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Technologies applied to prolong drug release: an integrative review

Tecnologias aplicadas para prolongar a liberação de fármacos: uma revisão integrativa

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A B S T R A C T

Extended-release systems have several advantages, such as greater availability of the drug in the bloodstream and fewer side effects, applying properly to drugs that have a short biological half-life, requiring a "means" for the drug to remain for an extended period, reaching its destination. The aim of this study was to show three technologies currently used in order to prolong the drug release/action. An integrative review was carried out, collecting articles from the following databases: BVS, Google Scholar, SciELO and PubMed, published in the last 10 years. Thus, the importance of these systems and their applicability was demonstrated, understanding the benefits for the patient, when using a drug with extended effect, since usually, it´s often necessary to ingest several doses, so that the therapeutic effect is obtained. It´s concluded that the implementation of these systems has satisfactory performance in relation to drugs that do not use these technologies, favoring the patient a better therapeutic effect, due to a more facilitated adherence.

R E S U M O

Os sistemas de liberação prolongada possuem diversas vantagens, como maior disponibilidade do fármaco na corrente sanguínea e menos efeitos colaterais, aplicando-se adequadamente a fármacos que possuem meia-vida biológica curta, sendo necessário um "meio" para que o fármaco permaneça por um período estendido, atingindo seu destino. O objetivo deste estudo foi mostrar três tecnologias utilizadas atualmente, a fim de prolongar a liberação/ação do fármaco. Foi realizada uma revisão integrativa, colhendo artigos das bases de dados: BVS, Google Scholar, SciELO e PubMed, publicado nos últimos 10 anos. Assim, foi demonstrada a importância desses sistemas e suas aplicabilidades, compreendendo os benefícios para o paciente, ao usar um medicamento com efeito estendido, já que usualmente, muitas vezes se faz necessário ingerir várias doses, para que o efeito terapêutico seja obtido. Conclui-se que a implementação desses sistemas possui desempenho satisfatório frente a medicamentos que não utilizam essas tecnologias, favorecendo ao paciente um efeito terapêutico melhor, devido a uma adesão mais facilitada.

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Introduction

The development of new drugs is not only limited to the discovery of new drugs, but also to the development of adequate delivery systems that have the function of making the drug available to the body, in a modified form, optimizing its therapeutic effect. This development is part of the broad scope of the pharmaceutical industry, as it aims at the introduction of new technologies in the market, allied to drugs already existing in the therapy, bringing advantages regarding the dosing regime, patient convenience, greater adherence to treatment, in addition to generating a greater added value to the final product (Kovalczuk, 2017).

Conventional drugs present an immediate release of the drug, generating a rapid increase in its blood concentration soon after its administration, presenting a subsequent decrease, according to the half-life of the active pharmaceutical ingredient. On the other hand, the controlled release presents a constancy in the release of the drug for a considerable time, when compared to conventional drugs, maintaining the therapeutic dose for a longer time range without the need to administer another dose (Nascimento, 2014).

For this reason, the technologies of controlled release of drugs represent one of the areas of science which involves different multidisciplinary aspects that can contribute greatly to the advancement of the same. The systems of controlled release of substances have been revolutionizing not only the pharmaceutical industry, but also the chemical industry (petroleum products, agribusiness and civil industry in the production of paints). Modern therapeutics is based on a rational design of controlled release and high specificity of compounds (Mirele et al., 2017).

Thus, the objective of this research was to present some of the modified drug delivery systems and the importance of these systems, which generate a reduction in the frequency of doses, increasing the effectiveness of the drug, reducing the required dose, providing constant serum concentrations of the active ingredient and minimizing adverse effects on the patient (Karna et al., 2015).

Methodology

The research was performed by integrative bibliographic review, based on data collection through full texts of journals, journals, books and dissertations, available in the databases BVS, Google Scholar, PubMed and SciELO, published in the last 10 years.

The following terms were used in the advanced search, using the Boolean operator OR: “System Drugs Delivery” OR “Drug Release Systems”, “Pharmaceutical Technology” OR “Pharmaceutical Technology”, “Drug Matrix Systems” OR “Matrix Drug System”, “Osmotic Pumps” OR “Osmotic Pumps”, “Drug Reservoir System” OR “Drug Reservoir System”. The results are shown in Table 1.

Table 1.

Number of articles found in the selected databases.

Keywords	SciELO	PubMed	BVS	Google Scholar
"Drug Delivery System" OR "Sistemas de Liberação de fármacos"	48	5,361	49,993	16,600
"Pharmaceutical Technology" OR "Tecnologia Farmacêutica"	7	7,443	4,833	8,070
"Drug Matrix Systems" OR "Sistema Matricial de Fármacos"	0	0	15	3
"Drugs Osmotics Pumps" OR "Bombas Osmóticas de Fármacos"	0	34	0	1
"Drug Reservoir System" OR "Sistema Reservatório de Fármacos"	3	1	1	21
Total articles found	58	12,839	54,842	24,695
Total articles analyzed	3	34	16	25

Source: The author (2022).

The first two terms of Table 1, used to perform the searches, were very nonspecific, generating a very large volume of material to be analyzed, in which most did not bring as the object of this research as a highlight, but only one of the terms described in some part of the text.

Thus, we chose to perform a better specificity of the terms, highlighted in blue in table 1, which generated a reasonable volume of material, with a better direction to the object of the research. After analysis, some articles were excluded from the research because they were not available in full text, required payment to have access to the content, had a central theme divergent from the object of this research, or were repeated in different databases.

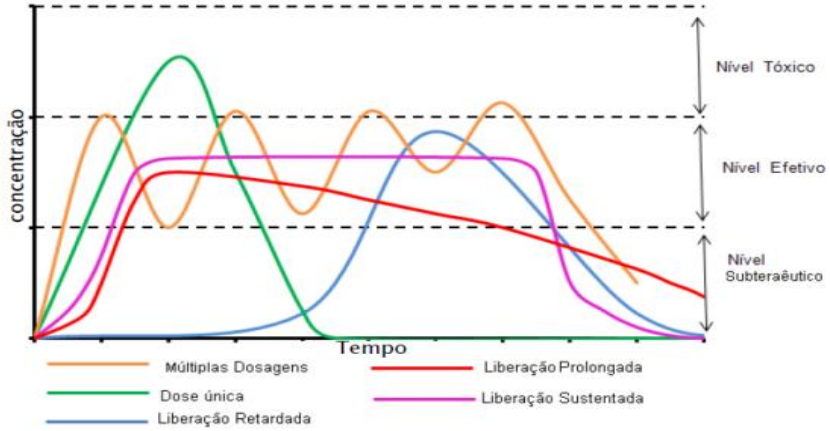
Results and Discussion

Modified release systems (SLM) are developed to make the drug available for a longer period of time within the therapeutic range, when compared to conventional systems. The use of SLM is important in some situations, because the concentration of the drug in the body can be influenced by the speed of release, absorption processes, biotransformation and elimination, and the appropriate technique allows fewer variations arising from these pharmacokinetic issues (Prista et al., 2014).

Through the modified release systems it´s possible to maintain the concentration of the drug in the body within the therapeutic range for a prolonged time, using a single dosage (Figure 1) (Moura, 2012).

Figure 1.

Plasma profiles of different forms of drug release.



Fonte: Albanez (2012).

In conventional formulations, the plasma concentration of the drug has a rapid increase when it´s administered, generating a peak of absorption, followed by a decrease until the next administration (Shaik et al., 2012). Thus, to maintain the concentration of the drug in the body within an effective therapeutic interval it´s necessary to administer it several times a day, resulting in a significant fluctuation of its levels in the body (Moura, 2012).

Thus, SLMs have the possibility of maximizing their therapeutic action, increasing treatment adherence, avoiding plasma drug fluctuations, reducing side effects, among others (Madhulatha; Naga, 2013).

Examples of systems used to prolong drug release:

The most commonly used technologies in modulation to prolong the release of drugs are: a) polymer matrix systems; b) osmotic pumps; c) reservoir systems.

A) Polymer matrix systems

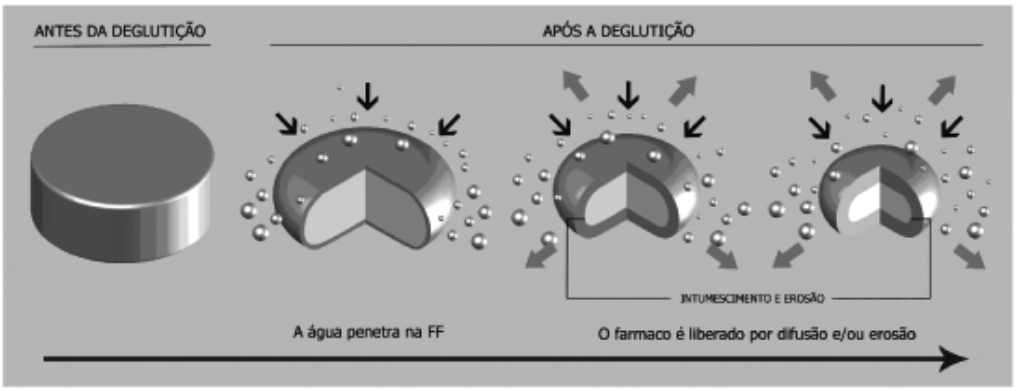
Hydrophilic polymer matrix systems are the most used to obtain pharmaceutical formulations intended for modified release due to their great versatility, efficacy, low cost and ease of production with conventional equipment and techniques, in addition to the possibility of incorporating considerably high amounts of drug (Nokhodchi et al., 2012).

A matrix system is a system that controls the release of drugs that are molecularly dispersed or dissolved in a disintegration-resistant support. The support in question can be a polymer or another matrix forming agent (Santos, 2018). Matrix systems can control the release of drugs through the processes of erosion, diffusion and swelling, (Figure 2)

and it´s often possible to coexist two or even of the three phenomena mentioned (Norkhodchi et al., 2012).

Figure 2.

Matrix system before and after swallowing.



Fonte: Pezzini (2007).

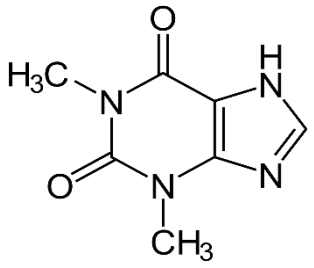
The release of drugs from hydrophilic matrix systems involves the steps of penetration of the dissolution fluid or biological fluid in the pharmaceutical form, dissolution of the drug in the matrix system, diffusion of the drug to the outside of the system and dissolution or erosion of the polymeric matrix (Lopes, 2016).

Once in the gastrointestinal tract, upon contact with biological fluids, the polymer existing on the surface of the pharmaceutical form is hydrated and swells. A gelled layer is then formed, which is later dissolved, until it undergoes erosion, giving rise to other layers or gelled fronts, which dissolve on the surface of the pharmaceutical form and, thus, the process is repeated successively. The drug is being released by diffusion from these layers and/or by erosion of the matrix system (Santos, 2018).

A study was conducted to verify the levels of release of the drug theophylline (Figure 3), using hydroxypropylmethylcellulose (HPMC); Water-soluble polymer widely used as a forming agent for hydrophilic matrix tablets, coupled with Guar Gum, which is a natural water-soluble polymer with an interest in the preparation of matrix tablets, due to its low cost, and its ability to form a diffusion barrier when swollen. The results showed that matrix tablets containing GG:HPMC showed better theophylline release control in 8 hours of dissolution assay (Oliveira et al., 2015).

Figure 3.

Structural formula of theophylline.

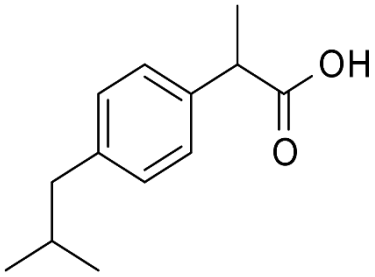


Fonte: Dreamstime (2022).

An evaluation of the ibuprofen release profile (IBF) (Figure 4) in the symmetrical membrane AC-AM10/IBF (cellulose acetate with the active ingredient ibuprofen incorporated) presented a continuous and slow release profile of the drug, with a high percentage of release. It took 28 hours to reach about 80% of IBF released and 56 hours to release almost 100% of the drug.

Figure 4.

Structural formula of Ibuprofen.



Fonte: Dreamstime (2022).

This amount of drug released and the release profile obtained can be explained in part by the morphology of this membrane of smaller pores (diameter of about 2 μm), flattened and more orderly, which make the access of the intestinal simulating fluid to the drug dispersed in the polymeric matrix easier (Ferreira et al., 2019).

This process of release of IBF occurs predominantly by diffusion/solution in the polymer matrix. The results showed that the interaction of the drug with the polymer and the

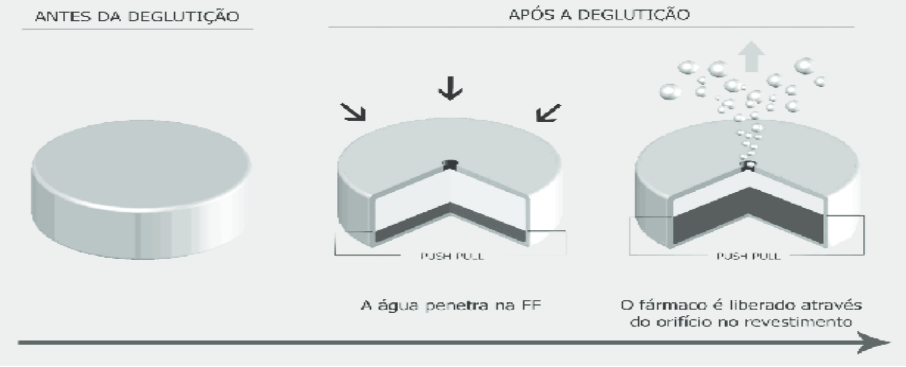
morphology of the membrane are important factors in the kinetic control of the drug release process, which culminated in significant changes in the release time and in the amount of drug retained, making the membranes viable candidates for application both in the treatment of chronic diseases, such as rheumatoid arthritis, as in the treatment of acute diseases, such as antipyretic or analgesic (Ferreira et al., 2019).

B) Osmotic pumps

Osmosis is the process that can control the delivery system of a drug by moving the solvent from the lowest concentration of the drug (gastrointestinal tract) to the highest concentration (internal medium of the formulation), by passing the solvent through a semipermeable membrane (Figure 5) (Kashmir et al., 2013).

Figura 5.

Osmotic pump system "push pull".



Fonte: Pezzini (2007).

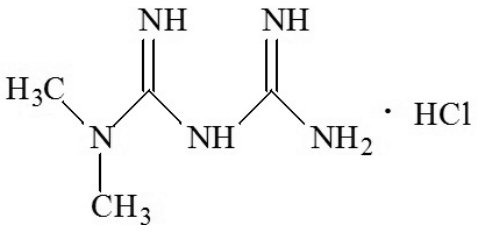
The osmotic pressure created inside the formulation regulates the release of the drug by the osmotic device. The rate of release of the drug from the osmotic pump is directly proportional to the osmotic pressure developed due to the soaking of fluids by the osmogen (Kashmir et al., 2013).

Osmotic pressure is a colligative property of a solution in which the magnitude of the osmotic pressure of the solution is independent of the number of discrete solute entities present in the solution. Therefore, the rate of drug release from osmotic release devices depends on solubility, molecular weight, and solute activity coefficient (osmogent) (Kashmir et al., 2013).

An in vitro study with one tablet of metformin hydrochloride (Figure 6) (MH) ($C_4H_{11}N_5$) and repaglinide (Figure 7), (RG) ($C_{27}H_{36}N_2O_4$) presented perfect multidrug therapeutic effect for diabetes type 2.

Figure 6.

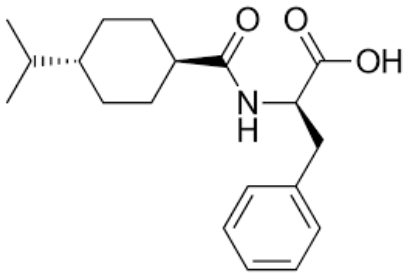
Structural formula of metformin.



Fonte: Wikipedia (2015).

Figure 7.

Structural formula of repaglinide.



Fonte: Wikipedia (2015).

However, due to the short half-life of the drugs, the tablet should be administered two to three times a day, causing inconvenience to the patient and fluctuations in plasma concentration. Thus, an osmotic pump tablet was developed to release both drugs simultaneously at a rate of order zero, in which MH and RG are carried in different layers of the formulation (Chao Qin, 2014).

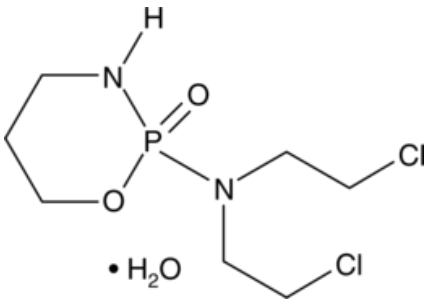
The osmotic pump tablet was prepared by a combination of three compression procedures and film coating method. The pharmacokinetic study was performed in beagle dogs and the concentration of the drug in the plasma samples was analyzed by high performance liquid chromatography/mass spectrum (HPLC-MS/MS). The simultaneous and controlled release of MH and GR in the first 8 to 12 hours was achieved from the optimized formulation. The authors of the research observed that significantly decreased Maximum Concentration

(Cmax), prolonged Maximum Time (Tmax) and satisfactory bioavailability of the osmotic pump tablet, and a good *in vivo – in vitro* correlation of the two drugs was also established. In summary, the osmotic pump tablet released MH and RG simultaneously at a zero order rate and exhibited a significant extended-release effect (Chao Qin, 2014).

Another study to prolong the release of the drug ketorolac tromethamine ($C_{15}H_{13}NO_3$), (Figure 8), used the osmotic pump system of controlled porosity to evaluate the bioavailability profile of this drug.

Figure 8.

Structural formula of tromethamine ketorolac.



Fonte: Interprise (2022).

Formulated by direct compression and coated with a membrane of leachable materials, the release of the drug was independent of pH and agitation intensity, but dependent on the osmotic pressure of the release medium. Based on the in vitro dissolution profile, the F3C1 formulation (containing 0.5g polyvinylpyrrolidone and 1g dibutylphthalate in the coating membrane) achieved a release of 93.67% of the drug in 12 hours and was therefore selected as the optimized formulation (Dasankoppa; Ningangowdar; Sholapur, 2013).

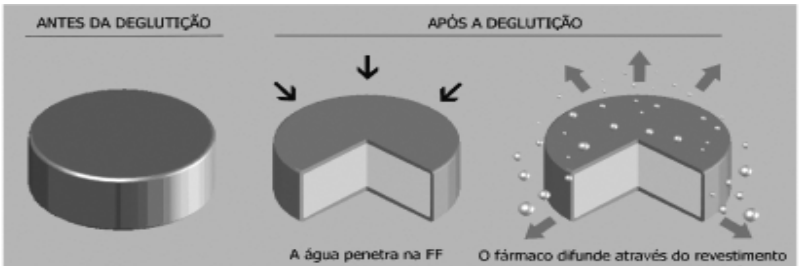
C) Reservoir systems

Precisely, ideal reservoir systems contain the drug dissolved in the central polymer, along with crystals of the same drug, which generates an immediate action capacity to a reservoir system (Siepmann; Siegel, 2012).

Once dissolved drug molecules diffuse across the membrane, the drug crystals dissolve in the central polymer and a constant gradient of drug concentration across the membrane is provided (Figure 9) (Koutsamanis et al., 2020).

Figure 9.

Membrane-coated reservoir system.



Fonte: Pezzini (2007).

Thus, the constant release of the drug is achieved over several weeks (Brache; Paýan; Faundes, 2013), months (Jhonson et al., 2012), even years (Sivin et al, 2005). This makes reservoir systems more desirable for medium and long-term administration to specific regions of the body, such as the vagina, uterus, or eye (Koutsamanis et al., 2020).

Koutsamanis et al. (2020) investigated *in vitro* the behavior of the formulation intravaginal ring with progesterone release, using ethylene-vinyl acetate as controlling polymer, obtaining satisfactory results. Based on the results observed, the rate of drug release was adjusted according to the variation of membrane thickness; increased progesterone release was achieved through a combination of diffusivity between the membrane and the nucleus, where high rates of progesterone release were obtained from the system, providing a controlled long-term release.

Final considerations

In view of the above, we can conclude that medicine users usually use repeated doses to maintain the concentration of the drug in the body for the desired purpose, which may cause difficulties in adherence during therapy. The studies found in the literature have shown that there are advantages of SLM in relation to conventional drugs, due to the applicability of these systems for a better prolongation of the release/action of the drugs, aiming at a therapeutic improvement, thus avoiding frequent doses and occurrences of adverse effects. In this context, this work has the perspective of exposing trends in the pharmaceutical market in the coming years, in terms of drug release. Where conventional excipients are increasingly giving way to functional excipients, with the ability to modulate the release of drugs.

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