Polymeric Materials and Formulation Technologies for Modified-Release Tablet Development

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Abstract: Over the last years significant advances have been made in the area of drug delivery with the development of modified-release (MR) dosage forms. The present review is divided into two parts, one dealing with technologies for the design of modified-release drug delivery tablets and the other with the use of synthetic and natural polymers that are capable of controlling drug release.

Key Words: Matrix tablets, modified-release, controlled-release, extended-release, multilayer, coating, zero-order, natural polymers.

1. INTRODUCCTION

Successful pharmacotherapy depends on many factors. While efficacy is obviously important, other factors such as availability of optimal dosage and delivery forms, treatment compliance and reduction of side effects need to be taken into account [1]. Over the last years significant advances have been made in the area of drug delivery with the development of modified-release dosage forms [2]. The main purpose of these novel formulations has been to improve the state of disease management by modifying the pharmacokinetic profiles of therapeutic agents normally administered as conventional tablets or capsules, which may be an advantage in chronic disease treatments [3].

The main limiting factors in long-term therapy for the treatment of chronic diseases are the high prevalence of systemic side effects, together with the possibility of developing dependency, resistance to the drug, and therapeutic failure. Controlled-release oral dosage forms allow for a gradual release of the drug, usually permitting once-daily administration and avoiding the disadvantages refered to above. Hence, trying to simplify treatment regimens in terms of dose frequency or reduction in polypharmacy, pharmaceutical industry has launched to the market many active agents formulated as controlled-release oral dosage forms. At the moment, the range of drugs marketed based on this technology is very extensive. In what follows, there are different therapeutic areas in which controlled-release formulations have been developed, describing the beneficial aspects of controlled-release compared with immediate release formulations.

The treatment of psychiatric diseases frequently requires long-term treatment and, as with most chronic illnesses, poor treatment compliance is a widespread phenomenon. Many studies have demonstrated that rates of noncompliance with psychotropic drugs are very high, may be as great as 50%. Moreover, it must be taken into account that disease-related factors, such as cognitive dysfunctions or memory deficits, also affect treatment compliance. Thus, new controlled-release formulations of psychotropics may improve treatment compliance over conventional formulations. Among all the antipsychotic drugs, the group of antidepressant agents has shown important advances. Venlafaxine, the first molecule of the dual reuptake inhibitor group, was microencapsulated in an extended release capsule (Effexor® XR) to enable once-daily administration [4]. Within the group of antidepressants, paroxetine and fluoxetine, the most usual selective serotonin reuptake inhibitors, were formulated as delayed-release oral dosage forms with the enteric film-coating technology. In the case of paroxetin, the new formulation (Paxil® CR) was designed to decrease the gastrointestinal side effects of immediate–release paroxetine [5]. On the other hand, fluoxetine is now available in capsules taken once weekly (Prozac® Weekly™) [4].

Another interesting antipsychotic group intended for chronic administration, is the group of central nervous system stimulant drugs indicated for attention deficit hyperactivity disorder (ADHD). Despite their efficacy, due to the short duration of action of available stimulants, multiple daily doses are needed for many children. Hence, the last dose of the day must be administered at a time when it will not adversely affect sleep. Thus, to solve the complexity of dosing schedules, osmotic-controlled release oral delivery system (OROS) methylphenidate (Concerta®) and double pulsed delivery system amphetamine (Aderall® XR) were formulated. In this case, both formulations employ advanced multilayer delivery technologies to permit once daily administration.

Another interesting application field for controlled-release formulations focuses on the treatment of chronic

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pain, which remains a highly prevalent problem for patients suffering from cancer or osteoarthritis. An optimal pain treatment involves a good assessment of the type of pain, followed by a correct treatment design based on the diagnosis. Moreover, vertigo, nausea, constipation, somnolence and flushing are common adverse events reported in patients with moderate to moderately severe chronic pain. Thus, opioid analgesics are interesting candidates for controlled-release formulations. For example, extended-release tramadol (ULTRAM® ER) and oxymorphone oral dosage forms can provide rapid pain control with a lower incidence of side effects than immediate release oral dosage forms [6, 7].

Over the last decade, enhanced topical activity and lower systemic activity corticosteroid formulations have been developed to decrease systemic side effects. Indeed, trying to achieve a uniform release of budesonide along the length of the colon, gastro-resistant, controlled-release tablets of budesonide characterized by a multimatrix structure (budesonide MMX®) are developed for the treatment of ileo(-cecal) active Crohn's disease with mild-to-moderate activity [8]. Furthermore, several oral dosage forms, which possess appropiate lag time for colonic drug delivery, have been developed. Thus, novel oral colon-specific drug delivery system (CDDS) have several benefits. First, improving safety and reducing toxicity for treating localized colonic diseases, i.e. ulcerative colitis, Crohn´s disease, constipation etc. Second, CDDS could provide reliable protection against gastrointestinal enzymatic degradation, thereafter resulting in remarkably increased bioavailability for protein and polypeptide. Moreover, CDDS would be advantageous when a delay in absorption is desirable from a therapeutical point of view. This last advantage is interesting for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadiam rhythms, such as nocturnal asthma, angina and rheumatoid arthritis [9, 10]. Besides the drugs already mentioned, antihypertensive, antianginal, antimicrobial, antiepileptic and hypoglycaemiant agents were also marketed as modified-release orally administered pharmaceutical forms. Table **1** summarices several active agents that have been developed with the above mentioned technologies.

Table 1. Examples of Active Agents Formulated as Modified Release Oral Delivery Systems

Drug	Therapeutic Group Description	Oral Delivery System	Ref.
budesonide	corticosteroid for inflammatory bowel diseases	MMX®-budesonide: multimatrix system tablets	[4]
venlafaxine (prodrug of desvenlafaxine)	serotonin-norepinephrine reuptake inhibitor	ER tablets	[1]
oxymorphone	semisynthetic opioid analgesic agonist	Opana® ER tablets	[84]
tramadol	centrally acting synthetic analgesic, μ-opioid receptors agonist	Ultram® ER tablets	[84]
ranolazine	antianginal agent that reduces calcium uptake indirectly by inhibiting late Na^+ channels	Ranexa® ER tablets	[85, 86]
gabapentin	GABA receptor agonist (epilepsy and seizures treatment)	ER tablets based on Depomed's AcuForm™ drug delivery technology	[87]
paliperidone (the major active metabolite of risperidone)	second-generation antipsychotic: D2 and 5-HT2A receptor antagonist	INVEGA® (OROS® tablets)	[88]
minocycline hydrochloride	tetracycline derivative for the treatment of inflammatory lesions of moderate to severe acne vulgaris	ER tablets	[89]
nisoldipine	antihypertensive agent: 1,4-dihydropyridine calcium antagonist	*coat-core* tablets	[90]
paroxetine	SSRI antidepressant agent	Paxil CR® (enteric film coated tablet)	[1]
methylphenidate	CNS stimulant for ADHD	OROS® tablets	[1]
metformin	hypoglycemiant agent (Type 2 diabetes mellitus treatment)	Glumetza™ (ER tablets based on Depomed's AcuForm® drug delivery technology)	[91]
clarithromycin	advanced generation macrolide indicated to acute exacerbations of chronic bronchitis, community-acquired pneumonia and acute maxillary sinusitis	Biaxin™ (ER tablets)	[92]
amoxicillin / clavunalate potassium	β-lactam antibiotic / anti-β-lactamase agent with increased activity against Streptococcus pneumoniae for the treatment of acute bacterial sinusitis and community-acquired pneumonia	Augmentin XR™, GlaxoSmithKline (amoxicillin/clavulanate potassium ER tablets)	[93]

ER: extended-release
IR: immediate-release
DR: delayed-release
OROS®: osmotic-controlled release oral-delivery systems
ADHD: attention deficit hyperactivity disorder

Therefore, it is clear that modified-release oral dosage forms have a very important role in the medical field. Principles for drug release retardation include coating of tablets, capsules and pellets, matrix or hydrocolloid embedding, osmotic controlled release and multiparticulate dosage froms [11]. Among all these strategies, matrix-based controlled-release tablet formulations are the most popular and easiest to produce on an industrial scale.

The aim of this review is to give an overview of the new formulation materials and technologies used for the development of modified-release tablets in the last decade, taking into account the variables involved to obtain a succesfull formulation, such as, the physicochemical properties of the drug and excipients and the release mechanism of the drug from the matrix. Moreover, special emphasis is laid on the new biopolymeric swellable matrix systems and several examples of natural polymers are given.

2. TECHNOLOGIES FOR THE DESIGN OF MODIFIED-RELEASE DRUG DELIVERY TABLETS

Over the past thirty years, many strategies have been chosen for the design and development of modified-release drug delivery tablets, such as different matrix systems, film coating, multi-layering and osmotic controlled release systems. It is also important to stress that different strategies are frequently combined in the same formulation and the drug release pattern depends on more than one factor involved in the global process.

2.1. Controlled-Release Matrix Tablets

A controlled-release matrix tablet consists of a compressed compact containing a mixture of one or more active ingredients with one or more release retardant agents. It can be prepared via granulation or by direct compression. The main characteristic of controlled-release matrices is that they are heterogeneous (porous) in nature and they must be distinguished from homogeneous matrices (non porous).

2.1.1. Monolithic Matrix Tablets

Monolithic systems, the simplest form of matrix systems, are commonly used in controlled drug release due to their low cost, broad Food and Drug Administration (FDA) acceptance, easiness of manufacturing, their favorable *in vivo* performance and their wide range of physico-chemical properties [12]. Thus, a large number of synthetic polymers has been employed as drug retarding agents, each of which presents a different approach to the matrix concept and is classified as hydrophilic, hydrophobic and plastic materials [13].

2.1.1.1- Monolithic Swellable Hydrophilic Matrix Tablets

Compared to other devices, hydrophilic matrices provide the possibility of introducing large proportions of the drug and a wide range of release profiles [14]. Polymers from hydrophilic matrix systems, when exposed to an aqueous medium, do not disintegrate, but, rather, immediately after hydration, they develop a highly viscous gelatinous surface barrier which controls the drug release [13]. Indeed, to achieve controlled drug release from matrix tablets the rapid formation of this viscous gel layer is an essential first step [15]. In fact, when a hydrophilic matrix comes into contact with an aqueous medium, a progressive change from the glassy to the rubbery state leads to a swelling process. This change in the solvated state is caused by the lowering of the polymer transition temperature, which depends on temperature and thermodynamic interactions of the polymer-water system [16].

Since Alderman´s (1984) review of the use of cellulose ethers in hydrophilic swellable matrices for oral controlled-release dosage forms [17], many types of polymers, used as rate controlling agents, have been extensively studied. Among all the synthetic hydrophilic polymers, cellulose ethers are probably the most frequently cited in pharmaceutical literature. Thus, several reports were found on the usage of cellulose ethers, such as hydroxypropylmethylcellulose (HPMC), methylcellulose (MC), sodium carboxymethylcellulose (NaCMC) [3, 18], hydroxyethylcellulose (HEC) and carboxymethylcellulose (CMC) [19] to formulate hydrophilic matrices. As shown in Fig. (**1**), the release profile of tablets formulated by different ratios of low-viscosity grades of HPMC (HPMC K-100 and HPMC 15cps), was relatively similar to that obtained with the marketed product "Fig. (**1**)".

2.1.1.2. Monolithic Hydrophobic Matrix Tablets

Hydrophobic polymers are suitable for developing controlled-release dosage forms for drugs with high water solubility and pH and moisture level dependent release, such as Baclofen, a widely used centrally acting skeletal muscle relaxant. Hydrophobic polymers, which include inert insoluble non-plastic and plastic polymers, are potentially erodable and they usually control the release of drug through pore diffusion and erosion. Among inert hydrophobic non-plastic polymers the ethylcellulose (EC) [20] and the Eudragit® group are suitable for monolithic matrix structures.

Polymers from the Eudragit® group are synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. Specifically, RL 30 D, RL PO, RL 100, RS 30 D, RS PO, RS 100, NE 30 D, NM 30 D, NE 40 D are the most used types of Eudragit® in monolithic controlled-release hydrophobic matrix tablet-development. Moreover, they are pH-independent, inert to the digestive tract, impermeable to water, as well as capable of swelling and releasing active ingredients by diffusion [21].

Besides hydrophobic non-plastic systems, plastic monolithic matrix systems have been widely used in controlled-release oral tablets, due to their chemical inertness and drug embedding ability. Polyvinylpyrrolidone derivatives, known as Kollidon®, have the best properties to be candidates as retardant agents in such systems. Among all the polymers from the Kollidon group, Kollidon SR (polyvinyl acetate and polyvinyl pyrrolidone) provide optimal properties for the manufacture of pH-independent controlled-release matrix tablets. They contain a non-ionic group, which render the polymer inert to the drug molecule [13]. Moreover the use of Kollidon SR as a plastic material to formulate controlled-release dosage forms has been extensivily reported [22, 23]. In such systems, unless channeling agents are used, liquid penetration into the matrix is the rate-limiting step. Nevertheless, despite not using channeling agents, the control of

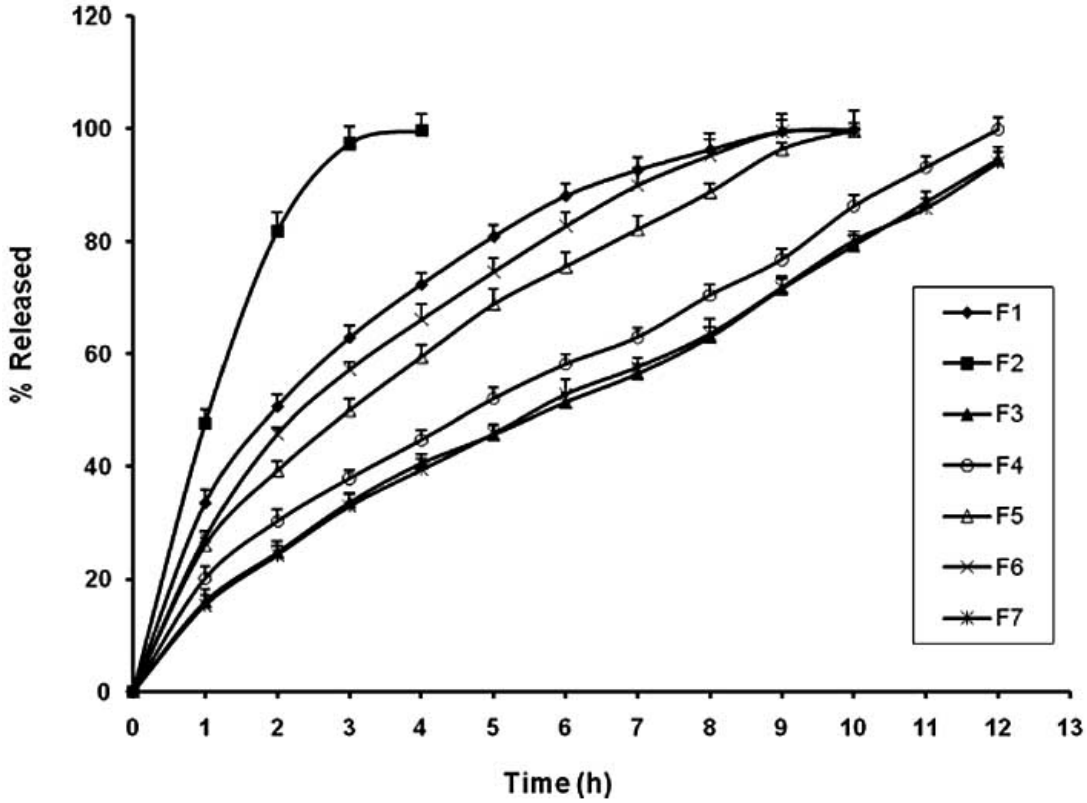

Fig. (1). In vitro release profiles showing the effect of different grades of HPMC on alfuzosin HCl matrix tablets and marketed product. Data represent the means ± SE of six experiments: (♦)F1: 50 mg/tablet of HPMC K-100, (■) F2: 50 mg/tablet of HPMC 15cps, (▲) F3: 50 mg/tablet of HPMC K-100 and 50 mg/tablet of HPMC 15cps , (❍) F4: 50 mg/tablet of HPMC K-100 and 25 mg/tablet of HPMC 15cps , (Δ) F5: 25 mg/tablet of HPMC K-100 and 25 mg/tablet of HPMC 15cps, (X) F6: 25 mg/tablet of HPMC K-100 and 15 mg/tablet of HPMC 15cps, and (*) F7: marketed product (reprinted with permission from [18]).

drug release from plastic matrices was found to be higher than that from waxy matrices [13].

2.1.2. Copolymers and Polymer Blends Matrix Based Tablets

As mentioned above, using monolithic gel-forming polymer matrix systems is possible to obtain a desirable controlled drug release profile. However, sometimes, such as in the case of highly water-soluble drugs, matrix properties modification is necessary to obtain a desirable release profile. Nevertheless, the variation of matrix polymer properties is generally restricted and it is sometimes difficult to adjust optimized release kinetics. An interesting possibility to overcome these restrictions is based on the use of copolymers. Over the last years several methyl methacrylate (MMA) copolymers have been used. Copolymers were synthesised by free radical copolymerisation of methyl methacrylate with starch or cellulose derivatives, using Ce(IV) as an initiator. Thus, the products obtained were alternatively dried by oven or freeze-drying techniques [24]. For example, (Fig. **2**) shows an anhydrous theophylline release for methyl methacrylate copolymer matrices dried in an oven vaccum compared with the ones with freeze-dried derivatives. "Fig. (**2**)".

In this respect, Bromberg *et al.* (2007) designed a novel block copolymer attaching Poly(acrylic acid) (PAA) on both termini of Pluronic P85 (EO27PO39EO27) via atom transfer radical polymerization. In fact, they demostrated the potential of this novel copolymeric matrix for the oral administration of Camptothecin, an oral chemotherapy agent. Hence, easiness of preparation and formulation of drugs with Pluronic-PAA polymers may enable the wider use of oral chemotherapy, resulting in a better patient compliance and improved life quality [25, 26].

However, the major drawback of copolymers is that new chemical entities with unknown toxicological profile are introduced, and a lot of time and resources must be spent in safety evaluation. In order to overcome this problem, innovations based on blends of two types of polymers, which are known to be non-toxic and exhibit different physicochemical characteristics (i.e. mechanical stability, water and drug permeability and solubility along the gastrointestinal solubility), were developed [27].

Among the polymer blends, interpolyelectrolyte complexes (IPECs) have attracted a considerable interest in pharmaceutical research and were formulated as a valuable tool to design drug delivery systems with specific physicochemical properties [28]. IPECs are composed of polycationic and polyanionic polymers mixing both polymers in aqueous solutions. Different polyanions of natural and synthetic origin were used as oppositely charged polyelectro-

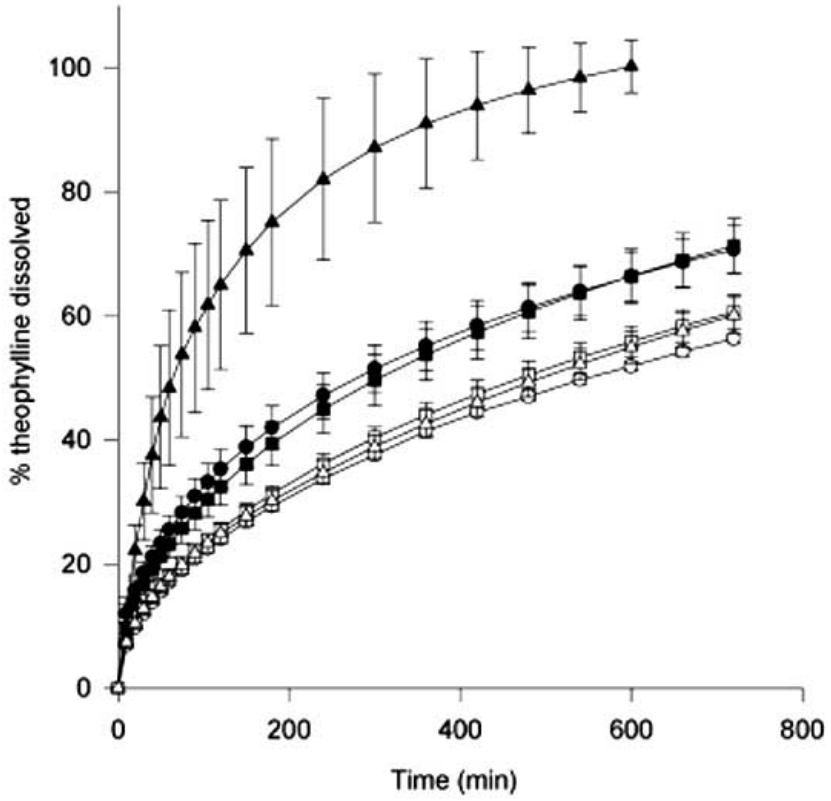

Fig. (2). Release profiles of anhydrous theophylline (over 12 h) from formulated tablets of hydroxypropylstarch-methyl methacrylate (HSMMA) (●), carboxymethylstarch-methyl methacrylate (CSMMA) (■) and hydroxypropylcellulose-methyl methacrylate (HCMMA) (▲) copolymers. The products dried either in a vacuum oven (OD copolymers) are represented by closed symbols and freeze-dried products (FD copolymers) by open ones. The bars show the standard deviation (n=6) (reprinted with permission from [24]).

lytes mostly with participation of chitosan (CS) as polycation [28]. After polymer verification compatibility, IPEC tablets were normally prepared by direct compression of the powder mixtures, by keeping both the total amount of drug and the drug-to-polymer ratio constant [29]. Table **2** shows examples of natural and synthetic polymers that have been used to design IPECs with CS.

However, electrostatic complexes are not always the best option. Therefore, various kinds of polymers mixtures with

Table 2. Examples of Polyanions Used in IPEC Formulation with CS for Controlled Release Dosage Forms

Type of polyanion	Polyanion Source	Delivery System	Drug	Ref.
Carbopol® 971	synthetic	ER tablet	theophylline	[94]
carrageenan	natural	prolonged release tablet	diltiazem	[95]
xanthan gum	natural	SR tablet	chlorpheniramine maleate	[73]
sodium alginate	natural	bioadhesive tablets for intraoral drug delivery	ketoprofen	[96]
alginate	natural	ER tablets	diltiazem	[95]
Carbopol® 971NF	synthetic	CR tablet	theophylline	[97]
Eudragit® L100	synthetic	CR tablet	diclofenac	[28]
CMC	synthetic	Gastric-specific delivery tablets-in-capsule	clarithromycin	[98]

CS: chitosan
ER: extended-release
CR: controlled-release
SR: sustained-release

different physicochemical properties polymeric compounds, such as HPMC, NaCMC, sodium alginate and xanthan gum (XG), have been tested to design non-electrostatic complexes. Nevertheless, when the diffusion of hydrophilic drug through the matrix is so fast, the hydrogel network needs the incorporation of hydrophobic polymers, such as EC along with an hydrophilic polymer to achieve the optimun release profile [30]. Moreover, Corti *et al*. (2008) observed that blends consisting of a hydrophilic swelling polymer (i.e. HPMC) with a pH-dependent one (i.e. Eudragit-L100-55) were more useful than single polymers in controlling metformin hydrochloride drug release, an anti-hyperglycaemic agent used in the treatment of type II non-insulin-dependent diabetes mellitus. These results could be attributed to the development of a suitable drug delivery system able to initiate release in the stomach and almost complete it in the jejunum. Thus, the addition of a pH dependent polymer allows to reach the prefixed goal. Furthermore, for treatment of allergic rhinitis, acrivastine with pseudoephedrine in capsules requires dosing every 6-8 hours. However, the combination of waxy retardant polymer Compritol 888 ATO and hydrophilic Methocel® produced optimal controlled drug release for longer than 8 hours for both acrivastine and pseudoephedrine [31].

Although less common other polymer blend examples, are the blends of more than two matrix ingredients. Thus, a balanced ternary blend of a non-ionic water soluble polymer (polyox), a swellable high molecular-weight and cross-linked acrylic polymer (carbopol) and lactose has been reported. Both Polyox and lactose increase theophylline release from the blend matrix whereas Carbopol suppressed the release of the drug. In this respect, thanks to the equilibrium reached by the mixture of the three polymers, it is possible to attain a zero-order theophylline release profile [32]. However, these systems are more complex than those based on only one polymer. For future research a thorough understanding of the polymeric structures at a molecular level would be highly desirable.

2.1.2.1. TIMERx® Technology

Within the matrix systems, particular attention has been given to a very versatile hydrogel-based controlled-release technology, called TIMERx (Penwest Pharmaceuticals). This technology, is based on a customized, agglomerated hydrophilic complex that forms a controlled-release matrix upon compression. The matrix consists of two natural polysaccharides, xanthan and locust bean gum. Interactions between these components in an aqueous environment form a tight gel with a slowly-eroding core [33].

In this respect, few years ago Endo Pharmaceuticals using Penwest's TIMERx proprietary drug delivery technology, designed a new oral long-acting formulation indicated for the treatment of moderate to severe chronic pain (low back, cancer, and osteoarthritis), Opana® ER (oxymorphone extended-release). In fact, Oxymorphone ER is the only long-acting opioid with low peak-to-trough fluctuations containing oxymorphone, which exhibits some distinct pharmacologic properties compared with most other opioids, including a longer half-life, a higher affinity for the micro-opioid receptor, and a lack of interaction with the CYPP450 drug-metabolizing system [34].

2.2. Other Technologies

2.2.1. Film Coating Technology

Film coating techniques have been widely applied in pharmaceutical industry for many reasons. For example, sugar-coated tablets can maske the unpleasant taste and odor of drugs and also provide protection to water sensitive drugs against the hydrolysis and oxidative degradation. Nevertheless, film coating technology is mostly used as an effective way to control the release of the drug. It is specially common in multiple unit dosage forms, such as prolonged release pellets, than in single unit tablets. In this technology, a drug-loaded core is coated with aqueous solutions or dispersions, but sometimes, depending on the viscosity of the polymer, organic solvents are necesary. Besides the coating polymer and the solvent, a plasticizer such as dibutyl sebacate (DBS) [35] or diethyl phthalate [9] is commonly used to prepare the coating solution, except when the tablets are coated by silicone elastomers [36].

Oral dosage forms formulated by film coating technology are considered reservoir systems and diffusion is the drug-release mechanism at work. The permeability of the polymer membrane, which is directly related to the water uptake or swelling of the polymer, is the main factor for the control of drug diffusion. The hydrogel hypothesis is widely applicable for swellable polymers like cellulose derivatives, such as HPMC, EC or cellulose acetate (CA). In the same way, diffusion is also the drug release mechanism observed in tablets coated with polyvinyl acetate (PVAc) / polyvinyl alcohol-polyethylene glycol graft copolymer (PVA-PEG) [11]. However, a more complex drug release mechanism may exist, i.e. Wagner and Gruetzmann observed that, in tablets coated with Eudragit RS, drug release was inversely proportional to the selectivity coefficient of the anion species toward the cationic quaternary ammonium group of the polymethacrylate and anions of the buffer solution [37].

Film coating technology is also applied in colonic drug delivery. In this respect, various approaches have been studied, including pressure-controlled delivery systems [38], prodrugs [39,40], microflora-triggered delivery systems [41, 42], gastrointestinal transit time-dependent delivery systems [43] and pH dependent delivery systems [44]. Among the different approaches, the use of polymers, specifically biodegraded by colonic bacterial enzymes, holds greater promise. The bacteria present in the colon, such as *Bacteroides*, *Bifidobacterium*, *Eubacterium*, *Peptococcus*, *Lactobacillus*, *Clostridium* etc., secrete a wide range of hydrolitic and reductive enzymes responsible for biodegradation of di-, tri- and polysaccharides. One of the latest technique developed for colonic drug delivery is based on a core tablet coated with three layers of polymeric coating (CODES™). The inner coat (next to the core), which restricts drug release in the small intestinal enviroment, is an acid soluble polymer, Eudragit, and the outer coat is an enteric coat, cellulose acetate phtalate (CAP). There is an HPMC barrier layer in between the inner and outer coat designed to prevent any interaction between the oppositely charged polymers. The core tablet is

comprised of any polysaccharide, which gets degraded by colonic microflora, i.e. guar gum, chitosan etc.[45].

2.2.2. Tablets Formulated by Multilayer Technology

Formulating oral controlled release tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most high solubility drugs, such as metoprolol tartrate [46] and propanolol hydrocloride (non-selestive beta-adrenergic blockers) [47], verapamil hydrochloride (calcium chanel blocker) [48], trimetazidine dihydrochloride (anti-ischemic metabolic agent) [49] etc., may present a faster release pattern than desired and are likely to produce toxic concentracions. Sometimes, it is very difficult that in conventional controlled-release matrix systems the release of the drug inherently follows a zero-order diffusion pattern. In those cases, an useful technique to maintain a constant time release are multilayer matrix devices where the matrix core, containing the drug, is covered by one or more modulating drug-free layers that act as rate-controling barriers [48].

Three layer matrix tablets are the most conventional multilayer matrix devices. A well known multi-layer delivery tablet system, which is a trademark of Jago Pharma, Muttenz, Switzerland, is Geomatrix® Technology. It consists of a hydrophilic matrix core, containing the active ingredient, and one or two impermeable or semi-permeable polymeric coatings (films or compressed barriers), applied on one or on both bases of the core [50].

Normally, the top and bottom layers, which act as release-retardant layers, are formed by cellulose derivatives hydrophilic polymers, such as, HPMC, NaCMC, HPC and MC. However, over the last years several new polymers have been tested as components of the sustaining layer in multilayer technology and the use of natural polymers as outer layer is increasing. Thus, several *in vitro* and *in vivo* studies based on multilayer tablets formulated by natural polymers have been carried out. For example, Siahi *et al*. (2005), demonstrated *in vitro* that tragacanth, a naturally occurring dried gum, has the potential for controlling the release of verapamil hydrochloride [48]. On the basis of *in vivo* studies, Al-Saidan *et al*. (2004) showed that guar gum multilayered tablets were able to provide oral controlled delivery of metoprolol tartrate in humans [51].

In some clinical situations biphasic drug release is necessary to obtain a successful therapy. Thus, biphasic delivery systems are designed to release a drug at two different rates or in two different periods of time and they are either quick/slow or slow/quick bilayer delivery systems [52, 53]. On the one hand, a quick/slow system provides initial burst of drug release achieving quickly high drug blood concentrations followed by a constant release rate over a defined period of time, thus avoiding repeated administrations. Suitable candidate drugs for these dosage forms include nonsteroidal anti-inflamatory drugs (NSAIDs) and anti-hypertensive and antihistaminic agents [47, 54]. On the other hand, slow/quick delivery systems are intended for the treatment of colon specific diseases that have peak symptoms in the early morning and diseases that exhibit circadiam rhythms, such as nocturnal asthma, angina and rheumatoid arthritis. However, as most multilayer systems are not able to achieve a biphasic release of the drug. Other strategies based on multilayer systems have been developed. Among them, special emphasis is laid on dual-component delivery systems.

2.2.3. Osmotic-Controlled Release Oral-Delivery System (OROS)

The OROS or osmotic pump tablet (OPT) system is an advanced drug-delivery technology which uses osmotic pressure as the driving force to deliver pharmacotherapy. The OROS has been applied in several therapeutic areas and the main objective of this technology is to obtain once daily administration frequency [55]. For example, according to results observed in Fig. (**3**), metoprolol Oros produced even plasma concentrations throughout the day after repeated once-daily administration. It should therefore be useful in the treatment of angina, cardiac arrhythmias and whenever selective β1-adrenoceptor blockade is required with less risk of poor compliance than occurs with multiple daily dosing [56] "Fig. (**3**)".

In the historical development of OPTs, Theeuwes was the first who introduced and brought forward the basic theory of the elementary osmotic pump (EOP) in the 1970s [57]. However, EOP systems are not suitable for water-insoluble drugs. In order to overcome these limitations, many novel technologies and formulations related to the OPT have been developed, such as osmotic drug delivery using swellable-core technology [58], effervescent OPT from a tradicional Chinese medicine compound recine [59], controlled-porosity OPT for sustained-release delivery [60], and controlled-porosity OPT for colon-specific delivery [40]. Nevertheless, all of these osmotic tablet systems need a sophisticated technique for their elaboration. In order to avoid additional production procedures, many researchers have attempted to produce a monolithic osmotic tablet system (MOTS), based on a tablet core with a suspending agent and a semipermeable coating membrane with a delivery orifice.

However, EOP and MOTS are more suitable for high solubility drugs, and it is crucial to find an appropiate polymer to the succesful release of poor water-soluble drugs from this osmotic tablet. Over the last decade there has been considerable exploration in developing MOTS for water-insoluble drugs: i.e. in 1987 Janicki *et al*. designed the first MOTS for sustained-delivery of isosorbide dinitrate (ISDN) [61], in 2000 Liu *et al*. used polyethylene oxide (PEO) as an osmotic agent to prepare nifedipine MOTS [62], and in 2003 Lu *et al*. found that two orifices in both side surfaces naproxen MOTS, with arabic gum as an osmotic agent, and cellulose acetate as semipermeable coating membrane, are able to deliver naproxen at a rate of approximately zero order up to 12 hours in pH 6.8. Moreover, compared to Janicki´s and Liu´s osmotic tablets, this gum arabic MOTS used less amount of excipient (drug:excipient from 1:14 to 1:9) and obtained the higher drug release rates [11,63].

Recently, Wang *et al*. (2003) developed a novel OPT using the core of drug-resin complexes for propanolol hydrochloride time-sustained delivery. Compared with the conventional OPT the drug-resin complexes OPT (DRCOPT) sustained a longer zero-order drug release pe-

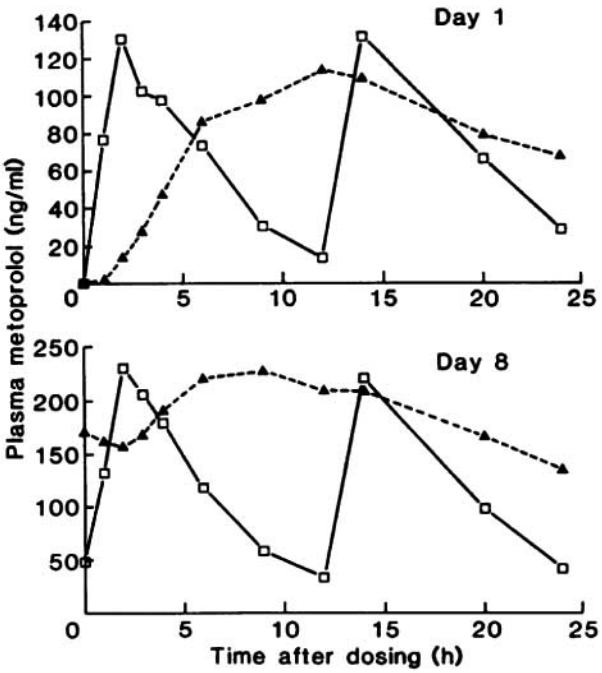

Fig. (3). Mean plasma concentration-time profiles after single and multiple dosing with 100 mg conventional metoprolol tablet twice daily (□) and 19/285 metoprolol Oros once daily (▲) (reprinted with permission from [56]).

riod, ranging from 2 hours to 14 hours. Additionally, the DRCOPT had a 2-hour-lag-time in the *in vitro* dissolution test, which may accommodate diseases such as hypertension and angina pectoris occurring during a certain period. On the whole, the DRCOPT preparation will provide a new concept for the development of osmotic pumps [63].

2.2.4. Dome Matrix® Technology

Recently, Lisapharma S.p.A. has patented a new modified drug delivery system based on "release modules assemblage" strategy named Dome Matrix®. This technology is characterized by a flexibile and swellable release matrix module with a convex and a concave base. The special shape of these release modules was designed to favor the assemblage of several modules in one unit system through the guided insertion of the convex base of a module into the concave base of the adjacent one ("piled configuration"). Otherwise, two modules could be stuck concave base towards concave base. In this case the system features an internal void space, which create what is known as a "void configuration".

Furthermore, with the aim of testing the applicability of Dome Matrix® technology for an adaptable control of drug delivery rate and site, Losi *et al.* (2006) demonstrated that using different modules containing polymeric excipients with different molecular weights or different formulations, the administered dose can be easily adjusted and multikinetics drug delivery can be achieved. In addition, module assemblage could allow for the delivery of two drugs in a single unit at a specific time and at a proper rate and duration. Thus, they shown that Dome Matrix® technology is an efficient way of modulating the release behavior and onset release by assembling several modules in a single combination [64].

3. NATURAL POLYMERS USED IN CONTROLLED-RELEASE TABLET DEVELOPMENT

Natural polymeric materials have been widely used in the pharmaceutical industry for many years, in particular in controlled-release matrix dosage forms. As the synthetic polymers used for this purpose in combination with various drugs have been protected by several patents, there is an increased interest in the pharmaceutical field in natural polymeric substances to circumvent these patents. Table **3** shows some examples of natural polymers used in modified-release tablet development.

3.1. Polysaccharides Derived from Plants

Nature possesses a variety of plant exudates and gums to be explored, and research in this field has yielded many useful gums like guar, acacia, tragacanth, etc.. Thus, from the eighties researchers began to use natural gums as matrix retardants in solid dosage forms.

Among all the natural gums, guar gum has presented promising *in vitro* and *in vivo* results. Guar gum is a nonionic polysaccharide derived from the seeds of *Cyamopsis tetragonolobus*, family *Leguminosae*. In pharmaceuticals, guar gum is used in solid dosage forms as a binder and disintegrant, although in the last decade several studies have demonstrated the potential of this polysaccharide to formulate controlled-release matrix systems. In this respect, the most representative study was carried out by Al-Saidan *et al*. in 2005. In their work, matrix tablets of diltiazem hydrochloride, using various viscosity grades of guar gum in different proportions, were prepared by wet granulation and subjected to *in vitro* and *in vivo* drug release studies. According to the drug release studies in simulated gastrointestinal and colonic fluids, diltiazem hydrochloride matrix tablets containing 50% (w/w) high-viscosity guar gum provided controlled-release comparable with marketed sustained-release diltiazem hydrochloride tablets (D-SR tablets). As Fig. (**4**) shows, when subjected to *in vivo* pharmacokinetic evaluation in healthy volunteers, the guar gum matrix tablets are superior to D-SR tablets in providing a slower and prolonged drug release in comparison with D-SR tablets [65]. Hence, natural polymers with similar characteristics to guar gum could be a new, cheaper, less toxic and easily available option than synthetic polymers to formulate controlled release matrix tablets for water-soluble drug "Fig. (**4**)".

In addition to guar gum, carrageenans are a good option as retardant agents. There are high molecular weight sulphated polysaccharides extracted from marine plants belonging to the class *Rhodophycae*. Previous studies which were conducted by Hariharan *et al.* (1997) and Gupta *et al.* (2001) indicated the feasibility of using a blend of iota- and lambda-carrageenans in the formulation of oral controlled-release tablet matrices to give zero-order release [66, 67]. Furthermore, recently it has been described that both lambda and iota carragenans can be used in combination with cellulose ethers for the formulation of controlled-release ibuprofen tablets [68].

Table 3. Examples of Natural Polymers Used in Modified-Release Tablet Development

Polymer	Source	Main properties or results	Complexes
guar gum	seeds of *Cyamopsis tetragonolobus*	non-ionic, slower and prolonged *in vivo*drug release in comparison with D-SR tablets	-
carrageenan	marine plants *Rhodophycae*	blend of iota- and lambda-carrageenans which give zero-order release	cellulose ethers
tragacanth gum	*Astragalus gummifer Labillardiere*	high gelling ability	-
acacia gum	*Sterculia foetida*	good gelling ability	-
Terminalia catappa Linn gum	tree of the family *Combretaceae*	unbeatable rheological properties	-
alginate	brown seaweeds	gelling ability in the presence of multivalent cations	chitosan, hyaluronate sodium, pectin
xanthan gum	*Xanthamonas campestris*, gram-negative bacterium	time independent drug release, negative charge, retardant excipient for pentoxifylline controlled-release tablets	galactomanan, chitosan
scleroglucans	microbial	non-ionic polysaccharide with potential rheological properties for direct compression	borax
dextrans	*Leuconostoc* or *Streptococci*	a new series of native dextran of high molecular weight derived from sugar cane (B110-1-2), similar profile than SUMIAL RETARD capsules	cellulose ethers
chitosan	crustaceans	protonated amine groups, IPECs based tablets	carboxylate groups of several polyanionic polymer

D-SR tablets: sustained-release diltiazem hydrochloride tablets
IPEC: interpolyelectrolyte complex

Other examples of polymers extracted from plants that have been tested as retarding agents for matrix tablets are briefly desribed bellow. Tragacanth and acacia gums, obtained from *Astragalus gummifer Labillardiere* and *Sterculia foetida* respectivily, have been tested as controlled release matrix excipients. Tragacanth has the potential for sustaining the release due to its high gelling ability, whereas acacia lacks such potential because of having a weaker gel forming ability [46]. Moreover, last year a new gum with unbeatable rheological properties was evaluated as a release retarding excipient. This novel polymer is a gum exudate of *Terminalia catappa* Linn, a tree belonging to the family *Combretaceae*, broadly distributed on tropical and subtropical beaches.

Finally, a special mention should be made of alginate, a polysaccharide found in brown seaweeds and commercially available as a sodium salt. The interest of alginate is due to its unique property of gel-forming in the presence of multivalent cations such as calcium in aqueous media. Thus, alginate turns out to be an attractive polymer for the development of controlled release delivery systems, specially for matrix tablets based on hydrophilic interpolymer complexes [69]. Furthermore, this mechanism, where calcium binding to polymer reduces solubility and induces crosslinking of carbohydrate chains, is also applied to the formulation of pectin matrix tablets to obtain sigmoidal release of the drug [70].

3.2. Polysaccharides Produced by Bacteria

The main exponent of polysaccharides produced by bacteria that are applied in matrix controlled-release tablets is the XG. XG is a high molecular weight extracellular heteropolysaccharide, produced by fermentation in *Xanthamonas campestris*, gram-negative bacterium. The primary structure of this naturally produced cellulose derivative consists of a cellulose backbone and trisaccharide side chains containing glucuronic acids that give this polymer a negative charge. In 1995 Talukdar and Kinget were the first to describe the swelling behaviour of this polymer for controlling drug release. They observed that the release of indomethacin, an insoluble acidic drug, has a direct relationship with the polymer matrix swelling, while a reciprocal relationship is observed with soluble drugs such as caffeine. Moreover, they also concluded that the swelling of the XG polymer matrix showed a square root of time dependence whereas drug release was almost time independent [71]. Thus, pentoxifylline, a water-soluble drug used to treat vascular dementia and intermittent claudication resulting from obstructed arteries in the limbs, was formulated as controlled-release tablets that were prepared using XG as a matrix retardant agent. Indeed, it was reported that pentoxifylline release rate decreased with increasing polymer concentration. On the contrary, a higher release rate of pentoxifylline was also observed using an acidic dissolution medium [72].

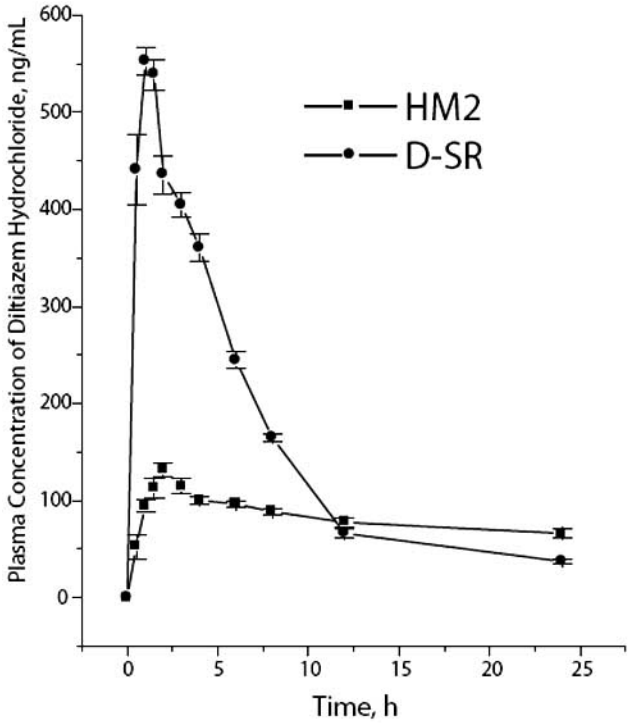

Fig. (4). Mean (± SEM) plasma concentration of diltiazem hydrochloride after oral administration (dose 90 mg) of matrix tablet containing 50% w/w of high-viscosity guar gum (HM2 tablet) or D-SR tablet in human volunteers (n = 6). The area under the plasma diltiazem hydrochloride concentration vs time curves ($AUC_{0-\infty}$) for the D-SR tablets and HM2 tablets were 3998.0 ± 216.4 ng.h/mL and 4614.6 ± 921.6 ng.h/mL respectively, which were not significantly different (reprinted with permission from [65]).

Recent research has evaluated and characterized by *in vitro* test the performance of xanthan gum as a potential polymer to combine with crosslinked chitosan. For example, in 2006 Fukuda *et al.* studied the chlorpheniramine maleate release pattern from hot-melt extruded tablets containing chitosan and xanthan gum [73]. Likewise, Phaechamud and Ritthidej (2008) evaluated the formulation variables that affect propranolol hydrochloride release from matrix system of chitosan and xanthan gum [74].

Another gum that is used in combination with xanthan is galactomanan. The results obtained from the combination of both gums have been very productive. Indeed, in 2002 Penwest Pharmaceuticals Company commercialized a drug delivery tablet system based on the synergistic interaction of xanthan and locust bean gum, a galactomanan extracted from the seeds of the Carob tree (1:1 at 50% concentration), which forms a strong binder gel in water in the presence of dextrose (50%).

Apart from xanthan gum other polysaccharides produced by bacteria, such as scleroglucans, dextrans, curdlan [75], etc., have been evaluated as retardant agents in matrix controlled-release tablets. In the case of scleroglucans they have been extensively studied thanks to their peculiar properties. This microbial non-ionic polysaccharide has potential rheological properties that allows for the formulation of scleroglucan matrix based tablets by direct compression [76]. Scleroglucan chains in aqueous media feature a triple helical conformation of remarkable stability. However, experimental data demonstrated that carboxylated scleroglucan (Sclerox) assumes a single helical conformation in aqueous solution due to the oxidation procedure. This conformation forms a physical hydrogel in the presence of divalent cations, in particular calcium. Thus, based on sclerox properties, a new physical hydrogel based on the Sclerox/Ca(II) system was developed with promising *in vitro* results [77]. On the other hand, tablets based on the hydrogel formed by the interaction between scleroglucan and borax have also been designed. In this case, a natural mineral, borax, was chosen as a crosslinker, unlike in the case of the Sclerox/Ca(II) system, where calcium was used. Furthermore, in comparison with the sclerox/Ca(II) matrix, the tablets prepared with a scleroglucan/borax matrix showed a remarkable anisotropic swelling and a drug release strongly dependent on the molecular size of the drug [78].

Dextrans, which are synthesized from sucrose by dextransucrases, glucansucrases, and glucosyltransferases produced by *Leuconostoc* or *Streptococci*, are another example of polysaccharides obtained from bacteria. Most published reports in the field are restricted to dextrans of commercial interest, in particular the commercial native dextran B512-F synthesized by *Leuconostoc mesenteroides*. However, a new series of native dextran of high molecular weight derived from sugar cane (B110-1-2) has been developed as innovative functional excipients for pharmaceutical tablets [79].

Indeed, our laboratory has participated in the development and optimization of a novel controlled-release dextran tablet formulation for propanolol hydrochloride [80]. *In vitro* studies clearly demonstrated the ability of B110-1-2 for controlled-release dosage forms. In this work, we carried out a comparative kinetic study between the matrix tablets that present optimal physical, mechanical and technological properties [dextran:HPMC ratio of 4:1 (w/w), matrix excipient:propanolol hydrochloride ratio of 60:40 (w/w) and with cetyl alcohol amount of 15% (w/w)] and commercial SUMIAL RETARD capsules (Spain). The results showed that the dissolution profiles of the two controlled-release oral dosage forms were similar. Moreover, in the same study Higuchi (diffusion) and Hixon–Crowell (erosion) kinetic profiles were reached and a codependent mechanism of drug release was established [80].

3.3. Chitosan

Chitosan is a natural cationic aminopolysaccharide copolymer of glucosamine and N-acetylglucosamine obtained by partial deacetylation of chitin. It is also the most abundant natural carbohydrate after cellulose. Due to its capacity to generate electrostatic interactions between protonated amine groups and carboxylate groups of polyanionic polymer, chitosan is widely used in IPECs based tablets.

In addition, chitosan amino groups (at C2 position) are suitable for chemical modifications. Several pharmaceutical applications have been reported for modified chitosan, such

as "intelligent" drug delivery systems by cross-linking with glutaraldehyde, regeneration of bone tissues or antioxidant agent by carboxymethylation, inhibitor in acute rejection following xenotransplantation conjugated with a-galactosyl, antimicrobial agent conjugated with vinylsulfonate and activator of blood anticoagulant factors conjugated with sulfate [81].

Indeed, glycol chitosan was modified with palmitoyl N-hydroxysuccinimide to form hydrogels that present amphiphilic characteristics, stabilized by hydrophobic interactions, and exhibit erosion-controlled drug release for 5-7 hours [82]. Based on this finding, researchers have developed new hydrophobic N-acylated chitosan matrices for controlled drug release. In this case, unmodified chitosan exhibited a lower degree of substitution and a weaker tablet crushing strength than modified chitosan. Tien *et al.* (2003) showed that the best mechanical characteristics and drug release properties were found for chitosan acylated with long side chain fatty acid (C_8-C_{16}), particularly palmitoyl chitosan. Furthermore, they suggested that the release of drug is controlled by diffusion, depending on both the acyl chain length and the degree of acylation [81].

3.4. Proteins

Over the last decade, there has been an increasing number of studies concentrating on zein proteins obtained from maize seeds and their applications in pharmacy, with particular interests in encapsulating and coating. Commercially available zein protein extracts are hydrophobic, potentially making them good candidates for a controlled oral drug delivery matrix.

Recently, a research group from the University of East Anglia (Norwich, United Kingdom) has examined the use of zein proteins as the major component for controlled-release tablets. On the basis of dissolution profiles in water, 0.1 M HCl (pH = 1) and phosphate buffer (pH = 6.8) only a limited amount of theophylline was released after 4.5 h, suggesting that zein proteins could act as a potential vehicle for oral controlled drug release. Thus, Georget *et al.* (2008) concluded that zeins could be successfully applied as pharmaceutical excipients, and in particular as matrix in monolithic controlled-release tablets [83].

4. CONCLUSIONS

A number of innovative delivery systems has been developed over the last decades to address suboptimal therapy outcomes by controling drug delivery, reducing side effects and improving patient compliance. Among all these systems, the monolithic matrix tablets offer numerous advantages. Their simplicity, low cost, broad FDA acceptance, easiness of manufacturing, favorable *in vivo* performance and wide range of physico-chemical properties make them an excellent option as controlled release delivery systems.

Hydrophilic matrices composed by cellulose ether have been the most evaluated matrix systems both *in vitro* and *in vivo*, are the. Due to their good swelling properties, good compression characteristics, low toxicity, ability to accommodate a large percentage of drug and negligible influence of the processing variables on drug release rate, HPMC has been used as a model polymer in the study of the critical points governing the control of drug release from hydrophilic matrices.

Recently, there has also been an increasing interest in natural polymeric substances, whose, main advantage lies in safety, free availability, and a relatively low price. Thereby, they represent an interesting possibility to extend the selection of novel constitutive auxiliary substances, and they are often preferred over synthetic ones. In fact, even though scarce, there are controlled-release products elaborated with natural polymers that have reached the marketplace: one example, Tridural ^{TM} (tramadol hydrochloride extended-release), whose matrix is composed by xanthan gum.

The use of natural polymers for different biomedical applications is subject to the regulatory requirements of the pharmaceutical industry. Besides, due to the variable nature of the source of these materials, a major hurdle lies in obtaining a good batch to batch reproducibility. The limiting factors when using naturally occurring polymers are their variable gelation characteristics, uncontrolled rate of hydration, thickening, drop in viscosity on storage and microbial contamination. However, because of their inertness, biocompatibility, pH independent behaviour, cost-effectiveness and regulatory acceptance, natural polymers are among the most popular hydrophilic polymers used in controlled-release matrix technologies.

One would hope that future research in the field would improve the quality of natural polymers in order to make up of better materials for drug controlled-release delivery systems.

ABBREVIATIONS

ADHD	=	Attention deficit hyperactivity disorder
B110-1-2	=	Native dextran of high molecular weight Derived from sugar cane
CA	=	Cellulose acetate
CAP	=	Cellulose acetate phtalate
CDDS	=	Colon-specific drug delivery system
CMC	=	Carboxymethylcellulose
CS	=	Chitosan
CSMMA	=	Carboxymethylstarch-methyl methacrylate copolymer
DBS	=	Dibutyl sebacate
DRCOPT	=	Drug-resin complexes OPT
D-SR	=	Sustained-release diltiazem hydrochloride
EC	=	Ethylcellulose
EOP	=	Elementary osmotic pump
ER	=	Extended-release
FDA	=	Food and Drug Administration
HCMMA	=	Hydroxypropylcellulose-methyl methacrylate copolymer

HEC	=	Hydroxyethylcellulose
HM2 tablet	=	High-viscosity guar gum tablet
HPC	=	Hydroxypropilcellulose
HPMC	=	Hydroxypropylmethylcellulose
HSMMA	=	Hydroxypropylstarch-methyl methacrylate copolymer
IPEC	=	Interpolyelectrolyte complex
ISDN	=	Isosorbide dinitrate
MC	=	Methylcellulose
MMA	=	Methyl methacrylate
MOTS	=	Monolithic osmotic tablet system
MR	=	Modified-release
NaCMC	=	Sodium carboxymethylcellulose
NSAID	=	Nonsteroidal anti-inflamatory drug
OPT	=	Osmotic pump tablet
OROS	=	Osmotic-controlled release oral-delivery system
PEO	=	Polyethylene oxide
Pluronic-PAA	=	Copolymer of Pluronic® 127 and poly-(acrylic acid)
PVAc	=	Polyvinyl acetate
PVA-PEG	=	Polyvinyl alcohol-polyethylene glycol graft copolymer
Sclerox	=	Carboxylated scleroglucan
XG	=	Xanthan gum

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