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8. Technological, biopharmaceutical and pharmacokinetic advances: New formulations of application on the skin and oral mucosa

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Abstract. Currently a growing interest to improve the pharmacological therapy exists, not only by the production and the appearance of new drugs, but guaranteeing that the uses of those which already exist, become more effective. In fact, the conventional pharmaceutical formulations of different drugs present a few secondary effects due to oral administration. In order to avoid these undesired side effects, the purpose of current therapeutic is the development and research of formulations as an alternative to others routes of administration. Therefore, in spite of the undoubtedly complete parenteral absorption, the transdermal and transbuccal routes appear to be a rather attractive alternative to provide an efficient absorption. In this chapter a new technological, biopharmaceutical and pharmacokinetic approach of strategies for application on skin and buccal mucosa are reported.

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In the future new transdermal drug delivery systems will emerge to be more effective, equipped with an improved aesthetic appearance, better adherence and greater diffusion. But to reach these aims, it is necessary previous knowledge of histology and physiology of skin, and factors involved in the penetration of drugs through it.

Introduction

The pharmaceutical sciences are faced with a need to develop alternative dosage forms for transdermal and transmucosal absorption. In addition to oral and parenteral routes, the suitable sites for administering drugs are the nasal, vaginal, rectal or ocular mucosa. However the oral mucosa represents the most popular route, because of its excellent permeability, good accessibility, high patient acceptance and compliance, the dosage forms can be easily attached to and removed from the mucosa. Moreover oral mucosa is routinely exposed to different compounds and therefore is supposed to be rather robust and less prone to irreversible irritation or damage by the drug, the dosage form, absorption promoters, etc. In fact, the turnover time for the buccal epithelium has been estimated at 5–6 days [1].

Within the oral mucosal cavity, the buccal region offers an attractive route of administration over peroral administration; buccal routes offer the advantages of avoiding hepatic first-pass metabolism, local intestinal enzymes and secretions and are deficient in enzymatic degradation.

In the other hand, the transdermal administration of drugs offers advantages that can enhance the therapeutic benefits of the active substances. This route of administration avoids the gastrointestinal tract and biotransformation due to the first-pass effect and metabolism in the liver. Drug release is targeted at the specific site where it is needed, and the percentage of absorption can be controlled. Delayed release formulations can be used. Systemic secondary effects are reduced, and topical formulations are easy to apply, a factor that improves patient compliance. Substantial concentrations of the drug can be reached in the soft tissues at the site of application. In addition, transdermal formulations can be used in readily accessible sites, and such formulations are nontoxic and easy to use.

These advantages, in both routes, are particularly useful with drugs that can break down in the gastrointestinal tract, or drugs used for long-term treatments, intravenously, or for osteoarticular wounds.

1. Anatomy, physiology and permeability of the oral mucosa and skin

Despite the advantages of transdermal and transbuccal pathways, the primary function of skin and oral mucosa is the protection of the underlying tissue. Therefore, to set the stage for subsequent discussion of strategies for

use of dosage forms in transdermal and transmucosal drug delivery, basic physiological characteristic of the skin and oral mucosa should be mentioned.

1.1. Oral mucosa

Drugs can be absorbed from any of the mucosal tissues in the oral cavity: maxillary artery supplies blood to buccal mucosa and blood flow is faster and richer (2.4 mL/min/cm²) than that in the sublingual (beneath the tongue), gingival and palatal regions, thus facilitates passive diffusion of drug molecules across the mucosa.

Buccal mucosa is composed of several layers of different cells, but consists principally of two components, an epithelium and an underlying connective tissue (basal lamina, propria lamina and submucosa). Also numerous racemose, mucous, serous glands and major blood vessels and nerves are present in the submucous tissue of the cheeks [2]. The epithelium of the human oral mucosa shows two distinct patterns of maturation, non-keratinized and keratinized. The most interesting, non-keratinized epithelium forms the surface of the distensible lining of the soft palate, ventral surface of the tongue, floor of the mouth, alveolar mucosa, vestibule, lips, and cheek.

The epithelium and its basal lamina constitute the major resistance barrier [3]. Substances can cross the buccal epithelial membrane by the mechanisms of simple diffusion, carrier-mediated diffusion (intercellular or intracellular), active transport, and endocytosis [4]. Most permeability studies (large molecules) point towards intercellular via [5].

The flux of drug through the membrane under sink condition for paracellular route can be written as Eq. (1)

$$J_p = \frac{D_p \varepsilon}{h_p} C_d$$

Where, **D_p** is the diffusion coefficient of the permeate in the intercellular spaces, **h_p** is the path length of the paracellular route, **ε** is the area fraction of the paracellular route and **C_d** is the donor drug concentration.

Similarly, flux of drug through the membrane under sink condition for transcellular route can be written as Eq. (2).

$$J_c = \frac{(1-\varepsilon)D_c K_c}{h_c} C_d$$

Where, **K_c** is the partition coefficient between lipophilic cell membrane and the aqueous phase, **D_c** is the diffusion coefficient of the drug in the transcellular spaces and **h_c** is the path length of the transcellular route [6].

In general, lipophilic drugs are absorbed through the intracellular route, whereas hydrophilic drugs are absorbed through the intercellular route, but the rate of penetration varies depending on the physicochemical properties of the molecule and the type of tissue being traversed. This has led to the suggestion that materials use one or more of the following routes simultaneously to cross the barrier region in the process of absorption, but one route is predominant over the other depending on the physicochemical properties of the diffusant [7]. So, the absorption potential of the buccal mucosa is influenced by the lipid solubility, molecular weight of the diffusant and carrier pH [8]. In addition, the microenvironment of the buccal cavity lends itself to modifications, in very few cases also the barriers such as saliva, mucus, membrane coating granules, retard the rate and extent of drug absorption through the buccal mucosa. All affects its bioavailability, hence development of unidirectional release systems with backing layer results high drug bioavailability [9].

1.2. Skin

The functions of the skin are thermoregulatory, immunological, mediation of sensation, social and protective. Barrier function plays the most important role in drug development and pharmacokinetic implications for both topically and systemically administered drugs. However the skin is the most accessible organ of the body but it is designed to isolate the organism from the external milieu, and thus poses a challenge to the pharmaceutical development of excipients that yield optimal permeation and cutaneous absorption of the active principles.

The skin is a complex organ consisting of three anatomical layers, the epidermis, the dermis and a subcutaneous fat layer. Moreover, the skin is pierced by the sebaceous and eccrine sweat glands and the hair follicles [10].

The epidermis is in humans 0.02-0.2 mm thin. The epidermis is made up of two layers: the stratum germinativum and the stratum corneum. The stratum corneum is a dead fully keratinised cells tissue. The functions are: protective, against external environment, occlusive, preventing body water loss (dehydration), and receptor for epidermal metabolic products. In fact, the stratum corneum provides the major barrier to penetration of topically applied drugs due to its lipid-rich nature and its low water content. The water content of the normal stratum corneum is 20-30%. The intracellular lipids consist of ceramides, fatty acids and cholesterol. There are also other intracellular lipids or lipids from the sebaceous glands or from epidermal fat [11].

The region below epidermis is called dermis. It supports and strengthens the epidermis. It ranges 5–20-times thicker than epidermis (approximately 2-3 mm thick). The dermis contains fibrous protein collagen, elastin,

histiocytes, mastocytes, water, ions, carbohydrates, blood and lymphatic vessels and nerves. The dermis is therefore a sensitive and highly irrigated tissue. Through the blood vessels in the dermis, the drugs enter the circulation system; firstly they have to cross the stratum corneum.

The subcutaneous fat layer or hipodermis represents the separation zone between the dermis and underlying tissues. It is composed of fat and elastic fibers. The hypodermis is the base of hair follicles and the sweat glands. It is also a well irrigated and innervated layer. Sometimes, the fat deposits may serve as a deep compartment for the drug and this can delay entry into the blood.

Number and type of hair follicles and glands is very relevant for drug penetration. In this zone of appendices, the stratum corneum thickness decreases, and even may disappear. Consequently the appendices are important access roads. The number of appendices varies depending on the species and anatomical region [12].

2. Cutaneous and transbuccal metabolism

Drug absorbed through the oral mucosa enters the systemic circulation directly via the jugular vein, avoiding the liver where they might be metabolized. However the drugs which are swallowed in the saliva do not avoid first pass metabolism and will be subjected to degradation by digestive juices. This may be partly overcome by using a drug delivery system which has a unidirectional drug outflow [13, 14].

Also, the enzymatic activity on the surface of the buccal mucosa should be evaluated as a barrier to drugs buccal delivery. In this way, the inclusion of enzyme inhibitors in buccal bioadhesive delivery systems could improve buccal bioavailability [15].

The viable part of the epidermis represents an enzymatic barrier for drugs after topical application. The distribution of the enzyme system will depend on the anatomical area and the species [16, 17], causing some differences in absorption and considerable transdermal first pass metabolism [18-20].

In vivo enzymatic activity in the epithelium can activate pro-drugs decreasing the delivery [21].

The stratum corneum can act as a reservoir for drugs, causing the pharmacological response to continue for a short time after the device has been removed. In other cases, depending on the delivery system, the drug will diffuse into underlying layers. The results presented indicate that most of the enzyme activity of the skin may be localized in the epidermal layer.

For this reason, the study of skin metabolism should take into account not only in the field of transdermal drug delivery but also for the safe and efficient local skin treatment with topically applied substances.

Finally, the oral mucosa contains the greatest variety of micro-organisms, which could alter drugs [22]. The entry into the body of these organisms is limited by the oral epithelium, which is not, as is often suggested, a highly permeable membrane.

Skin surface contains many and some potentially pathogenic microbiota. The drugs topically applied can be metabolised by bacteria on the skin surface [23]. Also, this bacterial population can encourage its growth due to heat or humidity transdermal system. It must be kept in mind when opening pores in skin and oral barrier.

Despite these disadvantages, the enzymes in the skin are essential in order to maintain skin good conditions contribute to the right skin pH and maintain skin protective capability against pathogens or reactive oxygen species.

Finally, it must be emphasized that the delivery system properties (e.g. permeation enhancers) and regional variations might be considered as a potential reason for inter- and intra-individual variations in metabolism and bioavailability of transdermally administered drugs [24, 25].

3. Pharmaceutical considerations

To a certain extent, the structure of the oral mucosa resembles that of the skin. For this reason some pharmaceutical considerations are general. Great care needs to be exercised while developing a safe and effective buccal adhesive drug delivery device. Factors influencing drug release and penetration through buccal mucosa, organoleptic factors, and effects of additives used to improve drug release pattern and absorption, the effects of local drug irritation caused at the site of application or texture of buccal mucosa, thickness of the mucus layer, its turn over time and effect of saliva are to be considered while designing a formulation. Also, the buccal epithelium is a lipoidal barrier, hence the majority of absorption of drugs is passive. However, some authors have demonstrated an active transport [26-28].

Another very important factor is the location of drug release system. The dosage form may be used as sublingual, buccal, local or periodontal delivery system. Variations in oral physiology will undoubtedly affect drug absorption.

In the other hand, the permeation of topically applied drugs into the systemic circulation consists of three phases:

- The release from the vehicle: the drug may be dissolved in the excipient and then diffuse to contact the skin surface.
- In a transdermal device, the primary design goal is the maintenance of the desired constant drug concentration at the skin surface for a suitable length of time.

- Penetration into the epidermis and permeabilization: Once the drug reaches the vehicle/skin surface interphase, it can penetrate through the sweat duct, hair follicles and sebaceous glands, being dissolved in sebum secretion (collectively called the shunt or transappendageal via) or directly across the stratum corneum (transepidermal via).
- The passage through the dermis and the entry into the systemic microcirculation.

There are several routes by which drugs can pass through the skin:

- The intercellular route, the passage of drug through the lipid matrix between corneocytes in the stratum corneum.
- The transcellular route, this occurs when drug passes through both the corneocytes and the lipid matrix within the stratum corneum.
- The appendageal route, the passage of drug through the appendages, such as hair follicles and sweat glands; therefore bypassing absorption through the stratum corneum.

The intercellular and transcellular route are also known as “transepidermal via”. It has been suggested that transappendageal via is more rapid than transepidermal via but it is considered unimportant. Transepidermal via is the most important pathway of passage, especially the intercellular route, but all this is depending on the molecules physicochemical properties.

Drug penetration through the skin depends on many factors, dependent on animal, drugs and formulation, which can modify the efficacy of a treatment.

The diffusion of drug across the stratum corneum is driven by a thermodynamic gradient and is not determined solely by a concentration gradient. According to Higuchi [29], drug permeation can be represented in a mathematical model for the purpose of predicting dermal absorption in this equation:

$$dQ/dt = P \cdot D \cdot S \cdot C/h$$

Where **S** corresponds to the total surface of application, **h** is the average thickness of the skin in this surface, **D** corresponds to the diffusion coefficient of a given drug across the skin, **C** is the applied drug concentration, and **P** the partition coefficient between the stratum corneum and the vehicle. From this equation it could be deduced the main factors affecting the rate of penetration:

3.1. Drug criteria

- Lipid/water partition coefficient. It is the most important factor of penetration in the stratum corneum, due to the lipid-rich nature of the

stratum corneum. Absorption of hydrophilic compounds is limited by the lipophilicity of the stratum corneum. However the dermis is much more hydrophilic than the stratum corneum and so act as a barrier to extremely hydrophobic compounds [30], once a hydrophilic compound has penetrated through this, it will partition readily into the epidermis and into systemic circulation [31]. So transdermal administration is ideal for substances with intermediate polarity.

- Molecular weight. This factor also impacts upon drug diffusion through the stratum corneum and dermis. Small molecules are more likely to cross skin. It is defined by its diffusion coefficient D , which is inversely proportional to the cube root of molecular weight. The larger the molecular weight, the lower the diffusion coefficient. However the lipophilic nature of the drug seems to play the most important role in this fact.
- Drug concentration. It is directly proportional to the penetration rate, although drug solubility in the vehicle, should not be exceeded.
- Degree of drug dissociation. It is depending not only on skin pH, but also on formulation pH.

Transdermal administration has several advantages, especially in those drugs with a low water solubility and low bioavailability, and/or those with a great first pass metabolism in comparison with the oral administration. Moreover, pre-systemic metabolism is avoided, permitting lower daily doses. Blood levels of the drug can be kept for extended periods of time prolonging drug action and reducing the dosing frequency. Inter and intra patient variability is reduced, and patient compliance and acceptability improved. Lastly, input of drug can be stopped by removal of the patch [32].

3.2. Vehicle criteria

The vehicle in which a drug is applied to the skin must be not only a support, but a delivery system that drives the drug to an appropriate area or biophase with an optimal rate of release. The absorption of a compound into the skin may be impeded if it is more soluble in the vehicle it is applied in than the stratum corneum [33]. Then it must exist an equilibrium between drug-vehicle and drug-skin affinity in order to ensure the maximal thermodynamic activity, and this is possible when the drug contained in the vehicle chamber is saturated. A lipophilic drug dissolved in an aqueous vehicle would be absorbed before than at the same concentration from a vehicle with other lipophilic solvent.

The vehicle is intended to function as a reservoir to provide a steady supply of drug and prolonging the effect. Therefore, it is important to take into consideration the vehicle effect will have on the dermal absorption drugs.

For a satisfactory release of drug from the vehicle, several conditions must be taken into account:

- Diffusion coefficient of drug in the vehicle must be optimal, for it drug must be solubilized, without possessing a selective affinity toward the vehicle.
- The lower the viscosity the greater the diffusion coefficient.
- Vehicle must improve the permeability by hydration, occlusion or direct penetration.
- Vehicle must not cause irritancy in the skin.

Optimization by a suitable formulation is responsible of residence time, local concentration of the drug in the mucosa and the amount of drug transported across the mucosa into the blood. The products for the buccal cavity must have good patient compliance, an ideal bioadhesive drug delivery system, should be easy to apply to the mucus and withstand salivation, tongue movement, and swallowing for a period of time. Buccal adhesive drug delivery systems with the size 1–3 cm² and a daily dose of 25 mg or less are preferable. The maximal duration of buccal delivery is approximately 4–6 h [34].

From a dermal point of view, the aim of skin applied formulations is to reach the skin surface, stratum corneum, viable epidermis, dermis, hair follicles, sweat glands or systemic circulation. Depending on the particular aim, the most appropriate biopharmaceutical and physicochemical aspects must be taken into account.

3.3. Others factors

Penetration of the substances into the skin can be modified by some factors as age, gender, location of the skin, skin damage or disease, as well as the well know regional variation in skin permeability to different molecules [35].

Also, tissue vascularity determines the rate of absorption. In man, dermal blood flow is about 2.5 mL min⁻¹ 100 g⁻¹.

Areas of the body where the stratum corneum is thickest, such as the palms of the hands (400 μm) and soles of the feet (600 μm) will be far less permeable to xenobiotic compounds than an area of the body where the stratum corneum is much thinner, such as the scrotum (5 μm) [36].

However several pharmacokinetic studies show bioequivalence of several anatomical sites after patch application: clonidine patch provides similar plasma concentration profile after application on arm and chest [37]. The rate

and extent of nicotine absorption from Nicoderm® were similar after application on upper outer arm, upper back and upper chest [38]. Plasma concentrations of norelgestromin and ethinyl estradiol from the contraceptive patch remain within the reference ranges throughout the wear period regardless of the application site [39].

Both, temperature and occlusion, increase passive diffusion [40].

Equally, in older people the stratum corneum thickens and becomes less hydrated, decreasing absorption [41].

Recent studies demonstrate that skin properties in the stratum corneum vary considerably among ethnic groups [42].

However, the main factors to consider are two: damage/disease of skin and its hydration. The skin sustains damage [43] or diseases [44, 45] can reduce barrier action and lead to increased permeability of the drugs. These processes are an important obstacle to the selection of the formulation. The degree of hydration of the skin improved contact and hydration of the lipid channels of the stratum corneum. When the skin is hydrated it reduces the evaporation of moisture from underlying tissues, so it is better to use emollients and occlusive substances that moisturizers. As a result, transdermal absorption increases.

4. Strategies for transdermal and transbuccal drug delivery systems: Current technologies of chemically and physically enhanced diffusive delivery

The objective of a transdermal and transbuccal delivery system is to provide a sustained concentration of drug for absorption avoiding local irritation. However the slow transport of many drugs across skin limits these administrations.

The administration of active principles on the skin and buccal mucosa with the aim of achieving a systemic and reservoir effect has led to pharmaceutical development of a new form of dosage. There are some methods by which penetration of compounds through the oral mucosa and skin can be improved: by the use of prodrug, co-administration of enzyme inhibitors, delivery systems, enhancers or physical methods. But particular caution should be taken with the creation of pores in the skin, as this has a large number and variety of microbiota, including pathogens.

4.1. Drug delivery system in buccal mucosa

Sublingual drug delivery is more commonly used to treat acute disorders, whereas the buccal route is chosen when a prolonged release of drug is needed

in chronic disorders [46]. However bioavailabilities of some drugs by the buccal route were still low due to its anatomical, physiological and technological factors such as texture of buccal mucosa, thickness of the mucus layer, its turnover time, effect of saliva, enzymatic barrier. These factors are to be considered in designing the dosage forms.

For example, one to two litres of fluid are excreted daily into the human mouth and there is a continuous, low basal secretion of 0.5 mL min^{-1} which will rapidly increase to more than 7 mL min^{-1} by the thought, smell or taste of food [47]. Therefore their contact with the oral mucosa is brief. In order to locally treat the mucosa, delivery systems have been designed to prolong residence in this area. These formulations include semisolid, mucoadhesive patches and bioadhesive tablets.

The use of adhesive polymers plays an important role in the development of mucoadhesive dosage forms, prolonging residence on the oral mucosa, improving absorption, targeting of specific tissues and allow for some degree of sustained release of the active principle [48]. Also some bioadhesive polymers, such as poly(acrylic acid), polycarbophil, and carbopol, can also inhibit certain proteolytic enzymes (trypsin, α -chymotrypsin, carboxypeptidases A and B, and leucine aminopeptidase) [49].

The polymers must have the following characteristics:

Polymer and its degradation products should be non-toxic, non-irritant, free from leachable impurities and easily available. Also they should have good spreadability, wetting, swelling and solubility, biodegradability, bioadhesive and viscoelastic properties, and should demonstrate local enzyme inhibition and penetration enhancement properties.

In general, buccal dosage forms can be categorized into unidirectional or multidirectional and reservoir or matrix type. They also must possess the requirements described above. If necessary, the drug may be formulated in certain physical states, such as microparticles [50], sponges [51], liposomes [52, 53] or nanoparticles [54, 55], prior to formulation of dosage form in order to achieve some desirable properties, e.g. enhanced activity and prolonged drug release.

Sprays and fast dissolving tablets are the two most widely used formulations for sublingual delivery. Tablets have been the most commonly investigated dosage form for buccal drug delivery to date, however they have a poor patient compliance.

Others dosage forms, such as buccal films and patches offer advantages due its flexibility and comfort [56]. Different drugs have been successfully studied obtaining optimal permeation values for a systemic effect [57, 58].

Certain bioadhesive polymers, e.g. pluronics show a phase change from a liquid to a semisolid with the corporal temperature. They have the advantage

of easy dispersion throughout the oral mucosa, rich retention at the site of application and adequate drug penetration [59].

In contrast to polymers utilized until now, a new generation of polymers can adhere directly to the cell surface, rather than to mucus [60].

4.2. Drug delivery system in skin

Currently the advances on transdermal delivery systems can be divided into three categories; physical methods, chemical methods and other complex systems. These last may include vesicles, eutectic mixtures, pro-drug, micelles, cyclodextrins microemulsions, nanoemulsions, cubic phases, colloids and synergistic mixtures.

It also noted the success in the permeation after the combination of several techniques such as chemical enhancers, physical enhancers and vesicles [61-63].

4.2.1. Other complex systems

4.2.1.1. Dosage forms (solid, liquid, semisolid)

Classical ointments, creams, lotions and gels are not suitable for action and/or controlled transdermal delivery.

When an active principle is administered topically, including in a conventional pharmaceutical way (solution, emulsion, gel...) through the skin, the latter has to release the active principle it contains so that it previously dissolves, is absorbed and reaches its area of activity, which in this case must be centred on the coetaneous tissue. Nevertheless, the arrival of the active principle at the area of activity may be insufficient; rather, by means of the circulating fluids, it can be distributed to certain tissues that can determine the emergence of undesirable effects.

On other occasions, the active principle reaches an adequate concentration of its specific receptors, but this concentration is maintained for a short period of time. This forces the administration of the active principle to be repeated at short intervals of time, using conventional dosage methods for immediate release.

From a pharmaceutical point of view, the solution to these problems could lie in the chemical association of the active substance with an appropriate delivery preparation capable of specificity of action [64]. In this way, vectoring is defined as the attainment of maximum efficacy of a drug, by increasing its release in the area where its pharmaceutical receptors are found, thereby minimizing its concentration in other areas of the organism, reducing the adverse effects. So, one of the objectives of pharmaceutical research in recent decades has been the development of systems that release the active

principle selectively at the level of the damaged organ, without producing changes in healthy tissue.

Several advances to this effect have been made in the last 2-3 decades and novel drug delivery systems have been investigated.

Ability to solubilize and stabilize drugs, their high viscosity hydromiscibility, thermosensitivity and micellar behavior make the Pluronic gels a feasible vehicle for oral and topical control drug delivery.

Gels of pluronic as the vehicles for the percutaneous administration of anti-inflammatory [65], analgesic [66], peptides [67], beta-blockers [68] and other active principles were studied and evaluated. Additionally, in the early 1990s Marty Jones and Lawson Kloesel [69] developed PLO (Pluronic Lecitin Organogel) as a transdermal drug carrier delivery system. Recently, efficacy of transdermal use of different drugs has been demonstrated.

Organogels are semi-solid systems, in which an organic liquid phase is immobilized by a three-dimensional network composed of self-assembled, intertwined gelator fibers [70, 71]. The application of different organogel systems to transdermal via has been studied [72, 73].

Microemulsions (clear, stable, isotropic mixtures of oil, water and surfactant in combination with a cosurfactant) are systems currently of interest to the pharmaceutical scientist because of their considerable potential to act as drug delivery transdermal vehicles (with diameters in the range of 20-100 nm) [74, 75]. However, it is necessary large amounts of surfactants to form microemulsions. Therefore, the use of these colloidal carrier systems in the future depends on the choice of well-tolerated surfactants and the restriction of their amounts.

Several excellent reviews discuss the advantages, limitations and opportunities offered by *patches* reservoir or matrix type in greater details and thus will not be covered in this review.

4.2.1.2. Nanosystems or vesicles

Compared with other external skin preparations, such as creams and liniments, nanosystems provide more adjustable parameters in their preparation, and in treatments offer the advantages of enhancing drug effects, shortening the expected treatment course and lowering side effects.

Among the multiple advantages of these vectors, the following are shown:

- Protects the active substance from deactivation (chemical, enzymatic or immunological), from the area of administration to the biophase.
- Improves transport of the active principles to places difficult to reach.
- Increases the specificity of action and efficacy at cellular and/or molecular level.

- Increases the average life span of the drug.
- Modifies the soluble properties of the active substance and reduces its immunogenicity and antigenicity.
- Decreases toxicity of certain organs by adjustment of the tissue distribution of the active principle.
- Lacking in toxicity, they are biodegradable and can be prepared industrially on a large scale.

The most important factor for potential nanotoxicity is the lack of biodegradability of many nanomaterials. After generation of these nanomaterials, they will stay forever and pollute the environment and, considering the circle in the environment, finally end up in the human body.

In the other hand, lipid analysis of buccal tissues shows the presence of phospholipid 76.3%, glucosphingolipid 23.0% and ceramide NS at 0.72%. Other lipids such as acyl glucosylated ceramide, and ceramides [76]. In Stratum corneum, cellular membranes of keratinocytes are composed mainly of phosphatidyl choline and sphingomyelin. Also, the intercorneocyte matrix is rich in phospholipids.

In view of the above, in recent years a great importance has been attached to using lipids as vehicular systems and permeants of active principles through the skin and oral mucosa. The outstanding advantage of lipid vesicles is their easy and complete biodegradation. Lipids are natural materials, are easily degraded by natural processes such as enzymes. Phospholipids as drug carriers have some unique advantages which other conventional external preparations do not have. Phospholipids share a high structural similarity with skin lipids and thus have many advantages. They can moreover affect molecular transport across skin barrier more directly by acting as skin permeation enhancers. This type of application is particularly suitable for certain chronic and relapsing skin diseases, such as chronic eczema, psoriasis, neurodermitis, etc.

Several different kinds of lipid vesicles have been described in the literature.

Liposomes consist of amphiphilic molecules in a bilayer conformation.

In an excess of water these amphiphilic molecules can form one (unilamellar vesicles) or more (multilamellar vesicles) concentric bilayers [77]. Due to its structure, hydrophilic, amphiphilic and lipophilic drugs can be entrapped.

In recent years, most investigators have concentrated on the potential use of liposomes for the transdermal delivery of antibiotics [78], antiviral [79], anesthetics [80] and antiinflammatories [81].

Niosomes are composed of non-ionic amphiphiles (surfactants) and are similar in function to the liposomes [82, 83].

Ethosomes are relatively new types of vesicle systems, primarily composed of water, ethanol and phospholipids [79].

Sufficiently deformable and elastic vesicles can enter skin barrier spontaneously, e.g. **transfersomes**, which cross the skin under the influence of a transepidermal water activity gradient. Transfersomes consist of phospholipids and an edge activator that increases the deformability of the bilayers and is often a single chain surfactant. Recent studies show the effectiveness of elastic liposomes for transdermal delivery of melatonin [84].

Solid Lipid Nanoparticles (SLN) and **Nanostructured Lipid Carriers (NLC)**, SLN are usually aqueous dispersions of solid lipid matrices stabilized by surfactants, or dry powders obtained by lyophilization [85] or spray drying [86], ranging from about 40 to 1000 nm. NCL are produced using blends of solid lipids and liquid lipids (oils) [87]. SLN and NLC exhibit many features for dermal application of cosmetics and pharmaceuticals, i.e. controlled release of actives, drug targeting, occlusion and associated with it penetration enhancement and increase of skin hydration. Specifically, since the last decade, SLN have been exploited for delivery of actives via dermal [88-91]. They are an alternative carrier system to emulsions, liposomes and polymeric nanoparticles. Drugs for dermal application using lipid nanoparticles at the present are glucocorticoids, retinoids, non-steroidal anti-inflammatory drugs, COX-2 inhibitors, psoralens and antimycotics. It was shown that it is possible to enhance the percutaneous absorption with lipid nanoparticles. These carriers may even allow drug targeting to the skin or even to its substructures. Thus they might have the potential to improve the benefit/risk ratio of topical drug therapy [92].

In the context it is noteworthy that physico-chemical characteristics of all these vesicles (size, charge, thermodynamic phase, lamellarity and bilayer elasticity) have a significant effect on the behaviour of the vesicles and hence on their effectiveness as a drug delivery system. Taking in account our aim they may serve as:

- A local depot for the sustained release of dermal active compounds.
- Penetration enhancer and facilitate dermal delivery leading to higher localized drug concentrations.
- Rate-limiting membrane barrier for the modulation of systemic absorption or controlled transdermal delivery systems.

4.2.2. Chemical enhancers

Generally the usual vehicles are not able to penetrate into stratum corneum by themselves. Penetration enhancement technology is a challenging

development that would increase the number of drugs available for transdermal administration. Thus for years different compounds capable of penetrating and transporting drugs have been studied, these are chemical substances temporarily diminishing the barrier of the skin and known as penetration promoters [93]. Promoters or accelerant can enhance drug flux, may act by one or more of three main mechanisms [94]:

- Disruption of the highly ordered structure of stratum corneum lipid.
- Interaction with intercellular protein.
- Improved partition of the drug, coenhancer or solvent into the stratum corneum.

The selection of enhancer and its efficacy depends on the physicochemical properties of the drug, site of administration, nature of the vehicle and other excipients. These permeation enhancers should be safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic. The different permeation enhancers available are:

- Chelators: EDTA, citric acid, sodium salicylate, methoxy salicylates.
- Surfactants: sodium lauryl sulphate, polyoxyethylene, Polyoxyethylene-9-laurylether, Polyoxyethylene-20-cetylether, Benzalkonium chloride, 23-lauryl ether, cetylpyridinium chloride, cetyltrimethyl ammonium bromide.
- Bile salts: sodium glycocholate, sodium deoxycholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate.
- Fatty acids: oleic acid, capric acid, lauric acid, lauric acid/propylene glycol, methyloleate, lysophosphatidylcholine, phosphatidylcholine.
- Non-surfactants: unsaturated cyclic ureas.
- Hydrocarbons: alkanes, alkenes, halogenated alkanes, squalane, squalene and mineral oil.
- Alcohols: alkanols, alkenols, glycols, polyglycols and glycerols.
- Amines, amides, esters as isopropyl myristate.
- Others: Terpenes, terpenoids, essential oils and phospholipids.
- Thiolated polymers: chitosan-4-thiobutylamide, chitosan-4-thiobutylamide/GSH, chitosan-cysteine, Poly (acrylicacid)-homocysteine, polycarbophil-cysteine, polycarbophil-cysteine/GSH, chitosan-4-thioethylamide/GSH, chitosan-4-thioglycolic acid.

In general, it is challenging to strike an optimum balance between the safety and potency of chemical enhancers. In order to develop a transdermal penetration enhancer which a low irritation to the skin, alkyldisiloxanes containing sugar moiety with various alkyl chain length were investigated [95].

Nevertheless studies show that treatment with enhancers did not cause major morphological changes in the buccal tissue [96].

Based on such limitations, one can design synthetic enhancers [97] that are significantly more potent in their skin permeabilizing ability as compared to conventional chemicals as Azone (1-dodecylazacycloheptan-2-one).

Also, these limitations can be solved by synergistic effects between enhancers [98] and more polar co-solvents (e.g. ethanol, propylene glycol). Similarly, solvents such as Transcutol® are proposed to act by improving drug solubility within the membrane rather than by increasing drug diffusivity across it [99].

4.2.3. Physical enhancers: Devices

The ideal characteristics an active principle should have to penetrate the stratum corneum are: Aqueous solubility 1 mg mL^{-1} , lipophilicity 10 Ko/w <1000, molecular weight <500 Da, melting point < 200 °C, pH of saturated aqueous solution pH 5-9, dose deliverable 10 mg/day.

Unfortunately, drugs such as peptides, proteins and oligonucleotides are usually large, polar and/or charged, characteristics that normally preclude transdermal delivery. However, recent advances in physical enhancement technologies solve these problems.

These methods employed for increasing transport of drug molecules across the skin use some form of mechanical, electrical, magnetic or thermal energy source to promote transport of macromolecules by disrupting the skin membrane. With these new technologies the number of drugs potentially useful for transdermal administration has greatly increased, and restrictions related to molecular weight, particle size, dosage, pH, etc. have been reduced.

Examples of physical approaches include the use of iontophoresis, electroporation, sonoporation, high velocity particles, ultrasound, electric current, abrasion, lasers, pressure waves, magnetophoresis and thermophoresis [100].

Other modern methods for skin barrier breaching are micro-scale devices for transdermal macromolecular delivery: liquid jet injectors, powder injectors, microneedles, and thermal microablation [101].

Some of the obstacles in transdermal physical enhancers can be overcome by combining with other physical enhancement techniques for the delivery of macromolecules [102, 103].

Similarly to transdermal, application studies on the mucosa physical enhancers improve the absorption of drugs, e.g. permeation of naltrexone on buccal mucosa was evaluated in presence of chemical enhancers or iontophoresis. No significant differences in penetration rate were observed

using chemical enhancers; in contrast, J_s and K_p were extensively affected by application of electric fields [104].

A particularly interesting perspective is the application of various physical methods used for gene delivery [105].

Finally, note that some of these methods as iontophoresis, can be used as an in-vivo model for studying physiologic mechanisms and on the analysis and interpretation of dose–response data [106].

5. Predicting transdermal and transbuccal delivery: In vitro - in vivo correlation

The main objective in the design and optimization of transdermal and transbuccal dosage forms lies in obtaining a good in vivo performance. Thus, one of the main challenges of biopharmaceutical research is finding a correlation between ex vivo, animal and human studies for prediction of percutaneous and transbuccal absorption in humans.

The permeability of oral mucosa and the efficacy of penetration enhancers have been investigated in numerous in vivo and in vitro models. Various types of diffusion cells, including continuous flow perfusion chambers, Franz cells and Grass-Sweetana cells, have been used to determine the permeability of oral mucosa [107]. Animal models generally are more available than human skin, but only rabbits and pigs have a non-keratinized mucosal lining similar to that in humans.

As for skin studies, several factors should be considered. The ideal model for in vitro permeation studies is the human skin. In this regard, skin from cadavers has approximately the same permeability as living skin, suggesting that the underlying tissues present little resistance to drug adsorption.

A wide range of animal models has been suggested as a suitable replacement for human skin and has been used to evaluate percutaneous permeation of molecules. However the most relevant animal model for human skin is the pig [108] and has less variability than the human skin model [109], also we can see that a synergistic mechanical and chemical on pig skin models exhibit similar permeabilities and pore radii, but the human skin models do not [110]. In fact, drug permeation through human skin at a selected skin site can vary from 46% to 66% among individuals [111]. Specifically, pig ear skin, which closely resembles human skin, is a candidate ex vivo alternative model for the investigation of xenobiotics penetration and metabolism. Also, due to its availability, skin of rodents (mice and rats) is commonly used in vitro and in vivo percutaneous permeation studies.

On the other hand several studies with frozen or fresh skin have been made, highlighting the similarities between the two procedures. However, in general, the results demonstrate that the permeability of the drugs across the skin depends on the storage condition, the length of storage, vehicle and the physicochemical properties of the drug under study [112-114].

To extrapolate the results obtained from experimentation with animal skin *in vitro* and *in vivo* to the human situation must be avoided unless scientific validation exists to show that this is appropriate for the given agent.

Cultured epithelial cell lines have also been developed as an *in vitro* model for studying drug transport and metabolism at biological barriers as well as to elucidate the possible mechanisms of action of penetration enhancers [115, 116]. However, the overall use of skin cultures is likely to be limited due to questionable performance as a barrier in skin permeation studies, as well as due to their cost and data reproducibility [117, 118].

In order to assess the potential of transdermal therapy have been developed some pharmacokinetic models which are based on the physicochemical properties of the penetrant. Most models have focused on the contributions of molecular size and the solubility in stratum corneum lipids. These models provide kinetic equations which allow calculation of the plasma levels achieved after a drug is applied transdermally and transbuccally. A database of *in vitro* skin permeability coefficient values has been consolidated and over 20 empirical equations have been published estimating permeability coefficients for chemicals penetrating the human skin from aqueous vehicles [119].

Plasma concentration time profiles for most of the transdermal and transbuccal systems are characterized in terms of AUC_{0-t} (area under the time concentration curve from time 0 to time t), $AUC_{0-\infty}$ (area under the time concentration curve from time 0 to infinity), C_{max} (maximal plasma drug concentration) and T_{max} (time to maximal plasma drug concentration). C_{max} provides a practical estimate of C_{ss} (plasma concentration at steady state) [120].

6. Conclusions

In many cases buccal and transdermal dose forms can obtain the same bioavailability as intravenous formulations without the disadvantages of this route of administration.

Despite the many advantages of the skin and oral mucosa as sites of drug delivery, only a few of drugs are currently in the market as transdermal delivery system (estradiol, ethinyl estradiol/levonorgestrol, ethinyl estradiol/norelgestromin, ethinyl estradiol/norethindrone, clonidine,

oxybutinin, fentanyl, methylphenidate, nicotine, nitroglycerin, selegiline, scopolamine, testosterone, rivastigmine and rotigotine).

Because the stratum corneum limits the amount of drug reaching the blood supply and unless the barrier function is reduced with a penetration enhancer it is unlikely that plasma levels above 100 ng/mL will be attained.

This paper explains why and how skin or oral mucosa preclude essentially any large molecules transport into body, the achievements of transdermal and transmucosal scientists and the new technologies for enhancement the dosage forms across these routes. In this way several physical, chemical and nanosystems methods have been investigated, which can only enhance the drug disposal in the skin and others however, could lead to therapeutic drug concentrations in the systemic circulation.

To face the design of these and others excipients, "in vitro" release studies will constitute an essential tool for its development. It also will let us know the dermal penetration values of drugs and the effectiveness of vehicles.

Therefore, in order to assess the potential of transdermal or transbuccal therapy, it is necessary the development of more experiences and new release vehicles for transdermal and transbuccal drugs.

Lastly it should be noted that other routes, such as nasal, ocular, pulmonary, rectal, and vaginal drug administration, have provided excellent opportunities for the delivery of a variety of compounds.

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