Research, Society and Development, v. 11, n. 6, e2411628700, 2022
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v11i6.28700

Drug delivery systems in oral and transdermal hormone therapies

Sistemas de liberação de medicamentos em terapias hormonais orais e transdérmicas

Sistemas de administración de fármacos en terapias hormonales orales y transdérmicas

Received: 03/31/2022 | Reviewed: 04/09/2022 | Accept: 04/13/2022 | Published: 04/18/2022

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Abstract
The purpose of any drug delivery system is to deliver appropriate therapeutic amounts of drugs to the body in order to achieve and maintain the desired concentration of the administered substance. The aim of this work to analyze innovations in drug delivery systems by oral and transdermal route by the pharmaceutical industry. It is integrative review of literature, analyzing studies in some databases such as in PubMed, SciELO and LILACS, with the descriptors: drug delivery systems, pharmaceutical industry, hormones, oral and transdermal. The papers selected for the study range from 2000 to 2021, excluding duplicate studies and those that were not related to the topic. The research initially identified 5360 studies, being 5336 of those papers excluded after the application of exclusion criteria. A greater number of studies with the descriptor hormones was observed, substantially greater in the range from 2006 to 2011. There was a greater predominance of transdermals than oral in which concerns selected studies. This information reinforces, therefore, the great advantage of treatments with these types of systems, as they improve the patient's therapy bringing an adequate cure or palliative. In addition, it is also noted that a greater incentive is needed to study these systems orally, providing new insulin therapies, for example, orally, bringing more adherence, without the routine stings.
Keywords: Drug delivery systems; Liposomes; Transdermal patch.

Resumo
O propósito de qualquer sistema de entrega de princípio ativo é ofertar as quantidades terapêuticas adequadas do fármaco no corpo para atingir e manter a concentração desejada da substância administrada. Este trabalho tem como objetivo analisar as inovações em sistemas de liberação de fármacos por via oral e transdérmica pela indústria farmacêutica. Trata-se de uma revisão da literatura integrativa, avaliando estudos pesquisados no PubMed, SciELO e LILACS, com os descritores: sistemas de liberação de fármacos, indústria farmacêutica, hormônios, oral e transdérmica. Foram utilizados artigos no corte de tempo de 2000 a 2021, excluídos estudos em duplicidade e os que não tinham relação com o tema. A pesquisa identificou inicialmente 5.360 estudos, sendo 5.336 desses artigos excluídos após a aplicação dos critérios de exclusão. Foi observado uma maior quantidade de estudos com o descritor hormônios, substancialmente maior na faixa de 2006 a 2011. Já de estudos selecionados, houve uma predominância maior de transdérmicos que oral. Tais informações reforçam, assim, a tamanha vantagem de tratamentos com esses tipos de sistemas, pois eles melhoram o tratamento o paciente, trazendo cura ou paliativo adequados. Além disso, se nota também que é necessário um maior incentivo a estudos desses sistemas por via oral, proporcionando novas terapias, por exemplo a administração de insulina por via oral, trazendo mais adesão, sem as administrações invasivas por meio de uma agulha.
Palavras-chave: Sistemas de liberação de medicamentos; Lipossomas; Adesivos transdérmicos.

Resumen
El propósito de cualquier sistema de administración de ingredientes activos es ofrecer las cantidades terapéuticas apropiadas del medicamento en el cuerpo para lograr y mantener la concentración deseada de la sustancia administrada. Este trabajo tiene como objetivo analizar las innovaciones en los sistemas de administración de fármacos orales y transdérmicos por parte de la industria farmacéutica. Esta es una revisión de la literatura integradora, evaluando estudios investigados en PubMed, SciELO y LILACS, con los descriptores: sistemas de liberación de fármacos, industria farmacéutica, hormonas, oral y transdérmica. Los artículos se utilizaron en el corte de tiempo de 2000 a 2021, excluyendo los estudios duplicados y aquellos que no estaban relacionados con el tema. La investigación identificó inicialmente 5360 estudios, siendo 5336 de esos artículos excluidos después de la aplicación de los criterios de exclusión. Se observó un mayor número de estudios con el descriptor hormonal, sustancialmente mayor en el rango de 2006 a 2011. A partir de los estudios seleccionados, hubo un mayor predominio de transdérmicos que orales. Dicha información refuerza así la ventaja de los tratamientos con este tipo de sistemas, porque mejoran el tratamiento del paciente, aportando una cura adecuada o paliativa. Además, también se observa que es necesario fomentar los estudios de estos sistemas por vía oral, proporcionando nuevas terapias, por ejemplo la administración de insulina por vía oral, aportando más apoyo, sin administraciones invasivas a través de una aguja.
Palabras clave: Sistemas de liberación de medicamentos; Liposomas; Parche transdérmico.

1. Introduction

Developing a safe and efficient drug delivery system is an objective of both the pharmaceutical industry and the pharmaceutical researcher (Zhang & Mao, 2017). The purpose of any active ingredient delivery system is to make the therapeutic quantities of an active ingredient available to the appropriate place in the body in order to promptly achieve and maintain the desired concentration of the administered substance. However, conventionally formulated drugs that use the systemic distribution mechanism may not meet these requirements and present many deficiencies, such as side effects in undirected cells and tissues, nonspecific toxicity and inability to accurately control dosage (Santini et al., 2000).

Controlled release systems that are based on the mediation of physical properties and environments offer advantages over their counterparts due to their non-invasivity and versatility in design and tuning. Thus, those systems can overcome many barriers of conventional drug delivery systems in order to increase the efficacy and targeting of the drug and decrease drug toxicity (Rodriguez-devora et al., 2012).

Most of the fundamental knowledge of controlled drug release, mainly orally and transdermal, was obtained between 1950 and 1980. However, the administration of oral medicines is the most convenient, contributing to the creation of c-release drugs controlled by this route, which continues to be developed (Yun et al., 2015).

Transdermal administration has obtained great attention due to the advantages over conventional oral dosage forms. In addition, transdermal administration can benefit from circumventing first-pass hepatic metabolism and factors that alter pharmacokinetics in the gastrointestinal tract, which may result in reduced absorption of hormones. Thus, this route of administration obtains significant gains regarding bioavailability and has risks and side effects associated with bioavailability reduction (Ching & Gupta, 2020).

On the other hand, in hormonal therapies, the continuous dosage of hormones induces the deregulation of hormone receptors in target cells that escape the usefulness of medications. Thus, controlled drug delivery systems through activation by external stimuli are of great applicability in the case of peptide hormones, such as insulin, calcitonin and human growth hormones (hGH) (Doostmohammadi et al., 2019).

Conventional drug administration has applicability characterized by limited efficacy, poor distribution and lack of selectivity. These limitations can be circumvented through the usability of controlled release systems (Wilczewska et al., 2012). Thus, the pharmaceutical industry taking advantage of controlled release systems can reduce drug toxicity, increase efficacy and achieve better dosage control. Therefore, it would optimize pharmacotherapeutic treatment, with the present study aiming to analyze innovations in drug delivery systems regarding both oral and transdermal hormone therapies by the pharmaceutical industry.

2. Methodology

The methodology adopted is based on an integrative type review of literature, which purpose was to synthesize a vast production of knowledge, providing reflections on the themes studied and gaps of knowledge that need to be filled (Sousa, Silva & Carvalho, 2010).

The study had as a guide question 'what is the role of the pharmaceutical industry in the innovations of oral and transdermal drug release system in hormonal treatments?' Since then, searches were conducted in bibliographic databases, *Scientific Electronic Library Online* (SciELO), *U.S. National Library of Medicine* (PUBMED) and Latin American and Caribbean Literature in Health Sciences (LILACS).

The boolean operator AND was used as a tool for the search of articles, which were correlated by the descriptors: Drug release systems AND new drugs AND hormones AND oral AND transdermal, all of them in English language. Those descriptors were chosen for a better specificity of studies and were analyzed in the basis of health descriptors (DeCS) of the VHL (Virtual Health Library).

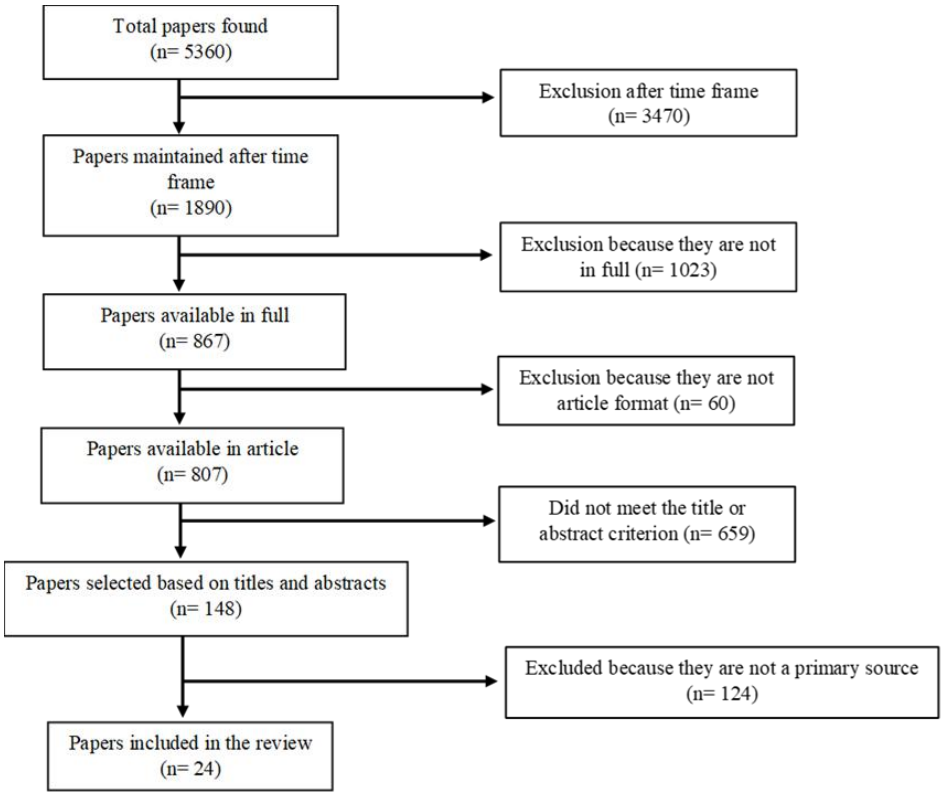
The inclusion criteria were online available primary source articles related to drug delivery systems, published between 2000 and 2021 written in English and Portuguese. In addition, parts of textbooks were included, as well as other review articles, bringing a more general overview of the discussion of the subject under study in this review.

Exclusion criteria were articles that were not related to the theme of the current work, articles published before 2000 and duplicate papers.

3. Results and Discussion

X The research initially identified 5360 studies, being 5336 of those papers excluded after the application of exclusion criteria (Figure 1).

Figure 1. Flowchart of the article selection process.



Source: Research data (2021).

The survey in the search engine of PubMed scientific articles results on the number of papers published in relation to the descriptors that were used, which were "drug delivery system", "pharmaceutical industry", "hormones", "oral" and "transdermal" (Table 1).

Table 1. Number of studies published in PubMed using the search engines "Drug release system", "New Drugs", "Hormones", "Oral", "Transdermal", in the last 20 years.

Descriptors	2000 to 2005	2006 to 2011	2012 to 2016	2017 to 2021	Total
Drug release system	20533	41655	52512	51828	166528
New drugs	12603	16450	17851	19962	66866
Hormones	206578	241327	222403	178673	848981
Oral	132634	181423	212034	223320	749411
Transdermal	7610	10057	10010	9136	36813

Source: Research data (2021).

A greater number of studies on hormones can be verified, being substantially higher from 2006 to 2011 in a pair with the other descriptors used in the research. In addition, it can be noted that studies on drug delivery systems have doubled, considering the years 2000 to 2005 and 2017 to 2021. On the other hand, studies on transdermal care reached levels little

beyond what was observed from 2006 to 2011 and 2012 to 2016, suggesting that studies with this type of system do not arouse a greater interest of researchers.

Regarding the detailed reading of the studies, 24 articles were selected because they met all previously established criteria. Thus, the discussion and analysis of the results were performed, presenting general characteristics such as author and year of publication, title of the study, type of release system used (oral or transdermal) and which pharmaceutical form used (Chart 1).

Chart 1. Overview of selected studies.

Reference	**Title of the study**	**System type**	**Therapy**	**Pharmaceutical form**
Morishita et al., 2006.	Novel oral insulin delivery systems based on complexation polymer hydrogels: Single and multiple administration studies in type 1 and 2 diabetic rats	Oral	Insulintherapy	Hydrogels
Araújo; Pinto; Braga; Paula, 2003.	Formulações de Anestésicos Locais de Liberação Controlada: Aplicações Terapêuticas	Transdermal	Local anesthetics	Liposomes
Morishita et al., 2002.	Elucidation of the mechanism of incorporation of insulin in controlled release systems based on complexation polymers	Oral	Insulintherapy	Gel microparticles
Santos; Castanho, 2002.	Lipossomas: a bala mágica acertou?	*	*	Liposomes
Jain; Panda; Majumdar, 2004.	Eudragit S100 Entrapped Insulin Microspheres for Oral Delivery	Oral	Insulintherapy	Microspheres
Silva et al., 2010.	Administração cutânea de fármacos: desafios e estratégias para o desenvolvimento de formulações transdérmicas	Transdermal	*	Transdermal patches
Habali et al., 2019.	Transdermal patches: Design and current approaches to painless drug delivery	Transdermal	*	*
Chorilli; Brizante, 2007.	Aspectos gerais em sistemas transdérmicos de liberação de fármacos	Transdermal	*	Transdermal patches

Chart 1. (Continuation).

Reference	**Title of the study**	**System type**	**Therapy**	**Pharmaceutical form**
Santos et al., 2011.	Influence of Rivastigmine transdermal on butyrylcholinesterase levels in patients with Alzheimer's disease	Transdermal	Cholinergic agent	Transdermal patches
Villanova; Oréfice; Cunha, 2010.	Aplicações Farmacêuticas de Polímeros	*	*	*
Lauretti et al., 2009.	Avaliação do efeito antinociceptivo do fentanil transdérmico no controle da dor lombar pós-operatória	Transdermal	Antinociceptivo	Transdermal patches
Yun; Lee; Park, 2015.	Controlled Drug Delivery: Historical perspective for the next generation	*	*	*
Marwah, et al, 2014.	Permeation enhancer strategies in transdermal drug delivery	Transdermal	*	*
Devora, et al, 2012.	Physically facilitating drug-delivery systems	*	Oncology	Nanomoléculas
Wilczewska, et, 2012.	Nanoparticles as drug delivery systems	*	Oncology	Liposomes
Alyautdin, et al, 2014.	Nanoscale drug delivery systems and the blood–brain barrier	*	Central nervous system	nanocarreador and liposomes

Chart 1. (Continuation).

Reference	**Title of the study**	**System type**	**Therapy**	**Pharmaceutical form**
Regenthal, et al, 2018.	Pharmacokinetic evaluation of a transdermal anastrozole-in-adhesive formula	Transdermal	Hormone-sensitive	Transdermal release
Department, et al, 2013.	SMART Drug Delivery Systems: Back to the Future vs. Clinical Reality	*	Oncology	liposomes, polymers, micelles
Abramson, et al. 2019	A luminal unfolding microneedle injector for oral delivery of macromolecules	Oral	Insulintherapy	ingestible capsule
Massaro, et al, 2018.	Halloysite nanotubes for efficient loading, stabilization and controlled release of insulin	Oral	Insulintherapy	Halloysite nanotubes for insulin
Takeuchi, et al, 2017.	Estradiol-loaded PLGA nanoparticles for improving low bone mineral density of cancellous bone caused by osteoporosis:	Transdermal	Osteoporosis	PLGA poli nanoparticles
Shah, et al, 2021.	Nanostructured Non-Ionic Surfactant Carrier-Based Gel for Topical Delivery of Desoximetasone	Transdermal	cutaneous psoriasis	Topical deoxymethasone gel
Rajabalaya, et al, 2017.	Oral and transdermal drug delivery systems: role of lipid-based lyotropic	Oral	*	Lipid-based liotropic liquid crystals
Ng; Guptaa, 2019.	Transdermal drug delivery systems in diabetes management: A review	transdermal	Insulintherapy	Transdermal patches

* Not identified in manuscripts. Source: Research data (2021).

The analyses of the articles make evident a greater number of studies transdermal than orally, especially in the forms of transdermal patches, making evident the difficulty of developing oral drug delivery systems.

3.1 Drug delivery systems - General aspects

As it can be seen through the analysis of the selected articles, release systems were found in adhesive forms, in liposome, micro and nanoneedles formats, in which they provide a controlled release in the gastrointestinal system of such system active ingredients.

Controlled drug delivery systems solve active-principle physical-chemical problems, providing new therapeutic forms and new treatments for diseases. The prosperous future of active principles in delivery systems depends on whether the new delivery systems can exceed the limits set by humans the physiology and development process can be accelerated with new ways of thinking (Yun et al., 2015).

Innovations in drug delivery systems can be improved with the application of polymers, a class of materials quite correct for use in manipulations, that serves as an alternative to assist in the treatment of diseases (Rodriguez-Devora et al., 2012; Villanova et al., 2010).

Current advances in nanotechnology have rekindled interest in drug distribution. Therefore, the alternatives of new research in controlled drug delivery systems occur with a more rational approach, bringing good perspectives for new forms of the delivery of drugs into biological systems (Lammers, 2013).

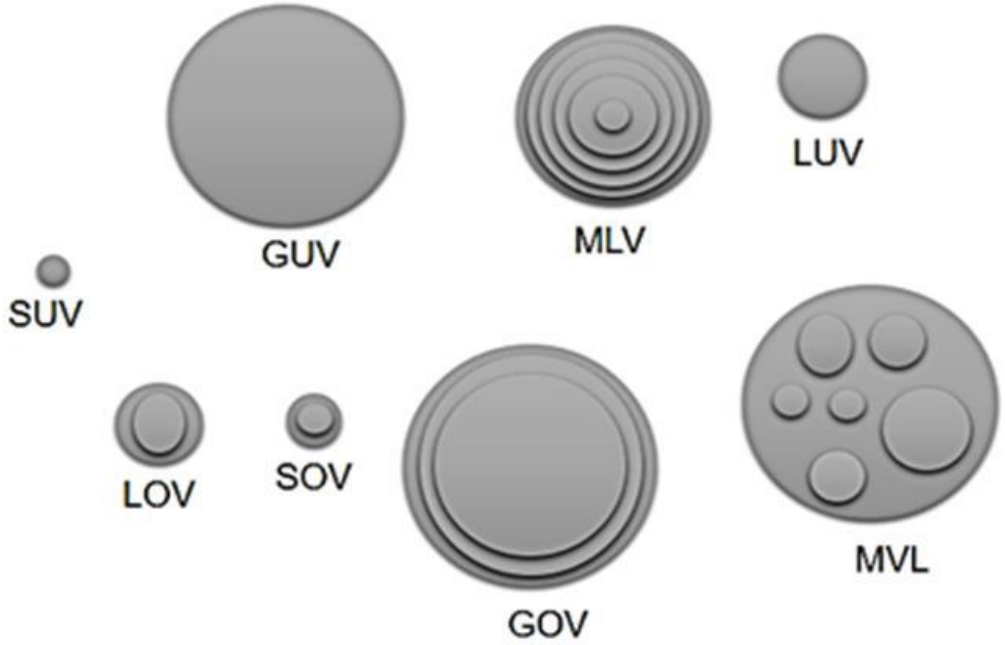
Oral and transdermal forms of controlled drug release are one of the most viable alternatives for therapy, providing more constant plasma levels of active ingredients with targeted release at the site of action, in addition of reducing toxicity and undesirable side effects (Rajabalaya et al., 2017).

3.2 Oral use systems

Articles that reported the aspects of oral drug release mentioned controlled release systems in nanoparticle or microparticulate formats, liposomes, which makes it worth noting that these systems orally try, as much as possible, to resemble the plasma membrane of cells, having the intention of providing a more effective absorption of the active ingredient used.

Being a widely used system, liposomes are structures formed by one or more concentric phospholipid bilayers, organized around an internal aqueous compartment. They may perform the function of drug carriers, biomolecules or diagnostic agents. There are several types of liposomes, some such as multilamelar vesicles (MVL), composed of several lipid bilayers, in addition to large unilamelar vesicles (UVL) and small vesicles (SUV), as well as giant unilamelars vesicles (GUV) and medium unilamelar vesicles (MUV). We also have multivesiculars (MVL) and oligolamelar vesicles (OLV) that have similarities with the unilamelar vesicles, and can be subdivided into small, large and giant (SOV, LOV and GOV) (Figure 2) (Santos & Castanho, 2002).

Figure 2. Liposome structures.



Schematic representation of liposome types. (SUV) small unilamelar vesicles. (GUV) giant unilamelar vesicles. (MLV) multilamelar vesicles. (LUV) large unilamelar vesicles. (LOV) large oligolamelar vesicles. (SOV) small oligolamelar vesicles. (GOV) multivesicular giant oligolamelar vesicles (MVL). Source: Adapted from Santos e Castanho (2002).

Several nanostructures, including polymer liposomes, dendrorors, silicon or carbon materials, and magnetic nanoparticles, have been tested as transporters in drug delivery systems. All of them provide a better specificity of the active ingredient used, bringing modern forms of therapy, especially when there is a therapeutic and toxic range nearby. Numerous polymers are used for these systems, such as poly (lactic acid) (PLA), poly (lactic acid-co-glycolic acid) (PLGA), poly (ε-caprolactone) (PCL) and also the copolymers of methacrylic acid and an acrylic or methacrylic terster (Wilczewska et al., 2012).

An alternative for the treatment of diabetes comes from oral administration, through drug-releasing systems such as hydrogels, microspheres, nanotubes and other forms of using, for example, complex polymers, All of these forms are somewhat innovative as, for several times, there have been studied alternative methods of oral administration of insulin, which can have as a hindrance the size of the molecule. These release systems are promising for such type of administration (Morishita et al., 2006; Jain, Panda & Majumdar, 2005; Morishita et al., 2002; Massaro et al., 2018).

Drug delivery systems appear as an alternative for molecules to pass through the blood-brain barrier (BHE) and exert their pharmacological activity. Systems such as nanocarriers and liposomes are used to pass drugs through BHE due to their lipophilic properties to cross the barrier (Alyautdin et al., 2014).

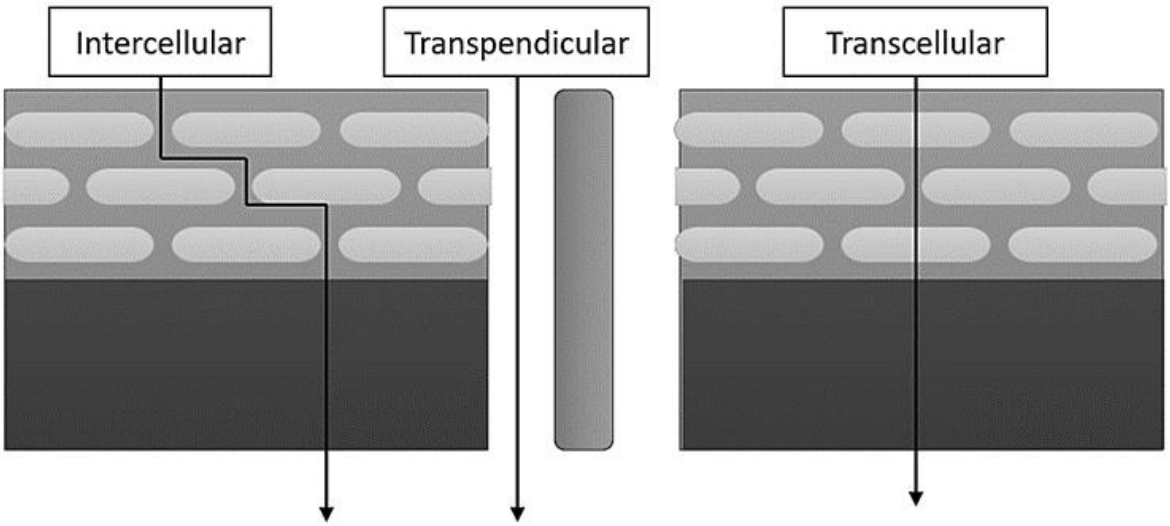
Nanoparticles are also used for the treatment of bone disorders, having the use of estradiol, through nanoparticle system with PLGA, presented a significant improvement in bone density in vivo assays, and being these relevant data acquired through the controlled release of drugs in the biological system (Takeuchi et al., 2017).

A studied system that proves to be quite interesting for the delivery of macromolecules are luminal-releasing microneedles orally. This type of system can guarantee the administration of active ingredients with large molecular chains, which prevent them from being used orally. This way, insulin and some drugs are administered intravenously, and may bring better treatment support (Abramson et al., 2019).

3.3 Transdermal systems

The mechanisms of permeation of drugs by the skin can be divided into transcellular (between the stratum corneum), intercellular (by stratum corneum) and transpendicular (by follicles and glands) (Figure 3) (Chorilli et al., 2007).

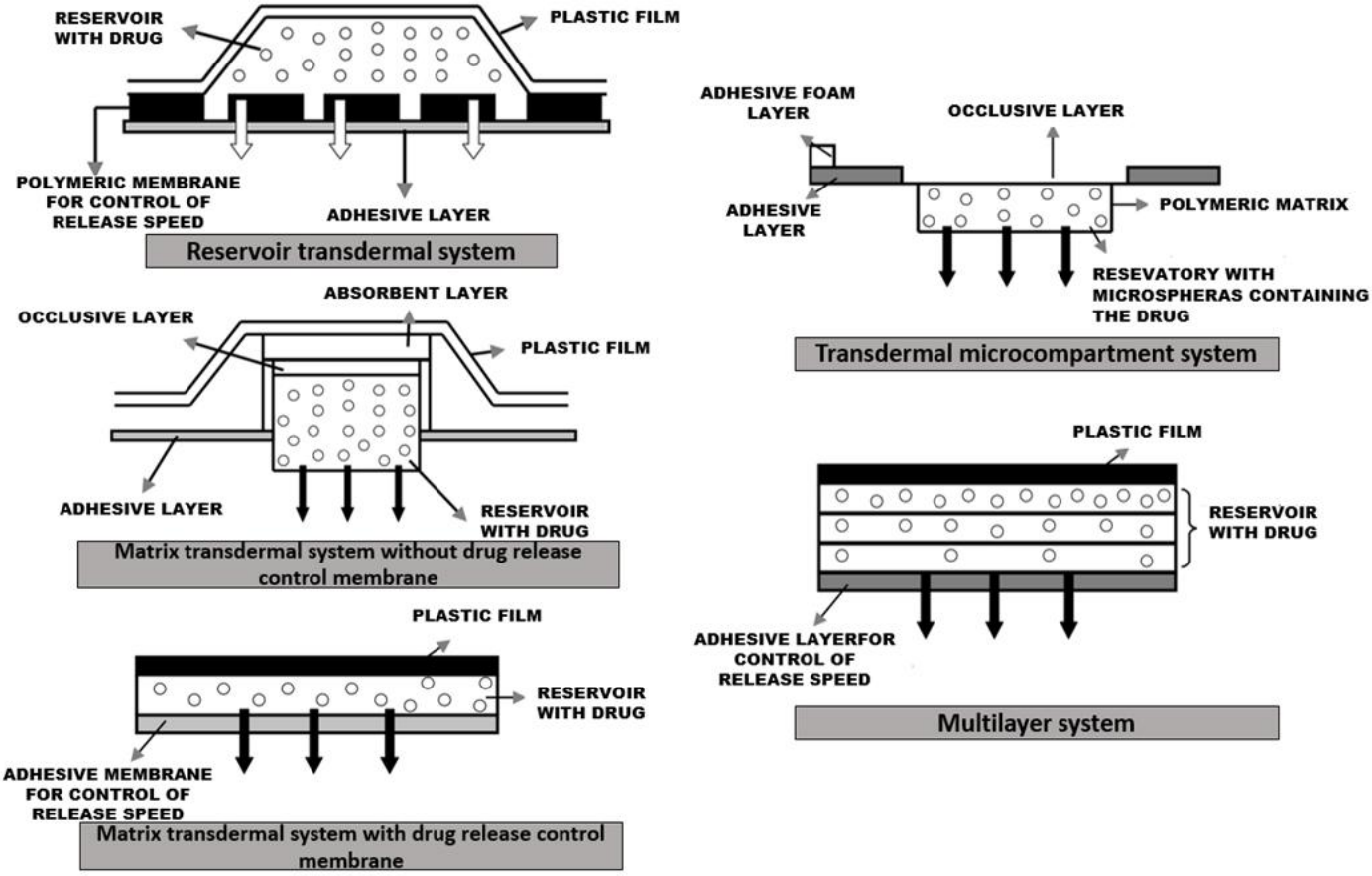
Figure 3. Permeation of drugs on the skin.



Source: Adapted from Chorilliet al. (2007).

There are two basic types of transdermal release systems: those that control the speed of drug release to the skin (reservoir system) and those that allow the skin to control the absorption speed (matrix system without controlling membrane and membrane). In addition, microcompartment and multi-layer systems (Figure 4) (Chorilli et al., 2007).

Figure 4. Types of transdermal adhesive systems.



Source: Adapted from Chorilli et al. (2007).

3.4 Transdermal patches

Development of formulation for the skin is an interesting transport strategy. The effect is the skin remedy itself, which represents alternative ways to overcome unnecessary aspects related to pharmacokinetic and pharmacodynamic characteristics of medications (Silva et al., 2010).

Such use of transdermal patches can prevent many problems related to oral medications, e.g.: first-pass hepatic metabolism, attacks of enzymatic digestion, hydrolysis of drugs and acid degradation, drug fluctuations and gastrointestinal irritation (Hanbali et al., 2019).

This pharmaceutical form has a simple, painless purpose and does not cause bleeding, having additional advantages such as ease of manufacture, distribution and elimination of drugs like nicotine patches (Silva et al., 2010).

3.5 Transdermal permeation

Ensure effective penetration through skin barriers is important for the development of this pharmaceutical form, as well as aspects such as concentration and nature of active ingredients, appropriate choice of excipients and the type of system that will be used to transport the drug (Silva et al., 2010).

These drugs present high hydrophilia when they are destined to permeation of the cutaneous pathway present difficulty in penetrating the stratum corneum, which will cause their retention. However, it is important that the drug presents a balance between its hydrophilia or lipophilia, having a partition coefficient between 1 and 3 (Silva et al., 2010).

Other chemical physical factors are relevant in transdermal administration such as molecular size, solubility, ionization and diffusion coefficient. However, it is important to emphasize the importance of considering the individual factors of each individual, as the physiology of each skin directly interferes with the permeation of the transdermal drug, such as young skins of newborns who have their surface slightly hydrophobic (Marwah et al., 2014).

3.6 Hormonal treatments of diseases

Diabetes mellitus is a chronic pathology that happens when the pancreas does not produce enough amounts of insulin. Its treatment is difficult due to the necessity of a continuous control of blood glucose. In order to do this, the patient uses oral tablets or administration of injectable insulin. The two forms of control treatment often present low patient adtake (Ching-ng & Gupta, 2020).

Though, transdermal systems can be used to optimize diabetes control treatment. Because they have advantages with greater bioavailability than the oral route due to the first-pass hepatic metabolization does not occurring, it is less invasive than intravenous methods, as well as it is painless, and, as a controlled release system, it reduces the dosage and frequency of application of this pharmaceutical form for a prolonged glucose control, thus improving treatment adhering (Ching-ng & Gupta, 2020).

Other disease treatments, such as postmenopausal hormone-sensitive breast cancer and chronic autoimmune skin psoriasis, have also greatly benefited from the new controlled drug delivery systems. For example, this type of breast cancer is treated with oral anastrozole and is often associated with serious side effects. However, this pharmaceutical innovation comes as a new treatment alternative for various diseases (Regenthal et al., 2018; Shah et al., 2021).

3.7 Medicines using new drug delivery systems already in the pharmaceutical Market

Table 2. Drugs in a controlled oral and transdermal release system available on the Market.

Drug	Pharmaceutical form	Trade name	Manufacturer	Use	Clinical use
Nicotine	Adhesive	Nicoderm/Nicontrol®	Marion Merrel Dow Parke-Davis	T	Tobacco addicts
Fentanyl	Adhesive	Duragesic®	Janssen Pharm	T	Severe pain
Scopolamine	Adhesive	Transderm-Scop®	Alza/Novartis	T	Feeling sick and severe cramps
Clonidine	Adhesive	Catapress TTS®	Alza Corp./Boehringer Ingelhein	T	Antihypertensive
Estradiol	Adhesive	Estraderm®	Alza Corp./Novartis	T	Estrogen deficiency
Diclofenac	Coated tablets	Biofenac®	Aché	O	Anti-inflammatory
Diltiazem Hydrochloride	Capsules containing pallets	Cardizem®	Baldacci	O	Angina pectoris vasospastic
Nphedipine	Pill medicine	Adalat®	Bayer	O	systemic arterial hypertension
Paroxetine hydrochloride	Coated tablets	Aropax®	GlaxoSmithKline	O	Depressive disorder
Lithium carbonate	Pill medicine	Carbolitium®	Eurofarma	O	Bipolar disorder

T = Transdermal. O = Oral. Source: Research data (2021).

4. Conclusion

It is evident that this field of research of the pharmaceutical industry is quite promising due to the periodic inclusion of new drugs that deliver the active principle in a release system capable of modulating its release in the pharmaceutical market. The new systems of controlled drug release have emerged to solve difficulties present in traditional drugs, improving pharmacokinetic properties for better treatment, decreasing side effects and increasing dosage accuracy, thereby improving patient's treatment of treatment.

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