

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].

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 idoxuridine 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 aciclovir 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 alphacalcidol (a vitamin D3 metabolite) [$1\alpha(\text{OH})\text{D}_3$]. In the following years, Morimoto et al. performed successful studies in larger group of psoriasis patients with alphacalcidol and its hydroxylated metabolite calcitriol [$1,25(\text{OH})_2\text{D}_3$] [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 $\mu\text{g/g}$ 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	Benzylamine	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 unpredictable 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 × 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.

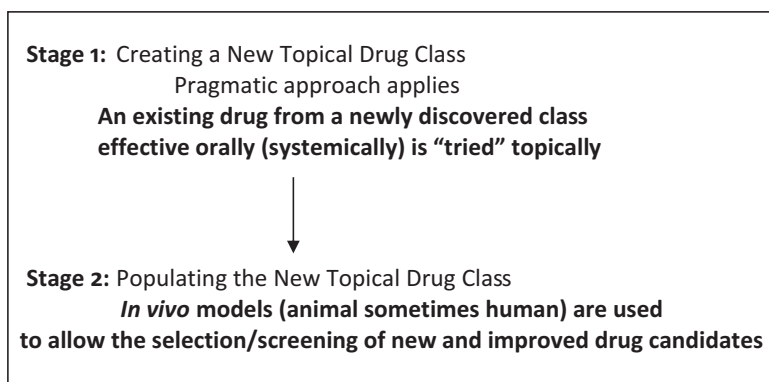


Fig. 2.1 Building up a new topical drug class

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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