properties of the vehicle will drive compliance. Without good compliance, a promising medicine will deliver less efficacy as the medicine will not be applied regularly leading to large periods of "drug holiday" (without target engagement). Vehicles with good aesthetics offer, however, suboptimal delivery properties. It is, therefore, important to select a candidate molecule with strong capacity to engage its target (i.e., good potency vs its flux potential). This will give some spare capacity to allow to formulate such a molecule in a good aesthetic vehicle.

11.10 "Don't Expect a Large Molecule to Cross the Stratum Corneum"

Nowadays many types of large molecules (peptides, proteins, mABs, oligonucleotides…) are developed successfully as medicines. It can be tempting to consider their use in a topical format especially as they are most often extremely potent molecules. There is, however, a strong probability that such attempts will fail. Such molecules are, as of today, unable to cross the intestinal barrier which is a much more permeable membrane than the stratum corneum. Claims of

delivery of such molecules through or into the skin should be considered but with high caution.

11.11 "If Possible, Chose a Candidate Molecule with a Long Skin Crossing Time"

The consideration of such a data is not yet clearly demonstrated, but theoretically it should be the equivalent of the half-life for a systemically delivered drug, so a valuable criteria to consider. In the paragraph ""In silico" PK/PD approaches" in Chap. 6, the case for using such a parameter is attempted.

11.12 "Put a Relevant Screening Cascade: Discharge Early the Key Risks of a Topical Drug… Delay the Other Data"

In Chap. 10 and especially in the paragraph "Comparison of the criteria used to select an oral/systemic candidate and a topical one", the various interesting topical parameters are discussed. Data such as in vitro potency, percutaneous flux, stability in water, UV absorbance and in vitro local irritation are five key parameters to assess as early as possible. If possible/available, using a topically relevant PD model, would be a strong added element too before considering candidate selection. Other parameters are likely to affect only slightly the quality of the candidate molecule and so could be delayed or even not considered at all.

11.13 "Deeper the Target the More Difficult to Engage the Target"

Following topical application, a steep concentration gradient will exist in skin, with very high concentrations in the stratum corneum and much lower ones deep down in the dermis and lower tissues. Reaching the relevant concentrations that will allow target engagement will, therefore, be easier in the upper layers of the skin. This is well demonstrated in the history of topical drug development and summarised in Table 3.3 in Chap. 3. This thought may be worth considering when selecting the target. A target for which only poorly potent chemical series could be effective if the target is in the stratum corneum… but not if deep down in the lower dermis.

11.14 "Think 'Ligand Efficiency' as a Way to Improve the 'Compound Topical Power'"

Today's trend in medicinal chemistry is to consider the Ligand Efficiency (LE) (Eq. 10.1 in Chap. 10) in order to keep good phys-chem properties of the chemical series being developed. Using LE during Lead Optimization helps to gain in potency without (or with limited) phys-chem properties loss. Such an approach is likely even more important with topicals than for orals as skin permeation is more dependant on phys-chem than intestinal permeation due to the severe impermeability of the skin membrane.

Chapter 12
Conclusions and Perspectives

Developing and selecting a candidate molecule for an oral/systemic indication is not easy and the attrition rate remains high despite strong and widespread knowledge available to develop an effective risk discharge cascade to identify good candidate molecules.

For a topical molecule, at first sight the perspectives to select a good candidate molecule are much lower. Indeed, several elements bend strongly in the wrong direction. (1) The know-how to define the good candidate criteria are generally absent in non-specialised dermal pharmaceutical companies. (2) The impermeable nature of skin makes it hard for molecules to reach their target site in sufficiently high concentration to exert a pharmacological activity. (3) Topical pharmacokinetics is generally not understood leading to the unability to predict topical target engagement. (4) Pragmatism will often push pharmaceutical companies to perform a repurpose exercise on a single molecule selected with oral/systemic criteria not with topical criteria. A single element, but an important one, however, goes in the good direction: The large absence of risk with regards to systemic tox which is likely the main reason for the early failure of oral/systemic drug development projects nowadays.

The apparent poor attractiveness of topical drug development could however become an opportunity if the right concepts and tools were used to select and develop topical candidates as summarised in Table 12.1.

Indeed, there could be substantial improvement on the quality of the topical candidates if the way the selection was performed would evolve:

- IF one was to consider to repurpose a whole chemical series instead of the single most advanced oral/systemic molecule, this would increase the chance of finding a candidate with the right topical properties.
- IF the topical PK concept were better understood and the relevant data generated and used, this would decrease the chance to select candidate that will fail in the clinic because of lack of target engagement.

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Table 12.1 Early drug development risks by route of administration and knowledge

	Oral/systemic	Classic topical[a]	Improved topical[b]
Number of molecules considered	✓	×	✓
Understanding PK and predicting target engagement	✓	×	✓
Know-how for other drug developability elements	✓	×	✓
Systemic Tox	×	✓	✓

[a]"Classic topical": assumes little knowledge of topical drug development and pragmatic approach
[b]"Improved topical": assumes good use of the various concepts described in earlier chapters

– IF a PD model (with relevant topical PK properties) was available and used this would furthermore discharge the risk of lack of target engagement in the clinical phases.
– IF UV absorbance, aqueous stability, local irritation were considered early, this would decrease the chance of struggling with some undesirable properties affecting time of development and patient acceptance of the formulation.

Working and applying all these changes could put the development of a topical drug at an interesting level of return on investment for the company sponsoring such an effort.

One could go even a step further and make the topical drug development approach even more attractive if one was to take into account two further elements:

1. Large number of assets to test are now available and there is economic sense to make use of them.
2. Faster and cheaper clinical proof of concepts for a topical may be available.

In the last decade, the move of the pharmaceutical industry has been to investigate new mechanisms of action in order to hopefully get better efficacy. The consequence of this move is that many new mechanisms and associated molecules to test are now available. Moreover because of the high risk of target related toxicity, a large number of such asset molecules for various targets end up being abandoned as no viable indication for a systemic use can be found. Some of these molecules could be of interest for a skin disease as systemic toxicology would not be an issue in most cases. These molecules and chemical series are, therefore, potential "repurposable" assets for a topical indication and companies holding such assets could be interested to develop them, pending available dermatology drug development expertise in their organisation. Potentially more interesting, these companies could out-license them to specialised dermatology companies to recover some of the losses incurred during the development of such assets. Similarly, companies specialised in developing topical molecules could be interested to have access to such assets as developing whole chemical series comes at a cost. There are therefore opportunities to get win/win situation where repurposable assets and expertise could meet (Fig. 12.1).

	Large Pharma	Small Dermatology Pharma
Number of Targets	High	Low
Capacity to generate Hits on a Target	High (large Cmpd Bank)	Low (small Cmpd Bank)
% of Targets considered for Dermatology Use	Low	High
Dermatology Know/How	Low	High

Fig. 12.1 Strength and weakness of large pharma and small dermatology pharma

The second point goes beyond the scope of this book as this is a step reached post candidate selection but this could have a strong impact on the cost associated with the discharge risks of a candidate molecule. One advantage of topical drugs is that they can be applied to a small part of the body without exposing the whole body to the tested molecule. This therefore can allow to go into the clinic with only a small toxicological package. This can be proven helpful for assessing the efficacy of a topical drug in a patient or an healthy subject providing a relevant biomarker is available. As seen before, this has been successfully tested after world war I with mustard gas pharmacology using the "nail head" method and as well during the development of the corticosteroids, from the 50s through the 70s using blanching (vasoconstrictor properties of corticoids) as the biomarker. More recently, the microplaque assay approach was developed in psoriasis. Microdialysis could be a next step as this technique requires a very small surface area, is not prone to surface contamination and is able to collect samples containing endogenous species. There has been as well progresses made on identifying and measuring biomarkers in the past years. Overall, the concept of testing on a small surface area could become an attractive opportunity for a company who would like to develop topical drugs and discharge some key risks fast at a reduced cost.

The concept of having access to more assets and getting faster to a proof of concept is starting to emerge in the industry. As an example, in order to boost R&D productivity, Eli Lilly has developed the "quick-win, fast-fail" model [1] which requires "abundance of drug discovery" and the ability to get fast to a POC as showed in Fig. 12.2. This is exactly the context just discussed for developing topical candidates: (1) large quantities of assets could be at hands and (2) topical delivery could allow faster and cheaper access to POC.

The Eli-Lilly model illustrates the contrast between the traditional drug development model (part a) and an alternative, the quick-win, fast-fail model (part b) with a greater focus on reaching proof-of-concept (POC) efficiently, faster and with lower cost. This approach allows to discharge risk as early as possible to avoid progressing assets that are likely to fail.

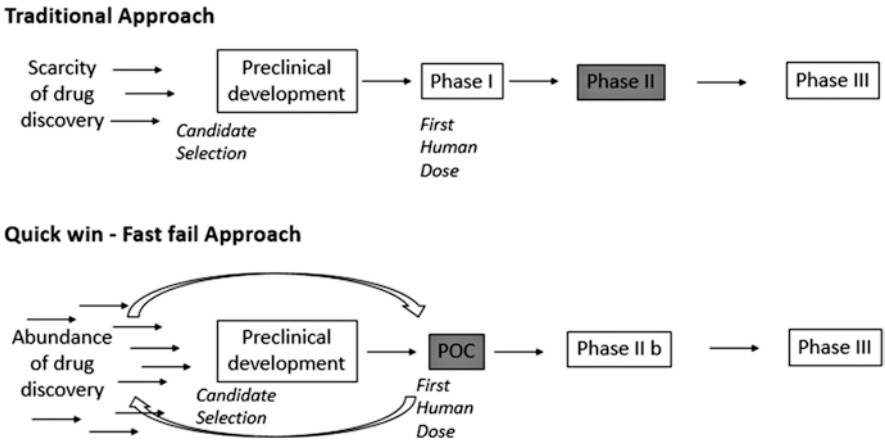

Fig. 12.2 The quick-win, fast-fail model from Eli Lilly

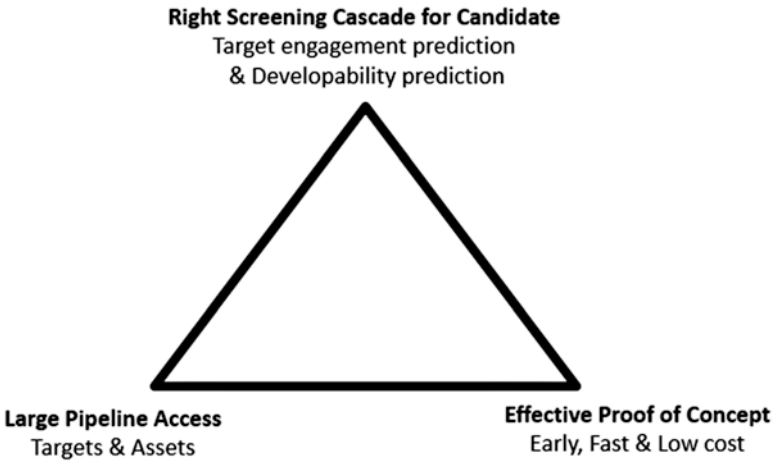

Fig. 12.3 Key topical development success tools

Overall, in order to maximise the potential for discovering, selecting and discharging the key risks of a topical candidate, one would need to have the following three independent "tools" (Fig. 12.3):

1. The right screening cascade and the assays associated for selecting the topical candidate (such as described in Chap. 10).
   => To select the topical candidate with the right properties.

2. A large pipeline of assets available to be repurposed (i.e., whole chemical series associated with several targets with good rationale for some skin diseases).
   => To maximise the chance to have access to several good topical candidates.
3. Clinical pharmacology expertise (including biomarker assessment and analysis) specialised in the development and running of effective proof of concept studies in dermatology.

=> To demonstrate target engagement (i.e., to discharge the key risk of absence of target engagement) fast at a relative low cost.

The three "tools" together are not required to be successful, as the screening cascade and/or the access to a large pipeline of relevant assets could be already good ingredients for success. However the three together would offer a strong platform for developing dermal drug candidates.

To conclude, though difficult and challenging because of some scientific gaps not fully explored, the development of dermal topical drugs could be an interesting area full of opportunities to treat skin diseases. However, to be successful, one would need to understand well the pros and cons of such developments, as well as the tricks and pitfalls along such a road.

This book will hopefully contribute to help some of the project teams embarking on developing topical drugs.

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