Pharmaceutical Approaches for Optimizing Oral Anti-Inflammatory Delivery Systems

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Abstract: The purpose of the present review is to compile the recent literature in the field of anti-inflammatory treatments, with special focus to the state-of-the-art on pharmaceutical approaches for optimizing oral administration. Attending to the drawbacks associated with the use of these types of drugs, the development of oral modulated release formulations is highly desirable in order to achieve improved therapeutic efficacy and patient compliance. Several technological systems and their advantages in modulated and targeted drug releases (gastroretention or colonic release) have been described: matrix systems, coated dosage forms, osmotic pressure based formulations, prodrugs, colloidal carriers, microparticles and other carriers. These new approaches seem to be promising and have been considered by pharmaceutical companies.

Keywords: Anti-inflammatory drugs, matrix systems, coated systems, osmotic systems, prodrugs, colloidal carriers, microparticles, gastroretentive systems, colon systems.

INTRODUCTION

Over the last years, many interests have been expressed related to the optimization of drug therapy by means of delivery systems design. An ideal drug delivery system (DDS) is based on the concept of optimization drug therapy, i.e. by delivering the appropriate amount of drug to the site where it is needed the most, and at the time when it is most effective. Existing formulation technology platforms such as matrix tablet, osmotic formulations, particle coating, multiple unit dosage forms, have been utilized to achieve improved performance of drug therapy. Anti-inflammatory agents are compounds that reduce the pain and the swelling associated with inflammation. There are two main groups of anti-inflammatory agents, the corticosteroids and non steroidal anti-inflammatory (NSAID`s). Anti-inflammatory drugs, namely NSAID`s, are among the most commonly prescribed agents worldwide. Nonetheless, this situation, there are still some relevant problems associated with anti-inflammatory treatments, like delivery of the drug to the appropriate site of action and adverse gastrointestinal tract (GIT) effects. Therefore, an alternative method to target therapeutic concentrations of anti-inflammatory agents is desirable.

The drawbacks of anti-inflammatory therapy can be dealt either by development of pharmacological agents without side effects or by targeting the currently available drugs to the specific sites, using special technological construction and design of the DDS itself. Concerning the first alternative, it is possible to refer to the use of dendrimers, which have substantial inherent anti-inflammatory activity [1], without causing any GIT complications and also can act as macromolecular drug delivery system for anti-inflammatory agents with sustained action and better targeting could be achieved [2].

There is an extensive approach to modulate drug release with the objective to optimize therapy, and some possibilities demand appropriate technological production equipment. Furthermore, the drug characteristics condition the type of release. Most of anti-inflammatory agents present short elimination half-life and multiple dosing is required to achieve and maintain therapeutic concentration, and adverse GIT reactions can occur. Therefore, development of oral controlled release formulations of anti-inflammatory agents is highly desirable in order to achieve improved therapeutic efficacy and patient compliance. Some references can be found in the literature to optimize a therapeutic with anti-inflammatory agents. For example, Colin McCoy of Queen's University Belfast and his colleagues have developed a light-controlled DDS that could minimize side effects [3]. The use of biodegradable polymer based controlled release devices, that are designed to deliver drugs locally in a pre-designed manner, can improve anti-inflammatory action [4].

Despite the existence of GIT barriers to drugs, the oral delivery is a widely accepted and preferred route of therapeutic agent's administration. In the recent years, novel technologies with better therapeutic performance, such as ease of dosing administration, flexibility in formulation and patient compliance have been developed. Advances in oral modulated release technology are attributed to the development of novel biocompatible materials, especially in polymer area, and machineries that allow preparation of novel DDS in a reproducible manner. This article provides a comprehensive review of pharmaceutical approaches for optimizing oral anti-inflammatory delivery systems.

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ANTI-INFLAMMATORY ORAL DELIVERY SYSTEMS

Matrix Systems

Numerous techniques are in the prior art for preparing sustained or controlled release pharmaceutical formulations. One widespread technique involves the use of monolithic matrices, which are an interesting and promising option when developing oral DDS due to their biopharmaceutical and pharmacokinetics advantages over the conventional dosage forms and manufacturing ease [5].

The matrix system, the most commonly used sustained release formulation platform, generally consists of a uniformly dissolved or dispersed drug within a resistant support to disintegration. A wide array of matrix forming agents are available to modulate the drug release from matrix system, such as hydrophilic materials (e.g. hydroxypropylmethylcellulose (HPMC), gums, polymers of acrylic acid, gelatine, dextran), lipids (e.g. carnauba wax, stearyl alcohol, stearic acid) and inert (e.g. ethylcellulose (EC)). In these systems, the profile and kinetics of drug release are functions of matrix agent type and level and physico-chemical nature of drug. A controlled plasma level profile of drug can be obtained by judicious combination of different classes of matrix agents and modulation of its content in the matrix system. Avachat and Kotwal concluded that the release of chondroitin sulphate and diclofenac sodium can be effectively controlled from a single tablet using HPMC matrix system [6]. Diclofenac sodium, a NSAID`s, controlled release was also achieved by using other matrix agents such as carnauba wax, Kollidon SR (polyvinyl acetate and polyvinyl pyrrolidone based matrix forming agent), EC and xanthan gum [7-9]. Some authors have investigated the effect of different matrix agent (e.g. HPMC, EC, hydrogenated castor oil, xyloglucan) in sustaining the naproxen release from matrix tablets [10-13]. Saeio *et al.* have studied the ketoprofen, a NSAID`s, sustained release from various kinds of derivatives based on cellulose polymers which have been used as matrix agents [14]. Mesnukul *et al.* concluded that both the enhancement of dissolution and the prolonged indomethacin release could be achieved by addition of HPMC into polyethylene glycol (PEG) matrix system [15]. The inclusion of xanthan gum as hydrophilic polymer in PEG matrix could prolong the indomethacin release [16].

In the last decade, much emphasis has been laid to the development of multiparticulate dosage forms, in preference to single unit systems, because of their potential benefits: (i) increased bioavailability, (ii) reduced risk of systemic toxicity, (iii) reduced risk of local irritation and (iv) predictable gastric emptying [17]. Multiparticulate approach delivery includes formulations in the form of mini-tablets, pellets, granules, beads, microparticles and nanoparticles. Multiparticulate DDS provides several opportunities for designing new controlled release oral formulations. In the area of anti-inflammatory therapy, this trend has been also explored [18-23]. Zaghloul *et al.* produced naproxen controlled release tablets with predictable drug release characteristics by compressing naproxen microspheres with Eudragit L100-55 [18]. Recently, Ivic *et al.* monitored the effect of different formulation factors on the *in vitro* release profile of diclofenac sodium from Carbopol® 71 G matrix based pellets [19]. Results of drug release studies indicated that release rates varied between different formulations. Lopes *et al.* prepared directly compressed mini tablets containing ibuprofen, as a NSAID`s agent, and either HPMC or EC, as release controlling agent [20]. For HPMC preparations the ibuprofen release approached to constant rate release during a period of 8 h. Sevgi *et al.* evaluated the use of biodegradable alginate beads as a controlled release system for mefenamic acid [23].

Based on matrix systems, various special oral systems have been patented in order to optimize drug delivery profile, such as TIMERx®, MASRx™/COSRx technologies. The TIMERx® technology controlled the drug release through a hydrophilic matrix of two polysaccharides, xanthan and locust bean gum. TIMERx® and its associated technologies, Geminex® and SyncroDose™, can provide a great flexibility of delivery profiles, ranging from zero order to chronotherapeutic release, for a wide range of drugs. SyncroDose™, a chronotherapeutic release TIMERx® technology, offers a variety of predetermined lag times, which can control when and where a drug is to be released, followed by a variety of customized drug-release profiles to include immediate and controlled release. Staniforth and Baichwal referred the interest of chronotherapeutic delivery in the treatment of rheumatoid arthritis, where early morning stiffness can be reduced or eliminated by bed-time administration of a SyncroDose™ tablet containing an anti-inflammatory drug [24].

The drawback of matrix delivery systems is the lack of constant rate delivery caused by changing effective surface area and drug diffusion path length with time. This drawback has been overcome by modifying the matrix geometry design (Geomatrix™, Smartrix®, RingCap™ and other technologies). This led to the development of matrix systems having: spherical, cylindrical, biconvex or donut shapes; hemispheres with a cavity; partially coated cores with a hole in the middle; oval bi-dose divisible tablets. RingCap™ is a capsule-shaped matrix tablet in which bands of insoluble material are applied circumferentially to the surface of the tablet. Dalton *et al.* studied the predictive ability of level A *in vitro-in vivo* correlation for RingCap™ controlled release acetaminophen tablets [25]. Geomatrix™, a multilayered hydrophilic matrix system, was developed as a means to obtain constant drug delivery by coating one or both sides of a matrix tablet with a swellable or erodible matrix barrier [26]. The Geomatrix™ technology, which is easily incurporated in the manufacturing line, is applied to achieve customized levels of controlled release of specific drugs and can achieve simultaneous release of two different drugs and different rates from a single tablet. SkyePharma Co manufactures two products containing anti-inflammatory agents based on Geomatrix™ technology: ZYFLO CR™, a controlled release formulation of zileuton, and Diclofenac-ratiopharm-uno®. El-Nabarawi prepared two layered device comprising of tenoxicam containing layer and a drug free membrane layer based on Geomatrix™ technology [27]. From this study it was concluded that, changing the geometry of drug layer by addition of drug free membrane layer and changing its composition and thickness plays an important role in determining whether the drug free membrane layer is rate controlling or modulator membrane. Hence it can facilitate the development of different

pharmaceutical products with different release pattern. Smartrix® represents other variation to the geomatrix approach. The Smartrix® device is a multilayered tablet very similar to the Geomatrix™ system, in which a geometrically designed drug containing core is combined with slowly eroding cover layers to provide a quasi-linear drug release [28]. Concerning geometric modifications, Kim prepared a triple layer, donut-shaped tablet, for various model drugs, including diclofenac sodium and naproxen sodium [29].

For many disease states (e.g. inflammatory, hypertension, allergy) the ideal dosage regimen is that by which an acceptable therapeutic concentration of drug at the site(s) of action is attained immediately and is then maintained constant for the desired span of the treatment. This ideal quick/slow biphasic delivery system can relieve rapidly the painful symptoms and can avoid repeated daily drug administrations. The multilayered tablets technologies (e.g. Geomatrix™) could be used to obtain quick/slow release patterns. Maggi *et al.* developed a compressed double-layer tablet to achieve a biphasic release of ketoprofen [30]. The quick release layer contained a super disintegration agent (cross-linked sodium starch glycolate) to increase the drug release rate. The slow release layer consisted of an HPMC matrix tablet. SkyePharma Co has one quick/slow release formulation on the German market: diclofenac-Ratiopharm Uno 25 mg Quick + 125 mg Slow, which has been produced using the Geomatrix™ technology for multiple-layer tablets. Lopes *et al.* applied two different approaches to achieve quick/slow ibuprofen delivery system: a compressed core and a mini-tablets-in-tablet system [31, 32]. To control the release of the ibuprofen, EC and HPMC were used as sustained release agents. Recently, Aburahma and Hamza proposed different strategies to optimize the quick/slow release of lornoxicam, a potent NSAID`s, with a short half-life [33-35].

Coated Dosage Forms

Coating technology is perhaps one of the oldest pharmaceutical processes still in existence. In pharmaceutical area, it offers many advantages namely: (i) improve the aesthetic qualities of the dosage form; (ii) mask unpleasant odor or taste; (iii) easy ingestion; (iv) improve product stability; (v) modify the release characteristics of the drug in tablets and multiparticulate dosage forms (e.g. pellets, granules, beads) [36]. It is widely used in enteric coating, controlled release system and osmotic pump systems [37]. In this section, it will be only referred with respect to the application of coating film in controlled release systems. The essential components of a coated dosage form are the core, which contains the drug and excipients, and the coating. The drug is initially loaded in the core matrix or encased and then one or more layers of the coating material are applied. Coats are formed often from polymeric materials, which are broadly classified as aqueous polymer dispersions, polymer solutions, molten polymers and dry powders [38]. To obtain a desired release profile, which is adapted to the pharmacokinetic/pharmacodynamic drug characteristics and type of drug treatment, different formulation and processing parameters can be made, such as the coating level, type of polymer and type and amount of added plasticizer [39-41]. Examples of common film former used in pharmaceutical applications include soluble polymers, such as alginates, carrageenans, HPMC, hydroxypropylcellulose, sodium carboxymethylcellulose, soluble acrylate and methacrylate, as well as dispersions of insoluble polymers such as EC, insoluble acrylate and methacrylate copolymers, water insoluble cellulosics, cellulose acetate and cellulose acetate phthalate. Many of the coating polymers used for controlled release have been formulated into aqueous dispersions to overcome the disadvantages associated with the use of organic polymer solutions. Various polymers such as HPMC, EC (Surrelase®, Aquocoat®), Eudragit®, kollicoat SR (containing polyvinyl acetate, povidone, and sodium lauryl sulfate), carboxymethylethylcellulose have been used for film coating of controlled release formulations containing different NSAID`s: aspirin [42], ibuprofen [43, 44], diclofenac sodium [45-48], ketoprofen [49, 50], etc. Different release profiles can be achieved, such as sustained, delayed, targeted and pulsative, depending on the type of coating material or by combining coatings with different erosion profiles and by the use of so called intelligent polymers (e.g. pH sensitive polymers).

The product Naprelan®, marketed in the United States of America, employs a special intestinal protective drug absorption system (IPDAS) developed by Elan, to enhance the gastric tolerability of potentially irritant or ulcerogenic drugs such as NSAID´s [51]. IPDAS is based on a controlled release beads compressed into a tablet dosage form. The controlled release can be achieved with the use of different polymers to coat the beads. Alternatively, the drug can also be coated into an inert carrier such as non-pareil seeds to produce instant release of multiparticulates units. The drug release from the beads occurs through a process of diffusion.

The Oruvail®, which is commercially available from Wyeth-Ayerst Laboratories, is an example of a ketoprofen controlled release formulation that employs the coated pellets technology containing EC.

Osmotic Systems

Osmotic pump systems are tablets coated with a semipermeable polymeric membrane fitted with a delivery orifice. Gastrointestinal fluids penetrate the coating membrane into the tablet core, creating a positive pressure which gradually expels the drug at a rate controlled by the osmotic properties of the tablet core and the membrane`s permeability to water. In some cases, a hydrogel is employed to push the active agent through the passageway in the membrane. In the last decade, the interest in osmotic devices has been increasing because these systems can deliver the drugs in a controlled pattern. In these systems, there are parameters which could be manipulated in order to obtain the desired control drug release, such as nature of osmotic agent, membrane thickness and orifice size [52-54].

In the field of anti-inflammatory agents, Philip and Pathak reported the osmotic pressure dependence of flurbiprofen release from a phase-transited, non-disintegrating, controlled release, asymmetric membrane capsular system [52-54]. The authors achieved excellent correlation between *in vitro* and *in vivo* pharmacokinetic studies, suggesting that the *in vivo* performance of the asymmetric membrane capsules could be accurately predicted from their *in vitro*

release profile [54]. In other study, the same authors employed the same system to control release characteristics of ketoprofen [55]. Recently, Yakubu *et al.* developed osmotic tablet cores containing ketoprofen, as poorly water-soluble model drug, and polyvinyl pyrrolidone (PVP), as an osmotic suspending/release retarding agent of drugs. The final formulation, containing PVP K-30 in the tablet core, was able to sustain the ketoprofen release over 24 h [56].

A monolithic osmotic tablet system with two orifices in both side surfaces was studied using naproxen [57]. Gum arabic was used as an osmotic, suspending and expanding agent and cellulose acetate was used as semipermeable membrane. Polyethylene glycol 400 (PEG-400) was employed as plasticizer for controlling membrane porosity. The influences of gum arabic, PEG-400, membrane thickness and orifice size on the naproxen release profiles were investigated. Kumar and Mishra used naproxen sodium to prepare an elementary osmotic pump tablet for per-oral administration [58]. The authors concluded that the rate and extent of naproxen sodium release were dependent on different osmotic agents, sodium lauryl sulphate and sodium bicarbonate in the core formulation and independent on the agitation intensity of release medium.

Shokri *et al.* designed a new type of elementary osmotic pump tablet, called swellable elementary osmotic pump (SEOP), for efficient delivery of poorly water-soluble/practically insoluble drugs using indomethacin as a model drug [59]. Indomethacin release from the system occurred through a delivery orifice in the form of a very fine dispersion ready for dissolution and absorption. The indomethacin release profile from osmotic devices showed that the type of polymer in the core formulation can markedly affect the drug release. The results showed that concentration of wetting agent in the core formulation was a very important parameter in total release after 24 h and release pattern of indomethacin from SEOP system. Increasing concentration of castor oil (hydrophobic) in the semipermeable membrane of the device or hydrophilic plasticizer (glycerin) in coating formulation markedly increased the lag time and decreased total release after 24 h. The results also demonstrated that aperture size is a critical parameter and should be optimized for each SEOP system. This study also revealed that optimization of semipermeable membrane thickness is very important for approaching zero order kinetics.

Sotthivirat *et al.* delineated the release mechanisms of a sparingly water-soluble drug, prednisolone, from a microporous or controlled porosity-osmotic pump pellet using sulfobutylether-β-cyclodextrin as both a solubilizing and osmotic agent [60].

Prodrugs

Some drugs present pharmacokinetic problems that lead to a low or lack of pharmacological activity [61]: (i) poor water solubility; (ii) low bioavailability; (iii) poor absorption through GIT; (iv) rapid first pass metabolism after administration; (v) toxicity; (vi) unpleasant organoleptic characteristics. The use of prodrugs has been studied since the 70's has a good alternative to resolve these problems. Prodrugs can be defined as a derivative inert compound of the drug, which is converted in the body to the desired pharmacological active compound. This conversion can be enzymatic or non-enzymatic [62].

In the field of oral anti-inflammatory drugs, the major problem is related to the toxicity on the GIT, originated by the use of NSAID´s. Therefore, the establishment of strategies that overcome these non-desirable effects is of main importance, especially when the drugs are required for chronic treatments. The use of a phospholipid derivative of indomethacin has been studied by Dvir *et al.* [63, 64]. They performed *in vivo* studies that showed the same therapeutic effect and lowered toxicity, compared to the base. Therefore, they claimed the use of this prodrug as alternative in chronic treatment of Alzeimer's disease and also for analgesia. Dahan *et al.* continued these studies and showed that the prodrug can be used for the control of drug release in the GIT [65, 66].

The use of nitric oxide (NO) in the GIT mucosa has a recognized protective effect [67]. This feature was used to prepare prodrugs from NSAID`s (NO-NSAID`s), by covalent attaching the NO to NSAID`s molecules, which avoids the toxicity associated to their oral administration. The drug delivery potential of NO-NSAIDs of aspirin, diclofenac, ibuprofen and indometacin has been studied. The *in vivo* experiments showed that NO-NSAID`s had similar pharmacological activity, with reduced adverse GIT side effects [68, 69]. The targeting of anti-inflammatory drugs to specific sites in the GIT (e.g. colon) has been studied for different proposes, which will be mentioned in section 3.2. Apart from the goal of target delivery in the GIT, this section will just mention the application of prodrugs as DDS, for the treatment of inflammatory bowel disease (IBD). Glucocorticoids, like budesonide, are frequently used in this treatment. However, the drug undergoes an extensive first pass metabolism, which leads to low bioavailability. A budesonide prodrug was synthesized and the *in vivo* release profile was studied by Varshosaz *et al.* [70].

Colloidal Carriers

The use of colloidal carriers, like polymeric and lipidic nanoparticles, micelles, dendrimers, aquasomes and quantum dots, have been described as one of the most promising strategies to improve drug delivery, presenting a good alternative to the use of traditional systems (e.g. tablets, capsules, pellets, and powders in sachets).

The applications of colloidal carriers could be particularly interesting in oral delivery of poorly water soluble compounds, like most of the anti-inflammatory agents. In recent years, several attempts have been made in order to improve and/or resolve formulation problems associated to the oral administration of these drugs. In the following subsections it will be discussed this in detail.

Polymeric Nanoparticles

Comparing with other colloidal carriers, oral delivery of active agents by means of polymeric nanoparticles presents advantages [71-75]: (i) biocompatibility and biodegradability; (ii) good GIT stability and protection of the encapsulated substances; (iii) high physical stability and possibility of modulation of the physicochemical properties; (iv) simple preparation methods; (v) sustained drug release

profiles, with good *in vitro* and *in vivo* behavior; (vi) low toxicity and poor immunogenic response.

These systems have sizes between 10 and 1000 nm and usually are divided into two sub-types: nanocapsules and nanospheres. Nanocapsules are constituted of an internal hydrophobic core (usually oil), which is inside a polymeric capsule, while nanospheres are composed of a polymeric homogeneous matrix. Depending on the type of polymeric nanoparticle, the drug can be entrapped, adsorbed on the particle surface or dissolved in the polymer matrix [76]. Additionally, the particle surface can be modified by adsorption or linkage of molecules, such as PEG, poloxamers and bioactive molecules [72, 77].

The prescription of oral NSAIDs to minimize or prevent inflammation is frequent between medical communities. As referred before, these drugs could give rise to gastric adverse effects that could be injurious for patients in chronic treatments [78]. Therefore, the use of carriers that overcome these effects would be desirable. Several efforts have been made on this way, especially with the use of polymers to encapsulate NSAID`s, creating nanosystems with controlled release and targeting properties, e.g. namobutene [79]; indomethacin [80-82]; naproxen [83, 84]; diclofenac [85, 86]; meloxican [87]; nimesulide [88].

The second most common type of anti-inflammatory drugs belongs to the corticosteroids class, which are highly lipophilic molecules and therefore, good candidates as model drugs to encapsulate in nanoparticles with hydrophobic cores. Successful encapsulations in polymeric nanoparticles of dexamethasone [89], hydrocortisone [90] and beclomethasone dipropionate [82] have been reported.

The treatment of IBD is commonly made with anti-inflammatory drugs, such as 5-aminosalicylic acid (5-ASA), also known as mesalazine or mesalamine. In this treatment the goal is to increase the residence time of the drug on the inflammation site, which could reduce the adverse effects [91]. Pertuit *et al.* demonstrated the therapeutic potential of polymeric nanoparticles for the treatment of IBD with 5-ASA, as target drug delivery systems to the inflamed tissue [92]. A peptide-loaded polymeric nanoparticle formulation was also reported which has a novel therapeutic approach for the IBD treatment [93].

Micelles

Due to its amphiphilic nature, surfactants tend to self-assemble in aqueous medium, when their concentration exceeds a critical value (critical micellar concentration, CMC), forming the so-called micelles. Therefore, micelles are colloidal molecular aggregates of surfactants with sizes between 5 and 100 nm, which have a hydrophobic core and a hydrophilic shell. This core can protect and deliver water-insoluble drugs until their target site of action [94]. Similar to surfactants, micelles can also be formed from amphiphilic polymers, providing more stable carriers [95].

Micelles present advantages over other colloidal carriers [95, 96]: (i) protection and solubilization of poorly water-soluble drugs; (ii) prolonged circulation high-life; (iii) site specific targeting of incorporated drugs; (iv) enhancement of drug permeation trough cell membranes; (v) low toxicity.

As stated above, several anti-inflammatory agents are poorly water-soluble molecules. This feature made these compounds good models to incorporate in micelles. Ibuprofen was successfully used as model hydrophobic drug to develop a new method of preparation of a water-soluble N-palmitoyl chitosan micelles [97]. The thermo-responsive behavior of prednisone acetate-loaded block co-polymer micelles was studied, in order to develop an intelligent drug delivery system that could respond to temperature variations [98]. Naproxen was one of the model drugs used to prepare dual drug release from the same micellar system [99].

Lipid Nanoparticles

The lipophilic character of most anti-inflammatory agents makes them good candidates for incorporation in lipidic systems like solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) and liposomes. However, in scientific literature there are only few publications referred to the application of these technologies. This is probably related with the difficulties of the systems to overcome the harsh conditions of the GIT and delivery the intact drugs to the gut.

Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC)

To overcome the disadvantages associated to the traditional colloidal systems (e.g. emulsions, liposomes and polymeric nanoparticles) solid lipid nanoparticles (SLN) were created. These carrier systems are composed of a solid lipid matrix made of physiological components, i.e. substances generally recognized as safe (GRAS). Lipid nanoparticles are solid at both room and body temperatures and have sizes between 50 and 1000 nm. Therefore, the toxicity associated to the use of SLN for oral drug delivery is nearly inexistent. [100].

In contrast to other colloidal carriers, it has been stated that SLN combines their advantages, while circumvent the disadvantages [101]: (i) good physical stability; (ii) protection of drugs from degradation; (iii) controlled drug release profiles; (iv) good physiological tolerability; (v) possibility of site specific targeting; (vi) effective production processes, avoiding the use of organic solvents and including the possibility of large scale production.

About five years after SLN creation, the nanostructured lipid carriers (NLC) emerged as an improved alternative to the first ones, in order to overcome their limitations. NLC are composed of mixtures of solid lipids with liquid lipids (oils), which produce structures with increased drug loading capacity, possibility of modulation of drug release profiles and higher long-term stability storage of incorporated substances [102].

Despite NLC are the last generation of lipid nanoparticles, there are no references in literature related with the incorporation of anti-inflammatory drugs for oral delivery and only a few report studies with SLN. Ibuprofen was successfully used as a model lipophilic drug for the development of oral SLN formulations with modified release profiles [103, 104]. Serpe *et al.* studied the effects of the improvement on the anti-inflammatory efficacy of butyrate and dexamethasone after incorporation into SLN, concluding

the efficacy of use those systems in the treatment of IBD [105].

Liposomes

Liposomes have been the most extensively investigated and successfully employed systems for the controlled release and site specific drug delivery [106]. These carriers are spherical vesicles consisting of one or more phospholipid bilayers (in most cases phosphatidylcholine) separated by internal aqueous compartments, which may differ in dimensions, composition, surface charge and structure [107]. The attractiveness of the use of liposomes in drug delivery resides on their ability to entrap hydrophilic and hydrophobic compounds, on the compatibility between their components with the body system, thereby presenting low toxicity potential. Hydrophilic drugs are solubilized in the inner aqueous core, while hydrophobic drugs can be incorporated within the lipid bilayers [108]. Depending on the method of preparation, lipid vesicles can be multi-, oligo- or unilamellar, containing many, a few, or one bilayer shell(s), respectively, with diameters between about 20 nm and a few hundred micrometers [109, 110].

Liposomes are easy to prepare, their composition can be varied to obtain more efficient preparations and their surface can also be modified. It is therefore surprising that there are still so few liposome formulations on the market, owing perhaps to some *in vivo* instability that may cause rapid release of the drug from the formulation [111]. Oral administration of indomethacin-encapsulated liposomes showed promising results, regarding their bioavailability and *in vivo* performances [112, 113]. Deniz *et al.* had good results with liposome encapsulation and release of celecoxib, in order to avoid the systemic side effects and low bioavailability of oral formulations [114]. Clares *et al.* developed a liposome system with good characteristics of encapsulation of triamcinolone acetonide [115].

Microparticles

Microparticles or microspheres are solid and spherical particles, with sizes from 1 to 1000 μm. They are commonly composed of polymers, but can be made by other materials (starches, gums, proteins, lipids and waxes) and used as drug carrier matrices for drug delivery. Although having bigger sizes, microparticles share some of the features and advantages of polymeric nanoparticles [116, 117]. One of the major problems associated to oral microparticles formulations is the rapid drug release in contact with gastric fluids, before reaching the intestine. Constantin *et al.* developed a multi-compartmental microparticle system based on the use of two polymers, which uses diclofenac as a model drug [118]. A water soluble salt of these NSAID`s, diclofenac sodium, was also used as a model to study and extend drug release from nanocapsule xerogel microparticles [119].

As already mentioned, for the treatment of IBD is desirable to maintain the drug on the inflammation site, during long periods [91]. One of the strategies studied to achieve this challenge is the coating of 5-ASA-loaded microparticles with chitosan, a polycationic polymer with mucoadhesive properties [120]. Despite being more effective at low dose, the use of prednisolone is generally a second choice drug for the treatment of IBD, because of the immunosuppression induction. Therefore, the development of site-specific delivery systems for this drug is of main importance. Onishi *et al.* studied the *in vitro* behavior of eudragit-coated chitosan microparticles of prednisolone, in order to obtain a target intestinal delivery of the drug [121].

Other Carriers

Aquasomes

Aquasomes are water-soluble colloidal carriers (sizes lower than 1000 nm), with hydrophobic inorganic cores, coated with polyhydroxyl molecules, which confers hydrophilic properties to the systems. The possibilities of administration in aqueous medium and the establishment of non-covalent links with other molecules for the improvement of long-term stability were claimed to be the advantages of these carriers. Rojas-Oviedo *et al.* have used indomethacin as model lipophilic drug to prepare and study the aquasomes potential as drug delivery systems [122].

Dendrimers

Dendrimers are macromolecules with a ramified branched tridimensional structure, which can have precise desired characteristics [123, 124]. These molecules can be used as drug carriers with different proposes: (i) encapsulate hydrophobic drugs on the internal cavity, improving their bioavailability; (ii) attach drugs to some functional groups of the macromolecules by means of covalent bounds for pro-drug delivery. According to their lipophilic character, ketoprofen [2] and naproxen [125] were used as model drugs to study the potential of dendrimers as carriers for sustained drug release.

SITE-SPECIFIC ORALLY ADMINISTERED CONTROLLED RELEASE

Gastroretentive Delivery Systems

In the last decade, scientific and technological advances have been made in order to control oral DDS by overcoming physiological harsh conditions, such as short gastric residence times and unpredictable gastric emptying times. Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper GIT for local or systemic effects. Prolonged gastric residence time improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the solubility of drugs that are less soluble in a high pH environment [126]. Additionally, prolonged gastric retention time in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer [127]. The controlled gastric retention of solid dosage forms can be achieved by: high-density (sinking) systems, which are retained in the bottom of the stomach; low-density (floating) systems, that causes buoyancy in gastric fluid; swelling and expandable systems, which limits emptying of the system through the pyloric sphincter of the stomach; mucoadhesive systems, that causes bioadhesion to stomach mucosa; superporous hydrogel systems, and magnetic systems [128].

In the anti-inflammatory therapy, floating DDS are one of the most important gastric retention approaches to obtain sufficient drug bioavailability. In addition, a blend of floating and pulsatile principles of DDS would have the advantage that a drug can be released in the upper GIT after a definite time period without drug release. Floating/pulsative drug delivery could be useful in chronopharmacotherapy of diseases (e.g. rheumatoid arthritis) for site and time specific release of drugs. The low density can be provided by the entrapment of air (e.g. hollow chambers) or by the incorporation of low density materials (e.g. fatty materials or oils, or foam powder). These following systems have been used for the design of floating dosage forms of single and multiparticulate unit systems. Basavaraj *et al.* prepared a multiparticulate (microballons) floating system with extended gastrointestinal transit time, capable of distributing widely throughout the GIT for effective enteric release of diclofenac sodium [129]. The microballoons (along with the surfactant) floated continuously for more than 12 h in the acidic medium *in vitro* conditions. The *in vitro* drug release profile of the formulation in the simulated gastric buffer showed no drug release, which emphasizes the enteric release property and in simulated intestinal buffer, a slow and controlled drug release was obtained over a period of 8 h. Badve *et al.* developed hollow calcium pectinate beads for floating-pulsatile release of diclofenac sodium intended for chronopharmacotherapy [130]. *In vivo* studies by gamma scintigraphy determined on rabbits showed gastroretention of beads up to 5 h. The floating beads provided expected two-phase release pattern with initial lag time during floating in acidic medium, followed by rapid pulse release in phosphate buffer. The authors suggested the use of hollow calcium pectinate microparticles as promising floating-pulsatile DDS. The same objective of floating pulsatile system using ibuprofen for chronotherapy in arthritis was explored by Sher *et al.* [131]. The objective of this delivery system lies in the availability of maximum drug amount for absorption in the wee hours as recommended. Sharma and Pawar deve-loped a multiparticulate floating-pulsatile drug delivery system using porous calcium silicate and sodium alginate, for time and site specific drug release of meloxicam [132]. Formulations showed a lag period ranging from 1.9 to 7.8 h in acidic medium followed by rapid release of meloxicam in simulated intestinal fluid (SIF) USP, without enzymes. Complete drug release in SIF occurred in less than 1h from the formulations. Floating time was controlled by density of beads and hydrophobic character of drug. A pulsatile release of meloxicam was demonstrated by a simple drug delivery system which could be useful in chronopharmacotherapy of rheumatoid arthritis.

Colon Delivery Systems

In the past years much attention has been focused on developing oral colon specific DDS to carry a variety of therapeutic agents, particularly glucocorticoids and other anti-inflammatory agents, to treat pathologies of chronic inflammatory states (e.g. ulcerative colitis, IBD). In addition, anti-inflammatory agents showed a promising activity for prevention and treatment of colitis and colon cancers [133, 134]. Directly drug release to its site of action may allow a reduction in dose, and consequently a reduction in potential systemic side effects, which are of a major importance in the treatment of these conditions [135]. Different systems have been developed to achieve colon target delivery, such as covalent linkage of a drug with a carrier, coating with pH sensitive polymer, time-dependent release systems, microbially controlled systems making use of the abundant enterobacteria in the colon, etc. [136]. Although the majority of colon DDS developed during the past decade are based on pH and time dependent features, they have practical *in vivo* limitations. In the case of pH dependent systems, minor variation in pH between the small intestine and the colon can result in poor colon specificity drug release [137]. Large *in vivo* variation of the small intestinal transit time makes time dependent systems less predictable, in terms of colon targeted drug release [138].

Oral pH based delivery systems to colon use coated enteric polymers (e.g. Eudragit®) that are insoluble in the stomach have relatively higher threshold pH for dissolution. The pH-dependent colonic formulations should maintain their integrity during passage through the stomach and small intestine and reach the large intestine where occurs the disintegration of the coat to release the drug locally. 5-ASA tablets coated with Eudragit® 100L are commercially available as Claversal™, Salofalk™, Mesasal® and Rowasa® [136]. Colon targeted drug pH dependent systems have been applied for different anti-inflammatory agents such as ibuprofen [139], diclofenac [140] and 5-ASA [141, 142]. The long lag times at the ileo-cecal junction and the rapid transit through the ascending colon indicate that enteric coated single unit formulations may not be the best dosage form for a colon targeted drug release. An alternative approach to overcome this issue is the use of multiparticulated dosage forms (e.g. pellets, granules, micro and nanoparticles). Recently, Makhof *et al.* designed novel pH-sensitive nanospheres for budesonide colon-specific delivery using polymeric mixtures of poly (lactic-co-glycolic) acid and methacrylate copolymers [143]. The proposed nanospheres system combines the properties of pH-sensitivity, controlled release, and particulate targeting that could be useful for colon-specific delivery in IBD.

The time controlled or delayed systems to colon targeted are particularly useful in the therapy of diseases, which depend on circadian rhythms. In these systems, the drug release occurs after a predetermined lag phase, which is precisely programmed by selecting a suitable component that prevents disintegration in upper GIT (e.g. pH dependent polymer coat) and other component that controlled dug release (e.g. hydrophilic polymer coat and osmotic pressure) [136]. Therefore, the combination of various dependence systems (e.g. pH and time dependent systems) could offer a means for achieving controlled release to colon. Patel *et al.* developed a dual combination system (time and pH-dependent system) for delivering 5-ASA to the colon [144]. This system consists of the core tablet of anti-inflammatory agent which is compression coated with hydroxypropyl methylcellulose (HPMC K4M) (time dependent factor). This is then coated with pH-dependent polymer Eudragit® L100. Using the same drug, Nunthanid *et al.* prepared a time and a pH controlled drug delivery due to the insolubility of EC suppressing water diffusion and the swelling of spray-dried chitosan acetate [145]. Chandran *et al.* developed microspheres of indomethacin with pH sensitive polymers (Eudragit® L100 or S100), and transit time EC dependent release properties for achieving targeted delivery to the colon [147]. The lag time in the initial release depended on the proportion of pH-sensitive polymer Eudragit®, while the duration of indomethacin release from microspheres was found to be directly proportional to proportion of the total polymer. Asghar *et al.* also formulated a pH and time controlled release matrix for colon-specific delivery of indomethacin using different pH and time controlled polymers [148].

Microbially sensitive systems, the most specific colon targeted approach, are based on the presence of biodegradeable enzymes only in the colon bioenvironment. Yehia *et al.* formulated budesonide compression-coated tablets using different approaches [149, 150]. Enzymatically controlled delivery systems were developed using pectin and guar gum in the compression coat. pH sensitive polymers (Eudragit®) and time-dependent polymers, HPMC and cellulose acetate butyrate, were also tried in an attempt to optimize drug release in the colon. Karrout *et al.* prepared 5-ASA-loaded beads coated with different Nutriose:EC blends [151]. Nutriose is a starch derivative, which is preferentially degraded by enzymes secreted by the microflora in the colon. Liu *et al.* had showed the high potential of a microbially triggered colon-targeted osmotic pump for budesonide release [152]. The gelable property under acid condition and colon-specific biodegradation of chitosan were used.

Colonic specific prodrugs are designed to undergo minimal absorption and hydrolysis in the upper gastrointestinal tract and undergo enzymatic hydrolysis in the colon, releasing the drug from the carrier. Recently, several studies have been reported the used of prodrugs for colonic target delivery of anti-inflammatory such as glucocorticoids (e.g. prednisolone budesonide) and NSAID`s (e.g. indomethacin, flurbiprofen, naproxen, keoprofen) using different colon targeting carriers (e.g. polyssacharides, cyclodextrins, azo compounds) [70, 133, 153-160].

CONCLUSION

Oral route is the most conventional and preferred route for drug administration in general and in particular for anti-inflammatory drugs. Usually, anti-inflammatory therapy involves frequent dosage administration, and the adverse GIT effects of these agents are well known, the chances of patient noncompliance increase drastically. In the last few years, various approaches have been made to overcome these problems. This review reports a full overview of the most recently developed DDS, used as therapeutic targets of anti-inflammatory action, which may potentially increase the efficacy of treatments. By now, a large number of pharmaceutical companies are focusing toward the commercialization of these advanced systems. However, further developments are needed to achieve more satisfactory results, especially those which are related with *in vivo* studies and human clinical trials.

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