Disciplinarum Scientia. Série: Naturais e Tecnológicas, Santa Maria, v. 18, n. 3, p. 545-566, 2017.
Recebido em: 21.08.2017. Aprovado em: 18.10.2017.

ISSN 2176-462X

CATIONIC NANOCAPSULES CONTAINING EUDRAGIT RS100® AND ITS POTENTIAL FOR APPLICATION IN NANOMEDICINE[1]

NANOCÁPSULAS CATIÔNICAS CONTENDO EUDRAGIT RS100® E SEU POTENCIAL PARA APLICAÇÃO NA NANOMEDICINA

Ana Júlia Figueiró Dalcin[2], Aline Ferreira Ourique[3] and Patrícia Gomes[4]

ABSTRACT

Cationic nanocapsules produced with the Eudragit RS100® polymer have received great prominence due to their advantages of mucoadhesion, sustained release of drugs and protection against UV radiation. Its use allows application by several routes of administration, proving to be a beneficial drug delivery system with the potential to be explored by nanomedicine. This review aims to provide a comprehensive, updated and detailed state of the art overview relating to the drug delivery advantages of cationic nanocapsules produced with the Eudragit RS100® polymer as well as its use in improving biological effects by different routes of administration. Promising results highlight the use of cationic nanocapsules as versatile drug carrier systems for use in different therapeutic applications.

Keywords: drug delivery, mucoadhesion, polymer nanoparticles, polymers, sustained release.

RESUMO

Nanocápsulas catiônicas produzidas com o polímero Eudragit RS100® têm recebido grande destaque devido suas vantagens de *mucoadesão, liberação sustentada de* fármacos *e proteção frente* às *radiaçõe*s *UV. Sua utilização permite aplicação por diversas vias de administração demostrando ser um benéfico sistema de entrega de fármacos com potencial a ser explorado pela nanomedicina. Esta revisão tem por objetivo fornecer uma visão geral, abrangente e atualizada do estado da arte relacionando às vantagens da entrega de fármacos por nanocápsulas poliméricas catiônicas produzidas com o polímero Eudragit RS100® bem como sua utilização na melhoria dos efeitos biológicos por diferentes vias de administração. Os resultados promissores evidenciam a utilização de nanocápsulas catiônicas como versáteis sistemas carreadores de fármacos com utiliza*ção *para diferentes aplicações terapêuticas.*

Palavras-chave: *entrega de fármacos, liberação sustentada, mucoadesão nanopartículas poliméricas, polímeros.*

[1] Review Article.

[2] PhD Student. Postgraduate Program in Nanosciences - Centro Universitário Franciscano. E-mail: anajuliadalcin@hotmail.com

[3] Co-advisor. Postgraduate Program in Nanosciences - Centro Universitário Franciscano. E-mail: alineourique@gmail.com

[4] Advisor. Postgraduate Program in Nanosciences - Centro Universitário Franciscano. E-mail: patriciagomes@unifra.br

INTRODUCTION

The nanoencapsulation of drugs is a strategy that is being reported for successful delivery of several drugs resulting in increased solubility, protection against toxicity, increased pharmacological activity and stability, sustained release, physical protection and protection against chemical degradation (FRANK et al., 2015; SANTOS et al., 2015; SARAF, 2010). The application of nanotechnology has the potential to alter conventional systems, allowing controlled release and target-specific delivery, resulting in improved absorption and biological activities (WANG et al., 2016).

Among the different types of nanostructures are polymeric nanoparticles, which have attracted more attention from the researchers and have been developed for a larger number of therapeutic applications and are planned for different routes of administration (BREGOLI et al., 2016; CRUCHO; BARROS, 2017; MALI; BATHE, 2015; MORA-HUERTAS; FESSI; ELAISSARI, 2010).

Cationic nanocapsules produced with the Eudragit RS100® polymer have received increased attention due to their advantages of mucoadhesion and sustained release of the drug, as well, the improvement of the different biological activities that include analgesic, antifungal, anti-inflammatory, photoprotection and other effects (CHAVES et al., 2017; CONTRI et al., 2016; CORTESI et al., 2012; ; EIDI et al., 2010; GAREKANIA; MOGHADDAM; SADEGHIC, 2013; GUPTA et al., 2013; JANA et al., 2014; LAMPRECHT et al., 2006; PECORA et al., 2016). Their applications may be reported by different routes of administration including ophthalmic (KATZER et al., 2014), nasal (SEREMETA; CHIAPPETTA; SOSNIK, 2013), oral (YOUNIS et al., 2016), sublingual (CHAVES et al., 2017), topical (CONTRI et al., 2015) and vaginal (GUPTA et al., 2013).

This article aims to describe a comprehensive, updated and detailed state of the art overview referring to the studies that have been carried out with different drugs associated with cationic nanocapsules containing the Eudragit RS100® polymer, as well as to address the administration routes for which these nanocapsules are being studied, their characteristics and their advantages. For this, a detailed bibliographic survey was carried out on the subject, based on scientific articles published in different periodicals.

NANOCARRIERS

The encapsulation of drugs is a possibility that has been studied by different areas of science in order to monitor, control, construct, repair, defend and improve human biological systems, working from the molecular level. The exploration of matter at the nanoscale opens a wide field of investigation and application that allows to investigate the physical properties different from those observed in micro or macro scale, due to the proportion in volume of particles that become much larger when the size is

reduced, so that, the nanoparticles have a large surface for chemical interactions with biomolecules (BOISSEAU; LOUBATO, 2011; SIA, 2017).

Materials or nanomaterials, with nanostructures in at least one of their dimensions, have showed satisfactory properties. Its applications have been established especially in the medical and pharmaceutical area, with the development of new pharmaceutical forms (MALI; BATHE, 2015; PUTHETI et al., 2008; WENG et al., 2017).

The use of nanostructures that perform different properties, optimize the release characteristics of the incorporated drugs (MALI; BATHE, 2015; PUTHETI et al., 2008; WENG et al., 2017).

With the use of nanotechnology, doses and the incidence of adverse effects can be reduced, as well as promoting the prolonged release of the drug at its place of action, increasing the interval between doses applied and obtaining the targeting of the drug to diseased tissues with the simultaneous protection of healthy tissues. These drug delivery systems can easily interact with biomolecules located on the surface of the cells or inside (ASLAM, 2008; BOISSEAU, LOUBATO, 2011; MALI; BATHE, 2015).

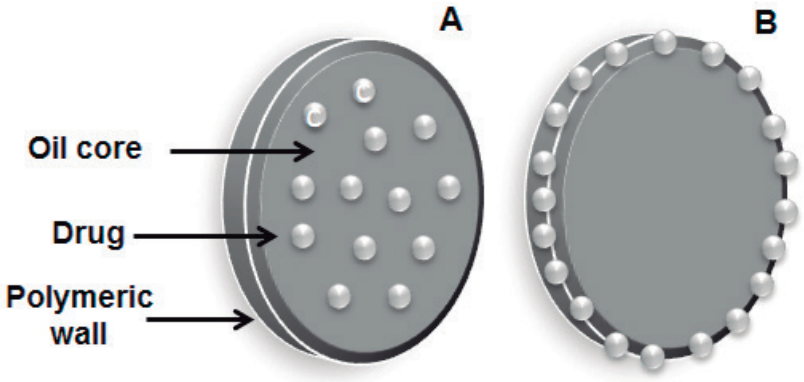
Many compounds including quercetin, genistein, naringin, piperine, capsaicin, eugenol, flavonoids, terpenoids, tannins and xanthones when administered through nanostructured systems have demonstrated a better absorption profile that allows them to cross the biological membrane, resulting in improved bioavailability at a lower dose with potentiated and prolonged therapeutic action (CONTRI et al., 2011; ESFANJANI; JAFARI, 2016; GIONGO et al., 2016; KESARWANI; GUPTA, 2013; LUONG et al., 2016; SARAF, 2010).

NANOCAPSULES

Among the different types of nanostructures are polymeric nanoparticles, the term polymer nanoparticles includes nanocapsules and nanospheres, which differ according to composition and structural organization. Nanocapsules (Figure 1) are defined by vesicular structures consisting of a thin polymeric wall and a normally oily central cavity, where the active substance may be dissolved. Due to this, it is considered a reservoir system, which has a submicron diameter of less than 1 μm, typically between 200-400 nm. The active component may be dissolved in the oily central cavity or may adsorb to the polymer wall (MALI; BATHE 2015; MORA-HUERTAS; FESSI; ELAISSARI, 2010; SOPPIMATH et al., 2001; SCHAFFAZICK et al., 2003).

In general, nanocapsules are composed of the drug, polymer, oil, surfactant and water and can be produced by different methods with narrow-size distributions having diameters smaller than 1 μm. The nanometric size provides greater surface area, and this feature is strongly correlated with their biological responses (FRANK et al., 2015).

Figure 1 - Schematic representation of nanocapsules: A) Drug dissolved in the oily nucleus of the nanocapsules; B) Drug adsorbed to the polymeric wall of the nanocapsules.



Polymeric nanoparticles have attracted increased attention from researchers due to their bioavailability, biodegradability, drug photostability, to modulate cell and tissue interaction, reduce drug adverse effects, increased encapsulation efficiency, increased solubility, reduced doses, stability in biological fluids and during storage (FRANK et al., 2015; MALI; BATHE, 2015; MORA-HUERTAS; FESSI; ELAISSARI, 2010; SARAF, 2010; SCHAFFAZICK et al., 2003; SOPPIMATH et al., 2001).

Nanocapsules are generally produced in aqueous media as a cloudy colloidal solution. This opalescent solution can be used as the final product or it can be incorporated into gels or converted into powder to facilitate its applications (FRANK et al., 2015).

As stated by different authors, these nanoparticulate materials show potential for a wide range of applications, such as drug diagnosis and delivery (BREGOLI et al., 2016; CRUCHO; BARROS, 2017; MALI; BATHE, 2015) and have been developed for a large number of therapeutic applications, and are mainly designed for parenteral, intradermal, pulmonary, nasal, oral or ophthalmic administration (BULCÃO et al., 2014; FLORINDO et al., 2009; HORIGUCHI et al., 2014; MALI; BATHE, 2015; SCHAFFAZICK et al., 2003).

The nanocapsules can be produced with natural or synthetic polymers and can be used to nanocapsulate drugs and bioactive compounds (SANTOS et al., 2016). In addition, the polymers have the purpose of protecting the lipophilic nucleus and controlling the release of drugs lipophilic (OLIVEIRA et al., 2017). Thus, the choice of the polymer is of great importance for achieving specific purposes and modulate the particulate release and degradation characteristics (MALI; BATHE, 2015; SANTOS et al., 2016).

POLYMERS

The polymers are widely used in the pharmaceutical industry for the administration of drugs, and they differ due to their natural or synthetic origin, the synthetic ones having the greatest advan-

tages by the capacity of adaptations through modifications of their properties during the synthesis process (LU; CHEN, 2004).

The purpose of the polymers is to protect the drug from degradation or metabolism, thereby promoting sustained release of the drug, maintaining plasma concentrations at therapeutic levels for certain periods of time, being of great importance in the control of drug release (CHAMPION; KATARE; MITRAGOTRI, 2007; FRANK et al., 2015; NIKAM et al., 2011). In this sense, maintaining concentration within a desired range may provide fewer administrations and better patient adherence to pharmacological treatment (NIKAM et al., 2011).

EUDRAGIT®

Eudragit® comprises a series of biocompatible copolymers used primarily for the coating of solid formulations and in the development and engineering of fabrics (LOPEDOTA et al., 2009; SEREMETA; CHIAPPETTA; SOSNIK, 2013). These polymers are classified as special and have different types and varying solubility characteristics (KIBBE, 2000; NIKAM et al., 2011).

The first Eudragit® were developed in 1953 and had alkaline solubility and thus were resistant to acidity of the stomach. The active substances were not released in the stomach, but in the intestine, where they should be activated. Eudragit® derivatives of this type are still used to coat solid medicaments for oral administration, such as tablets, capsules or granules (NIKAM et al., 2011).

In the late 1950s improvements were made and the Eudragit® came to possess characteristics of acid dissolution. Subsequently, other varieties became available, so as to allow the control in which the substances are released. These are resistant to stomach acid or intestinal alkalinity, greatly increasing the efficiency of certain therapies and applications (NIKAM et al., 2011).

The basis of the Eudragit® polymers are poly (meth) acrylates for pharmaceutical applications (NIKAM et al., 2011). And its use is generally considered non-toxic and non-irritant. A daily intake of 2 mg / kg body weight in humans is considered essentially safe and is included in the Food and Drug Administration (FDA), item capsules and oral tablets, as non-parenteral drugs licensed in the United Kingdom, and in the Canadian list of non-medicinal acceptable ingredients (PATRA et al., 2017). In addition, Eudragit® has been accepted by the regulatory agencies of the United States, Europe and Japan for oral and topical administration (EIDI et al., 2010; HOFFART et al., 2006).

Eudragit® are copolymers derived from esters of acrylic and methacrylic acid, and their physicochemical properties are determined by functional groups (R). They are available in a wide variety of different physical forms (aqueous dispersion, granules and powders) (EVONIK, 2012; NIKAM et al., 2011).

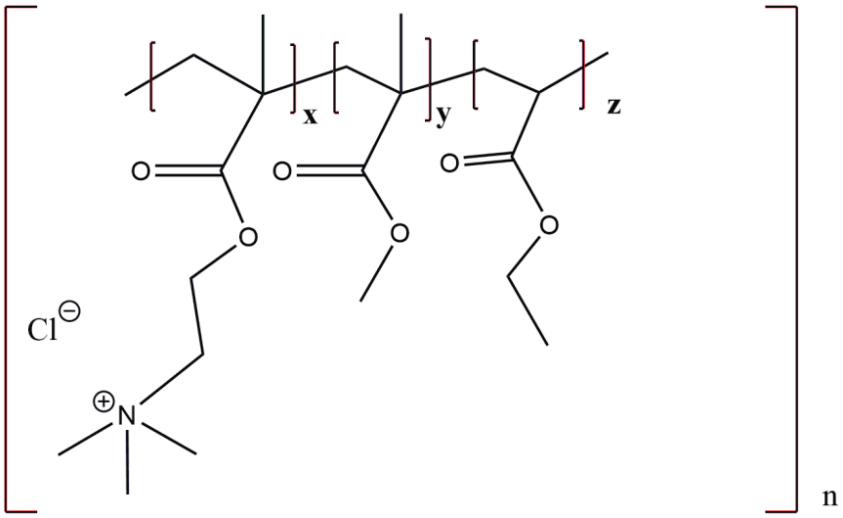
Further to the advantages of releasing the drug at the appropriate time and place other important functions performed by Eudragit® are moisture protection and / or taste/odor masking to increase patient compliance (JOSHI, 2013; NIKAM et al., 2011).

Although these copolymers are not biodegradable, several research groups using Eudragit® for parenteral drug administration report good biocompatibility of this biomaterial also by these routes (SCHAFFAZICK et al., 2008; ZAGO et al., 2013) Due to the rapid clearance of the systemic circulation by the mononuclear phagocytic system and its deposition in the liver (ROLLAND et al., 1989). Among the main ones, Eudragit ® products of the types E, L, S, RL and RS (KIBBE, 2000) are the most commonly used in pharmaceutical practice.

EUDRAGIT RS100®

Eudragit RS100® (Figure 2) is a positively charged polymer which has wide use due of its well established mucoadhesive characteristics. This copolymer is comprised of ethylacrylate, methylmethacrylate and a low methacrylic acid ester content with about 4.5 to 6.8% quaternary ammonium groups (trimethylammonioethyl methacrylate chloride). Ammonium groups are present in the form of salts and are responsible for the permeability of the polymer. The molar ratio of ethyl acrylate, methyl methacrylate and trimethylammonium ethyl methacrylate is about 1: 2: 0.1 (EIDI et al., 2010; EVONIK INDUSTRIES AG, 2012; PIGNATELLO et al., 2001).

Figure 2 - Chemical structure of Eudragit RS100®



Eudragit RS100® is found in the form of colourless granules with a slight amine odour (PATRA et al., 2017). This polymer was introduced in 1968 (NIKAM et al., 2011) and its use has been proposed in the formulation of systems of a wide variety of prolonged release products (PIGNATELLO et al., 2002a).

Eudragit RS100® is insoluble in water and has low permeability, but is permeable in digestive fluids, which has been developed to control the release of encapsulated drugs. Its use is widely

associated with the production of oral and topical formulations, and previous studies report its good biocompatibility in different applications (BASARKAR; SING, 2009; JOSHI, 2013; NIKAM et al., 2011; PATRA et al., 2017; SEREMETA; CHIAPPETTA; SOSNIK, 2013; SCHAFFAZICK et al., 2008; ZAGO et al., 2013).

It is also insoluble at physiological pH but swells in water (PIGNATELLO et al., 2002a), which represents a good material for the dispersion of drugs (YOUNIS et al., 2016). Eudragit RS100® can be used in the development of thermo-sensitive drugs, demonstrating safety to temperature sensitive drugs (FUJIMORI et al., 2002).

Eudragit RS100® has the latest chemical groups that provides positive surface to the polymer, through which it can interact with negatively charged drugs or target tissue cell surface, this feature can maximize cellular uptake of the drug polymer complex (DILLEN et al., 2006).

This polymer is non-biodegradable but has adequate biocompatibility and its use is associated with important performance due to its role in increasing the interaction with the mucosa (CONTRI et al., 2014; DAMGÉ; MAINCENT; UBRICH, 2007; FRANK et al., 2015). Regarding the physicochemical characteristics of the nanocapsules produced with Eudragit RS100®, they present a homogeneous, milky appearance and tyndall effect after preparation, which is characteristic of colloidal systems (DALCIN et al., 2017; SANTOS et al., 2014; SANTOS et al., 2013), exhibit spherical and irregular morphological characteristics. The size distribution and the mean particle diameters result in particles around 130-200 nm and low polydispersity index which demonstrates the good homogeneity of the systems (BEBER et al., 2016; DALCIN et al., 2017; CHAVES et al., 2017; CONTRI et al., 2015; FIEL et al., 2014; FRANK et al., 2015; SANTOS et al., 2014).

The values of zeta potential found are between +8 and +13 mV due to the presence of the cationic polymer Eudragit RS100® (BEBER et al., 2016; CHAVES et al., 2017; CONTRI et al., 2011; CONTRI et al., 2012; CONTRI et al., 2015; DALCIN et al., 2017; FRANK et al., 2015; JANA et al., 2014; SANTOS et al., 2013; SANTOS et al., 2014). Contri et al. (2012) report that this cationic charge of the surfaces can promote a better interaction with the negative charges of the skin, improving the bioadhesion of the nanoparticles and the desired action. The results showed high encapsulation efficiency, with values above 80% (CHAVES et al., 2017; DALCIN et al., 2017; SANTOS et al., 2014). In addition, they have stability over time and in different storage conditions (DALCIN et al, 2017; SANTOS et al., 2014) and their physicochemical characteristics show good potential for several applications.

Eudragit RS100® has been used in the development of nanocapsules containing several drugs with satisfactory results as described in table 1.

Table 1 - Biological effects reported by nanocapsules produced with the Eudragit RS100® polymer.

Drug	Result found	Application	Author
Carvedilol	controlled drug release profiles and mucoadhesive properties.	Sublingual application	Chaves et al. (2017)
Dihydromyricetin	Sustained release, antimicrobial and anti-biofilm effect against strains of *Pseudomonas aeruginosa*	Antimicrobial activity and antibiofilm in urinary catheters	Dalcin et al. (2017)
Silymarin	Beneficial effects on liver fibrosis	Sustained delivery by oral route of administration	Younis et al. (2016)
Nanocapsules without drug	Adhesion of the nanoparticles to the skin layers	Strong adhesion with potential for topical application	Contri et al. (2016)
Dexamethasone in carbopol hydrogels	Controlled Release	Anti-inflammatory topical	Beber et al. (2016)
Dihydromyricetin	Less susceptibility to acid hydrolysis, oxidative degradation, photolytic degradation and thermal degradation.	Promising strategy for delivery of Dihydromyricetin	Dalcin (2015)
Oil of rose hips in chitosan hydrogel	Less oxidation UVA and UVC	Potential for topical application	Contri et al. (2015)
Nanocapsules without drug in chitosan hydrogel	Mucoadhesion	Vaginal application	Frank et al. (2014)
Prednisolone	No irritation and toxicity ophthalmic	Ophthalmic application	Katzer et al. (2014)
Nebivolol	Sustained release	Potential application for treatment of hypertension	Jana et al. (2014)
Clotrimazole	Stability against UV radiation, sustained release and increased efficacy against *Candida albicans* and *glabrata* strains	Treatment of vulvovaginal candidiasis	Santos et al. (2014)
Clotrimazole	Bioadhesion and sustained release	Vaginal application	Gupta et al. (2013)
Theophylline	sustained release	Sustained Release Tablets	Garekania, Moghaddam e Sadeghic (2013)
Efavirenz	sustained release	Potential for intranasal administration	Seremeta, Chiappetta e Sosnik (2013)
Lansoprazole	sustained release	Potential application for treatment of gastric disorders such as ulcers and reflux	Alai e Lin (2013)
Capsaicin and dihydrocapsaicin in chitosan hydrogel	Adhesion of the nanocapsules to the skin and its ability to control the release of the drug	Potential topical analgesic effect for treatment of chronic pain	Contri et al. (2013)
Clotrimazole	Sustained release and antifungal activity against *Candida Albicans* and *Candida glabrata* strains	Antimicrobial effect	Santos et al. (2013)
Budesonide	Sustained release and better protection against gastric acidity	Potential specific application to the colon	Cortesi et al. (2012)

Vegetable oils (Brazil nut, sunflower seed, olive, rose hip, grape seed and carrot oils)	Alternatives for oily nucleus composition of polymeric nanoparticles	Cosmetic application, with additional advantages of skin protection, due to the antioxidant properties of the oils	Contri et al. (2012)
Diclofenac sodium	sustained release	Potential ophthalmic anti-inflammatory effect	Barzegar-Jalali et al. (2012)
Naproxen	sustained release	Increased anti-inflammatory effect for ocular or intra-articular administration	Adbkia et al. (2011)
Capsaicin and dihydrocapsaicin	Sustained release and stable over 90 days	Potential topical analgesic effect	Contri et al. (2011)
Low molecular weight heparin	Reduction of toxicity	Heparin delivery systems	Eidi et al. (2010)
Tulobuterol	sustained release	Improvement in drug administration	Kim e Park (2010)
DNA Plasmid	Introdução de transgene nas células	Potential for gene delivery	Gargouri et al. (2009)
Mefenamic Acid	Sustained release and effects on DNA damage	interaction with DNA	Sevgi et al. (2009)
Sildenafil	sustained release	Application in vaginal suppositories	Degim et al. (2008)
Insulin	Mucoadhesive properties, increased serum insulin levels and better glycemic profile	Potential oral application	Damgé, Maincent e Ubrich (2007)
Acetazolamide	sustained release	Potential ophthalmic application	Duarte et al. (2007)
Glutathione	Enzymatic and intestinal stability	Sustained delivery by oral route	Trapani et al. (2007)
Low molecular weight heparina	Increased bioavailability and mucoadhesion	Potential Heparin oral delivery systems	Lamprecht et al. (2006)
Cloricromene	sustained release	Potential ophthalmic application	Pignatello et al. (2006)
Ciprofloxacin	Sustained release and antimicrobial effect against strains *Pseudomonas aeruginosa* and *Staphylococcus aureus*	Antimicrobial effect	Dillen et al. (2006)
Oligodeoxynucleotides	Higher absorption	Potential Gene Delivery	Wang et al. (2003)
Flurbiprofen	Controlled release, absence of toxicity and anti-inflammatory activity	Potential ophthalmic application	Pignatello et al. (2002a)
Sodium ibuprofen	sustained release	Ophthalmic application for anti-inflammatory effect	Pignatello et al. (2002b)
Diflunisal	Increased photoprotection	Strategy of drug delivery system with photoprotection	Pignatello et al. (2001)

Various routes of administration have been described for application of nanoencapsulated drugs containing the Eudragit RS100® polymer, the results found are described below according to each route.

OPHTHALMIC ROUTE

Suspensions of nanocapsules containing sodium ibuprofen were produced with the aim of improving the anti-inflammatory availability of the drug via ocular. In vivo efficacy was evaluated in rabbit eyes after induction of ocular trauma. The results indicated that the nanoencapsulated drug was able to provide gradual and prolonged release, increased retention at the surface of the cornea and higher levels of drug in the aqueous humour. In addition, it resulted in a greater ability to inhibit myoses induced by surgical trauma, being described as a good candidate for therapy in the topical treatment of inflammatory conditions of the eye, as well as in the maintenance of mydriasis during surgery or postoperative traumatic events (PIGNATELLO et al., 2002a).

This same group of Pignatello et al. (2002b) produced nanocapsules containing flurbiprofen with the objective of improving the availability of the drug at an intraocular level for the prevention of induced miosis during extracapsular cataract surgery. In vitro release tests showed a profile of controlled release of the drug by the nanocapsules. In vivo anti-inflammatory efficacy was evaluated in rabbit eye following induction of ocular trauma, nanocapsules containing flurbiprofen showed no toxicity to ocular tissues. In addition, inhibition of the miotic response to surgical trauma comparable to a control formulation was obtained, and the content of the drug in the aqueous humour was also higher after the application of the nanocapsule containing suspensions.

Katzer et al. (2014) developed nanoparticles containing prednisolone as ocular drug delivery systems. Ocular irritation and cytotoxicity were evaluated in vitro on the chorioallantoic membrane (CAM) and rabbit corneal epithelial cell line. Both formulations (free and nanostructured prednisolone) were considered non-irritating in the CAM test and non-cytotoxic in relation to rabbit corneal epithelial cells. Thus, encapsulation of prednisolone in nanocapsules has been reported to be suitable for ocular application and for treatment of ocular inflammation without providing ophthalmic toxicity.

Nanocapsules containing terbinafine hydrochloride were produced and resulted in controlled release, increased residence time and ocular bioavailability, which could be used in the treatment of ocular fungal keratitis (TAYEL et al., 2013).

NASAL ROUTE

Seremeta, Chiappetta and Sosnik (2013) suggested that Eudragit RS100® reduced the burst effect and sustained the release of Efavirenz when compared to a formulation containing the Poly-ε-caprolactone polymer, which may be promising in the use of intranasal route in order to increase bioavailability in the central nervous system.

ORAL ROUTE

Nanocapsules containing insulin were prepared for use as a drug carrier for oral administration. When administered orally by forced feeding to diabetic rats, insulin-containing nanocapsules decreased fasting glycaemia in a dose-dependent manner, with a maximal effect observed at 100 IU / kg. The nanocapsules also increased serum insulin levels and improved the glycaemic response for an extended period of time. Fluorescence analyses demonstrated that insulin-containing nanocapsules strongly adhered to the intestinal mucosa. The authors concluded that the polymeric nanoparticles allowed preservation of the biological activity of insulin. In addition, the antidiabetic effect can be explained by the mucoadhesive properties of the Eudragit RS100® polymer allowing intestinal absorption of insulin (DAMGÉ; MAINCENT; UBRICH, 2007).

Trapani et al. (2007) investigated the nanoencapsulation of Glutathione (GSH) and the results found demonstrated sustained release, enzymatic and intestinal stability, and increased intestinal permeability, suggesting that GSH-containing nanocapsules represent a new sustained delivery system for the oral administration of tripeptide.

Aqueous dispersion of theophylline was compared with nanocapsules containing theophylline powders using spray-drying technique and tablets of nanocapsules containing theophylline. The release of the drug in tablet form was slower compared to other formulations, demonstrating potential application in sustained release formulation in the presentation of tablets for oral administration (GAREKANIA; MOGHADDAM; SADEGHIC, 2013).

The formulation nanocapsules containing silymarin improved cholestatic induced liver fibrosis, restoring hepatic regenerative capacities. The results demonstrated a significant decrease serum tumor necrosis factor (TNF-α), transforming growth factor-β1 (TGF-β1), hepatic hydroxyproline and low hepatic expression of tissue inhibitor metalloproteinase-1(TIMP-1) and cytokeratin-19 (CK-19). The livers of rats treated with nanocapsules containing silymarin showed very little collagen and restored the liver architecture compared to rats treated with the free drug. Demonstrating that the formulation of nanocapsule containing silymarin may represent a step further in the field of anti-fibrotic drug development (YOUNIS et al., 2016).

Nanocapsules containing lanzoprazole demonstrated sustained release and potential use in the treatment of disorders related to ulcerative diseases such as reflux, gastritis and ulcers (ALAI; LIN, 2013).

Cortesi et al. (2012) developed nanocapsules containing budesonide and reported sustained release and improvement drug protection from gastric acidity when compared to nanocapsules produced with Eudragit RL100® polymer. The budesonide-containing nanocapsules formulations produced with Eudragit RS100® have been shown to be a specific controlled delivery system in the colon.

Nanocapsules containing low molecular weight heparin demonstrated increased oral bioavailability of heparin. However, absorption mechanisms are still unclear and should be better understood (EIDI et al., 2010).

Drug binding and transport studies were performed on human colon adenocarcinoma cell line (Caco-2) for free and nanoencapsulated low molecular weight heparin. Nanocapsules showed greater mucoadhesion and increased binding of nanocapsules containing heparin to Caco-2 cells. The nanocapsules led to a greater transport of heparin in the presence of mucin due to the mucoadhesive properties of the nanocapsules that provide the prolonged and intensified contact with the epithelial barrier, resulting in greater absorption (LAMPRECHT et al., 2006).

SUBLINGUAL ROUTE

Chaves et al. (2017) developed nanocapsules loaded with carvedilol as delivery systems for the sublingual route. The in vitro interaction with mucin was performed to evaluate its mucoadhesion capacity and the permeability and washability profiles were evaluated using porcine sublingual mucosa. Nanoencapsulation of carvedilol improved mucosal retention time and permeation in the presence of salivary flow simulation. The study highlighted the suitability of the use of nanocapsules loaded with carvedilol in the development of innovative sublingual dosage forms.

TOPICAL ROUTE

The adhesion of nanocapsules prepared with Eudragit RS100® to the mucosa is well known and described, improving the performance of nanosystems. The mucosa presents a negative surface due to the presence of mucin. Therefore, to improve adhesion, it is interesting to use positively charged nanocapsules (FRANK et al., 2015).

Contri et al. (2016) verified that the penetration of cationic nanocapsules exceeded the penetration of anionic nanocapsules. Fluorescence was also seen in the epidermis and dermis. The surface cationic charge and the incorporation of the particles into the chitosan gel favored access to the deeper layers of the skin, demonstrating the strong adhesion of the cationic particles to the layers of the skin.

The effect of encapsulation of capsaicinoids (capsaicin and dihydrocapsaicin) on nanocapsules, as well as the incorporation of such nanoparticles into chitosan hydrogel was investigated in adhesion and penetration by Contri et al. (2013). The combination of the chitosan gel with the nanocapsules led to a greater bioadhesion to the skin and could be used as topical anesthetic for the treatment of chronic pain.

The effect of the nanoencapsulation of capsaicin and dihydrocapsaicin on chitosan hydrogels was also evaluated in human skin irritation due to the irritating properties of capsaicin which often discontinue

its use in topical analgesics. The chitosan hydrogel containing the nanoencapsulated drugs did not cause skin irritation, however, the non-nanoencapsulated capsaicinoid formulation provided skin irritation. The authors suggest that nanoencapsulation may have modulated the permeation of the skin by the controlled release properties of the drug so that the irritation sensation was greatly reduced (CONTRI et al., 2014).

Nanocapsules containing Rose-Hip oil were developed to verify the effect of nanoencapsulation on UV radiation-induced oxidation and to obtain topical formulations containing chitosan hydrogel. Nanocapsules containing Rose-Hip oil decreased the UVA and UVC oxidation of the oil. The chitosan gel containing the nanocapsules had adequate properties for cutaneous use and the formulation was considered an interesting alternative for nanoencapsular and incorporate Rose-Hip oil (CONTRI et al., 2015).

Beber et al. (2016) evaluated the behaviour of dexamethasone loaded nanocapsules in carbopol hydrogels in relation to the in vitro release of the drug and its retention in the skin. The presence of nanocapsules with dexamethasone in hydrogels promoted controlled release of the drug and increased the amount delivered to the epidermis, the main target tissue for the topical action of glucocorticoids. In addition, the formulation did not increase the risk of drug permeation in the dermis and recipient compartment, demonstrating no increased risk of systemic absorption, confirming that it is an innovative approach for the treatment of inflammatory and allergic skin disorders.

VAGINAL ROUTE

Vaginal bioadhesive tablets containing clotrimazole nanocapsules have been developed in order to provide long-term therapeutic activity at the site of infection. The formulation indicated an in vitro release of the controlled drug and good bioadhesive resistance. In vivo results confirmed the bioadhesion property and drug retention up to 24 hours after application, demonstrating that this drug delivery system can be exploited for the application of controlled release of intravaginal drugs (GUPTA et al., 2013).

Santos et al. (2014) also nanoencapsulated the antifungal clotrimazole and demonstrated that nanoencapsulation improved the stability of clotrimazole against UV radiation, provided prolonged release and the nanocapsules were more effective against strains of *Candida albicans* and *Candida glabrata* susceptible and resistant to antifungal fluconazole. The study demonstrates an alternative potential for the treatment of vulvovaginal candidiasis.

Because of the inexistence of a pharmaceutical form of sildenafil vaginally, the drug when administered vaginally could lead to an improvement in uterine blood flow and, together with ovarian hyperstimulation, would cause estrogen-induced proliferation. Degim et al. (2008) developed a formulation containing Sildenafil for the treatment of female infertility by administration in vaginal suppositories and verified a release of sildenafil for a longer period and could be used as a proposal for sustained release of the drug.

Frank et al. (2014) evaluate the performance of chitosan hydrogels containing cationic and anionic nanocapsules (Eudragit RS100® and Eudragit S100®, respectively). The adhesion and penetration properties of the formulations were evaluated when applied to the porcine vaginal mucosa. The chitosan formulation showed adequate viscosity for vaginal application and acid pH. The tensile stress test showed that both formulations containing nanocapsules presented higher mucoadhesion when compared to the formulation without nanocapsules. Confocal microscopy and quantification of fluorescence after mucosal extraction showed greater penetration when nanoencapsulated, especially by cationic nanocapsules, demonstrating applicability for vaginal delivery of hydrophobic substances.

GENE DELIVERY

Studies report the success of Eudragit RS100® in gene therapy. Oligodeoxynucleotides were successfully administered by nanoparticles containing Eudragit RS100® demonstrating to be a promising vehicle for gene delivery (WANG; CHEN; LIANG, 2003; NIKAM et al., 2011).

The objective of Gargouri and collaborators (2009) was to develop a new tool for delivery of DNA by nanocapsules containing Eudragit RS100®. Cytotoxicity tests (cell viability by MTT) revealed that the nanocapsules showed limited cytotoxicity and dependent of the evaluated nanocapsule concentration and cell line. Expression of the transgene was observed for MDA-MB 231 (invasive human breast adenocarcinoma), FaDu (pharynx carcinoma cells), and MCF-7 (non-invasive human breast adenocarcinoma) cell lines. The results showed that the transfection rates ranged from 4 to 7% and were achieved for all cells analysed. Particle size was not revealed as an important transfection factor. The results demonstrated that the nanocapsules were efficient to introduce the transgene into different cell lines, but were less effective than the lipofectamine control.

OTHER APPLICATIONS

The influence of DHM nanoencapsulation on antimicrobial activity and antibiofilm in urinary catheters infected with Pseudomonas aeruginosa was evaluated by Dalcin et al. (2017). Nanocapsules containing DHM demonstrated sustained release and more effective antibiofilm activity compared to free DHM, suggesting that the formulation of nanocapsules containing DHM can be used as a potentially innovative approach for the treatment or prevention of urinary catheter biofilms.

CONCLUSIONS

Cationic polymeric nanocapsules produced with the Eudragit RS100® polymer have been shown to have great potential for the production of modified release drugs. The studies show that

different drugs when inserted in nanoparticles produced with Eudragit RS100® present a more sustained release than free (non-nanostructured) drugs due to the combination of the individual properties of the polymer. The mucoadhesion of these formulations with target tissues or organs is also highlighted, which allows application through various administration routes, becoming very attractive and opening an interesting field of research to be further explored by nanomedicine.

REFERENCES

ADIBKIA, K. et al. Naproxen-eudragit® RS100 nanoparticles: Preparation and physicochemical characterization. **Colloids and Surfaces B: Biointerfaces,** v. 83, n. 1, p. 155-159, 2011.

ALAI, M. S.; LIN, W. J. A novel nanoparticulate system for sustained delivery of acid-labile lansoprazole. **Colloids and Surfaces B: Biointerfaces,** v. 111, p. 453-459, 2013.

ASLAM, S. Effect of antibacterials on biofilms. **American Journal of Infection Control,** v. 36, n. 10, p. 9-11, 2008.

BARZEGAR-JALALI, M. et al. Comparison of physicochemical characteristics and drug release of diclofenac sodium-eudragit® RS100 nanoparticles and solid dispersions. **Powder Technology,** v. 219, p. 211-216, 2012.

BASARKAR, A.; SINGH, J. Poly (lactide-co-glycolide)-polymethacrylate nanoparticles for intramuscular delivery of plasmid encoding interleukin-10 to prevent autoimmune diabetes in mice. **Pharmaceutical Research,** v. 26, n. 1, p. 72-81, 2009.

BEBER, T. C. et al. Cationic Polymeric Nanocapsules as a Strategy to Target Dexamethasone to Viable Epidermis: Skin Penetration and Permeation Studies. **Journal of Nanoscience and Nanotechnology,** v. 16, p. 1331-1338, 2016.

BOISSEAU, P.; LOUBATON B. Nanomedicine: nanotechnology in medicine. **Comptes Rendus Physique,** v. 12, p. 620-636, 2011.

BREGOLI, L. et al. Nanomedicine applied to translational oncology: A future perspective on cancer treatment. **Nanomedicine: Nanotechnology, Biology, and Medicine,** v. 12, n. 1, p. 81-103, 2016.

BULCÃO, R. P. et al. In vivo toxicological evaluation of polymeric nanocapsules after intradermal administration. **European Journal of Pharmaceutics and Biopharmaceutics,** v. 86, n. 2, p. 166-177, 2014.

CHAMPION, J. A.; KATARE, Y. K.; MITRAGOTRI, S. Particle shape: A new design parameter for micro- and nanoscale drug delivery carriers. **Journal of Controlled Release,** v. 121, p. 3-9, 2007.

CHAVES, P. S. et al. Carvedilol-loaded nanocapsules: Mucoadhesive properties and permeability across the sublingual mucosa. **European Journal of Pharmaceutics and Biopharmaceutics,** v. 114, p. 88-95, 2017.

CONTRI, R. V. et al. Simultaneous Control of Capsaicinoids Release from Polymeric Nanocapsules. **Journal of Nanoscience and Nanotechnology,** v. 11, n. 3, p. 2398-2406, 2011.

CONTRI, R. V. et al. Vegetable oils as core of cationic polymeric nanocapsules: influence on the physicochemical properties. **Journal of Experimental Nanoscience,** v. 8, n. 7, p. 1-12, 2012.

CONTRI, R. V. et al. Combined Effect of Polymeric Nanocapsules and Chitosan Hydrogel on the Increase of Capsaicinoids Adhesion to the Skin Surface. **Journal of Biomedical Nanotechnology,** v. 10, n. 5, p. 820-830, 2013.

CONTRI, R. V. et al. The use of nanoencapsulation to decrease human skin irritation caused by capsaicinoids. **International Journal of Nanomedicine,** v. 9, p. 951-962, 2014.

CONTRI, R. V. et al. Nanoencapsulation of Rose-Hip Oil Prevents Oil Oxidation and Allows Obtainment of Gel and Film Topical Formulations. **AAPS PharmSciTech,** v. 17, n. 4, p. 863-871, 2015.

CONTRI, R. V. et al. Skin penetration and dermal tolerability of acrylic nanocapsules: Influence of the surface charge and a chitosan gel used as vehicle. **International Journal of Pharmaceutics,** v. 507, n. 1, p. 12-20, 2016.

CORTESI, R. et al. Eudragit® Microparticles for the Release of Budesonide: A Comparative Study. **Indian Journal of Pharmaceutical Sciences,** v. 74, n. 5, p. 415-421, 2012.

CRUCHO, C. I. C.; BARROS, M. T. Polymeric nanoparticles: A study on the preparation variables and characterization methods. **Materials Science and Engineering C,** v. 80, p. 771-784, 2017.

DAMGÉ, C.; MAINCENT, P.; UBRICH, N. Oral delivery of insulin associated to polymeric nanoparticles in diabetic rats. **Journal of Controlled Release,** v. 117, n. 2, p. 163-170, 2007.

DALCIN, A. J. F. **Desenvolvimento, caracterização e avaliação da atividade antimicrobiana e antibiofilme de nanocápsulas de dihidromiricetina em cateteres urinários.** 2015. 97f. Dissertação (Mestrado em Nanociências) - Centro Universitário Franciscano, Santa Maria (RS), 2015.

DALCIN, A. J. F. et al. Anti-biofilm effect of dihydromyricetin-loaded nanocapsules onurinary catheter infected by *Pseudomonas aeruginosa.* **Colloids and Surfaces B: Biointerfaces,** v. 156, p. 282-291, 2017.

DEGIM, I. T. et al. Development of Controlled Release Sildenafil Formulations for Vaginal Administration. **Drug Delivery,** v. 15, n. 4, p. 259-265, 2008.

DILLEN, K. et al. Evaluation of ciprofloxacin-loaded Eudragit® RS100 or RL100/PLGA nanoparticles. **International Journal of Pharmaceutics,** v. 314, n. 1, p. 72-82, 2006.

DUARTE, A. R. et al. Preparation of acetazolamide composite microparticles by supercritical anti-solvent techniques. **International Journal of Pharmaceutics,** v. 332, n. 1-2, p. 132-9, 2007.

EIDI, H. et al. Cytotoxicity assessment of heparin nanoparticles in NR8383 macrophages. **International Journal of Pharmaceutics,** v. 396, n. 1, p. 156-165, 2010.

ESFANJANI, A. F.; JAFARI, S. M. Biopolymer nano-particles and natural nano-carriers fornano-encapsulation of phenolic compounds. **Colloids and Surfaces B: Biointerfaces,** v. 146, p. 532-543, 2016.

EVONIK INDUSTRIES AG. **Informe técnico 7.7/e**. 2012. p. 2-7.

FIEL, L. A. et al. Labeling the oily core of nanocapsules and lipid-core nanocapsules with a triglyceride conjugated to a fluorescent dye as a strategy to particle tracking in biological studies. **Nanoscale Research Letters**, v. 9, n. 233, p. 1-11, 2014.

FLORINDO, H. F. et al. The enhancement of the immune response against S. Equi antigens through the intranasal administration of poly-ε-caprolactone-based nanoparticles. **Biomaterials,** v. 30, n. 5, p. 879-891, 2009.

FRANK, L. A. et al. Chitosan gel containing polymeric nanocapsules: a new formulation for vaginal drug delivery. **International Journal of Nanomedicine,** v. 9, p. 3151-3161, 2014.

FRANK, L. A. et al. Improving drug biological effects by encapsulation into polymeric Nanocapsules. **WIREs Nanomedicine and Nanobiotechnology,** v. 7, n. 5, p. 623-639, 2015.

FUJIMORI, J. et al. Application of eudragit RS to thermo-sensitive drug delivery systems. I. Thermo--sensitive drug release from acetaminophen matrix tablets consisting of eudragit RS/PEG 400 blend polymers. **Chemical and Pharmaceutical Bulletin,** v. 50, n. 3, p. 408-12, 2002.

GAREKANIA, H. A.; MOGHADDAM, F.; SADEGHIC, F. Organic solution versus aqueous dispersion of Eudragit RS in preparation of sustained release microparticles of theophylline using spray drying. **Colloids and Surfaces B: Biointerfaces,** v. 108, p. 374-379, 2013.

GARGOURI, M. et al. Optimization of a New Non-viral Vector for Transfection: Eudragit Nanoparticles for the Delivery of a DNA plasmid**. Technology in Cancer Research & Treatment,** v. 8, n. 6, p. 433-443, 2009.

GIONGO, J. L. et al. Anti-Candida activity assessment of Pelargonium graveolens oil free and nanoemulsion in biofilm formation in hospital medical supplies. **Microbial Pathogenesis,** v. 100, p. 170-178, 2016.

GUPTA, N. V. et al. Bioadhesive vaginal tablets containing spray dried microspheres loaded with clotrimazole for treatment of vaginal Candidiasis. **Acta Pharmaceutica,** v. 63, n. 3, p. 359-372, 2013.

HOFFART, V. et al. Oral bioavailability of a low molecular weight heparin using a polymeric delivery system. **Journal of Controlled Release,** v. 113, n. 1 p. 38-42, 2006.

HORIGUCHI, M. et al. Pulmonary administration of integrin-nanoparticles regenerates collapsed alveoli. **Journal of Controlled Release,** v. 187, p. 167-174, 2014.

JANA, U. et al. Preparation and characterization of nebivolol nanoparticles using Eudragit® RS100. **Colloids and Surfaces B: Biointerfaces,** v. 113, p. 269-275, 2014.

JOSHI, M. Role of eudragit in targeted drug delivery. **International Journal of Current Pharmaceutical Research,** v. 5, n. 2, p. 58-62, 2013.

KATZER, T. et al. Prednisolone-loaded nanocapsules as ocular drug delivery system: development, in vitro drug release and eye toxicity. **Journal of microencapsulation,** v. 31, n. 6, p. 519-28, 2014.

KESARWANI, K.; GUPTA, R.; Bioavailability enhancers of herbal origin: An overview. **Asian Pacific Journal of Tropical Biomedicine,** v. 3, n. 4, p. 253-266, 2013.

KIBBE, A. H. **Handbook of Pharmaceutical Excipients.** 3. ed. London: United Kingdom, 2000.

KIM, K.; PARK, S. Characterization and release behaviors of porous PCL/Eudragit RS microcapsules containing tulobuterol**. Colloids and Surfaces B: Biointerfaces,** v. 76, n. 2, p. 404-409, 2010.

LAMPRECHT, L. et al. Low molecular weight heparin nanoparticles: mucoadhesion and behaviour in Caco-2 cells. **Nanotechnology,** v. 17, n. 15, p. 3673-3680, 2006.

LOPEDOTA, A. et al. The use of Eudragit RS 100/cyclodextrin nanoparticles for the transmucosal administration of glutathione. **European Journal of Pharmaceutics and Biopharmaceutics,** v. 72, n. 3, p. 509-520, 2009.

LU, Y.; CHEN, S. C. Mico and nano-fabrication of biodegradable polymers for drugs delivery. **Advanced drug delivery reviews,** v. 56, n. 1, p.1621-1633, 2004.

LUONG, D. et al. Solubility enhancement and targeted delivery of a potent anticancer flavonoid analogue to cancer cells using ligand decorated dendrimer nano-architectures. **Journal of Colloid and Interface Science,** v. 484, p. 33-43, 2016.

MALI, A. D.; BATHE, R. S. Updated review on nanoparticles as drug delivery systems. International Journal of Analytical. **Pharmaceutical and Biomedical Sciences,** v. 8, n. 9, p. 18-34, 2015.

MORA-HUERTAS, C. E.; FESSI, H.; ELAISSARI, A. Polymer-based nanocapsules for drug delivery. **International Journal of Pharmaceutics**, v. 385, n. 1-2, p. 113-142, 2010.

NIKAM, V. K. et al. Eudragit a versatile polymer: a review. **Pharmacologyonline,** v. 1, p. 152-164, 2011.

OLIVEIRA, L. T. et al. Impact of dose and surface features on plasmatic and liver concentrations of biodegradable polymeric nanocapsules. **European Journal of Pharmaceutical Sciences,** v. 105, p. 19-32, 2017.

PATRA, C. N. et al. Pharmaceutical significance of Eudragit: A review. **Future Journal of Pharmaceutical Sciences,** v. 3, n. 1, p. 33-45, 2017.

PECORA, T. M. G. et al. Preparation, characterization and photostability assessment of curcumin microencapsulated within methacrylic copolymers. **Journal of Drug Delivery Science and Technology,** v. 33, p. 88-97, 2016.

PIGNATELLO, R. et al. Preparation, characterisation and photosensitivity studies of solid dispersions of diflunisal and Eudragit RS100® and RL100®. **International Journal of Pharmaceutics,** v. 218, n. 1, p. 27-42, 2001.

PIGNATELLO, R. et al. J Flurbiprofen-loaded acrylate polymer nanosuspensions for ophthalmic application. **Biomaterials,** v. 23, n. 15, p. 3247-3255, 2002a.

PIGNATELLO, R. et al. Eudragit RS100® nanosuspensions for the ophthalmic controlled delivery of ibuprofen. **European Journal of Pharmaceutical Sciences,** v. 16, n. 1, p. 53-61, 2002b.

PIGNATELLO, R. et al. Preparation and Characterization of Eudragit Retard Nanosuspensions for the Ocular Delivery of Cloricromene. **AAPS PharmSciTech,** v. 7, n. 1, p. 2-7, 2006.

PUTHETI, R. R. et al. Nanotechnology importance in the pharmaceutical industry. **African Journal of Pure and Applied Chemistry,** v. 2, n. 3, p. 27-31, 2008.

ROLLAND, A. et al. Pharmacokinetics of low-dose methotrexate in rheumatoid arthritis patients. **Journal of Pharmaceutical Sciences,** v. 78, n. 2, p. 165-171,1989.

SANTOS, S. S. et al. Clotrimazole-loaded Eudragit® RS100 nanocapsules: Preparation, characterization and in vitro evaluation of antifungal activity against Candida species. **Materials Science and Engineering C,** v. 33, n. 3, p. 1389-394, 2013.

SANTOS, S. S. et al. Formulation and in vitro evaluation of coconut oil-core cationic nanocapsules intended for vaginal delivery of clotrimazole. **Colloids and Surfaces B: Biointerfaces,** v. 116, p. 270-276, 2014.

SANTOS, C. G. et al. uso de blendas poliméricas em nano e microencapsulação. **Disciplinarum Scientia. Série: Naturais e Tecnológicas,** v. 16, n. 2, p. 311-323, 2015.

SANTOS, P. P. et al. Biodegradable polymers as wall materials to the synthesis of bioactive compound nanocapsules. **Trends in Food Science & Technology,** v. 53, p. 23-33, 2016.

SARAF, A. S. Applications of novel drug delivery system for herbal formulations. **Fitoterapia,** v. 81, n. 7, p. 680-689, 2010.

SCHAFFAZICK, S. R. et al. Caracterização e Estabilidade Físico-Química de Sistemas Poliméricos Nanoparticulados para Administração de Fármacos. **Química Nova,** v. 26, n. 5, p. 726-737, 2003.

SCHAFFAZICK, S. R. et al. Incorporation in polymeric nanocapsules improves the antioxidant effect of melatonin against lipid peroxidation in mice brain and liver. **European Journal of Pharmaceutics and Biopharmaceutics,** v. 69, n. 1, p. 64-71, 2008.

SEVGI, F. et al. Studies on Mefenamic Acid Microparticles: Formulation, In Vitro Release, and In Situ Studies in Rats. **AAPS PharmSciTech,** v. 10, n. 1, p. 104-112, 2009.

SEREMETA, K. P.; CHIAPPETTA, D. A.; SOSNIK, A. Poly(e-caprolactone), Eudragit® RS 100 and poly(e-caprolactone)/Eudragit® RS 100 blend submicron particles for the sustained release of the antiretroviral efavirenz. **Colloids and Surfaces B: Biointerfaces,** v. 102, p. 441-449, 2013.

SIA, P. D. Nanotechnology among innovation, health and risks. **Procedia - Social and Behavioral Sciences,** v. 237, p. 1076-1080, 2017.

SOPPIMATH, K. S. et al. Biodegradable polymeric nanoparticles as drug delivery devices. **Journal of Controlled Release,** v. 70, n. 1, p. 1-20, 2001.

TAYEL, S. A. et al. Positively Charged Polymeric Nanoparticle Reservoirs of Terbinafine Hydrochloride: Preclinical Implications for Controlled Drug Delivery in the Aqueous Humor of Rabbits. **AAPS PharmSciTech,** v. 14, n. 2, p. 782-793, 2013.

TRAPANI, A. et al. Eudragit RS 100 microparticles containing 2-hydroxypropyl-β-cyclodextrin and glutathione: Physicochemical characterization, drug release and transport studies. **European Journal of Pharmaceutical Sciences,** v. 30, n. 1, p. 64-74, 2007.

YOUNIS, N.; SHAHEEN, N. A.; ABDALLAH, M. H. Silymarin-loaded Eudragit1 RS100 nanoparticles improved the ability of silymarin to resolve hepatic fibrosis in bile duct ligated rats. **Biomedicine & Pharmacotherapy,** v. 81, p. 93-103, 2016.

WANG, W. X.; CHEN, H. L.; LIANG, W. Q. Study on polymethacrylate nanoparticles as delivery system of antisense oligodeoxynucleotides. **Yao xue xue bao Acta pharmaceutica Sinica,** v. 38, n. 4, p. 298-301, 2003.

WANG, L. et al. Flavonoid composition, antibacterial and antioxidant properties of tartary buckwheat bran extract. **Industrial Crops and Products,** v. 49, p. 312-317, 2013.

WANG, P. et al. Nanotechnology: A New Opportunity in Plant Sciences. **Trends in Plant Science,** v. 21, n. 8, p. 699-712, 2016.

WENG, Y. et al. Nanotechnology-based strategies for treatment of ocular disease. **Acta Pharmaceutica Sinica B,** v. 7, n. 3, p. 281-291, 2017.

ZAGO, A. C. et al. J Local delivery of sirolimus nanoparticles for the treatment of in-stent restenosis. **Catheterization and Cardiovascular Interventions,** v. 81, n. 2, p. 124-9, 2013.