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Review

Site-specific drug delivery systems within the gastro-intestinal tract: From the mouth to the colon

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ABSTRACT

Delivery of drugs by the oral route remains the most spread route to administer medicines to patients. The manuscript takes into consideration the most important organs of the digestive system (mouth, oesophagus, stomach, small intestine and colon), their size, physiology and transit patterns of dosage forms while travelling in the digestive tract. For each organ several strategies are considered, namely, adhesion, chemical modification of drug and/or excipient moieties, technological features of dosage forms (e.g. porosity, disintegration time), pH variations or transit times. The manuscript considers strategies that are commonly used in practice for long-term administration of drugs, without interfering with human physiology, and feasible industrially.

Contents

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1. Introduction

The oral route remains the most considered one for administration of drugs. Several reasons can be pointed out to support this fact, namely ease of administration and full control of administration by the patient, together with a high degree of flexibility on dosing. However, due to differences on physiology, preferential site of drug absorption, dosage forms must be tailored to a specific organ or even a part of the organ. Site controlled release is usually controlled by environmental factors, like the pH or enzymes present in the lumen, whereas the drug release from time controlled systems is controlled primarily by the delivery system and ideally not by the environment (Bussemer et al., 2001). Knowledge of transit times allows the use of time controlled release systems to deliver a drug to a specific location in the digestive system. In fact, the use of particular polymers or mixtures of polymers may fine tune the release of a drug within the gastro intestinal tract (e.g. targeting to the colon) (Siepmann et al., 2008). The systems discussed in this review are more complex than conventional dosage forms requiring special care on production to accomplish their function. The strategies discussed are the ones that can be used on chronic diseases encompassing different materials, dosage forms, geometries and technologies. Other systems used in research, clinical trials or under the supervision of a health care professional are discussed superficially.

2. Delivery to the mouth

2.1. Sublingual administration

The sublingual route of administration has been considered for many years for acute situations, namely for the administration of nitro-glycerine, avoiding first pass metabolism and fast entry into the systemic circulation (Goswami et al., 2008). The same principle has been suggested for the administration of salbutamol sulphate in a fast dissolving film in an acute attack of asthma. The film was prepared by a solvent evaporation technique containing polyvinyl alcohol, glycerol and mannitol (Mashru et al., 2005). Other techniques include freeze-drying of materials and/or inclusion of high fractions of superdisintegrants. When the solubility of a drug is a problem (e.g. cannabidiol) inclosing complexes with cyclodextrins may minimize it (Mannila et al., 2007). The complexes can then be transformed into dosage forms (e.g. films, tablets).

2.2. Fast disintegration and effervescency

In recent years, the fast release of drugs in the mouth has attracted attention due to the advantages of such systems, namely, ease of administration and quick effect onset. Many patients (particularly paediatric and geriatric patients) find it difficult to swallow tablets and hard gelatine capsules and do not take their medication as prescribed (Seager, 1998). Fast dissolving drug delivery systems either dissolve or disintegrate in the mouth rapidly, without requiring any water to aid in swallowing. Processing techniques such as lyophilisation, tablet moulding, sublimation of formulation components, have been considered. Different formulations include sugar-based ingredients, foaming agents and disintegrants (Liang and Chen, 2001; Segale et al., 2007).

Combination of technologies has been suggested by Baldi and Malfertheiner (2003) by designing enteric coated microgranules compressed to produce a rapidly dispersing tablet: upon administration, the tablet disintegrates quickly releasing the enteric coated lansoprazole microgranules which were swallowed and dissolved in the small intestine. In a similar approach Giunchedi et al. (2002) proposed the production of tablets containing chlorhexidine diacetate in chitosan microspheres prepared by spray-drying. Tablets were prepared by direct compression of the microparticles with mannitol alone or with sodium alginate. The release of the drug was controlled by the microspheres polymer.

Chitosan diacetate has also been used in the preparation of mono or double layered films with alginate, hydroxypropyl methylcellulose by casting and solvent evaporation. The films were soft, flexible and easily handled, allowing an easy application in the buccal cavity (Juliano et al., 2008).

Orodispersible tablets containing tramadol have shown improved performance than conventional capsules. Tablets placed into the mouth disintegrate rapidly in contact with the saliva and then swallowed to the stomach and intestine where tramadol was absorbed. Due to the fact this orally dispersible formulation can be taken without liquids, it facilitates an early treatment of emergent pain, irrespective of the place or situation where it may arise (Tagarro et al., 2004).

Effervescency has been considered for the production of dosage forms for the mouth. Usually effervescence is produced in a glass containing water, and the resulting solution is given to patient. However, some suggestions have been made on designing an effervescent tablet to stay in the mouth. For instance, fentanyl has been administered as a buccal tablet (Messina et al., 2008), but it has been claimed that its absorption increases when fentanyl was delivered to patients in effervescent tablets, due to an enhanced penetration effect as a consequence of the presence of the gas on the buccal mucosa (Blick and Wagstaff, 2006).

2.3. Chewing dosage forms

Chewing gums have been used for many years, particularly in USA, since the release of the drug by chewing the dosage form is an interesting application of gums. Chewing gums based on solid paraffin, lycasin, sorbitol, menthol and peppermint have been described to the administration of antimycotics (miconazole and econazole) for topical application. The solubility problem of these drugs was minimized by the formation of inclusion complexes with cyclodextrins (Jacobsen et al., 1999). A different proposal considers a tablet with three layers comprising a gum core combined with two protective antiadherent external layers, which prevent the adhesion of the gum to the punches of the tabletting machine. In these systems, soluble drugs are freely and easily released from the chewing gums while for actives with reduced water solubility the release rate depends on the chewing time (Fig. 1a and b) (Maggi et al., 2005).

2.4. Effect of adhesion

Adhesion of dosage forms to the buccal mucosa is an attractive strategy to deliver drugs to the buccal cavity. Multiple examples can be found in the literature whereby Carbopol and some cellulose derivatives play a major role on adhesion.

Buccal adhesive films containing lidocaine and its hydrochloride salt have been prepared with Carbopol 971P and glycerol (as a plasticizer) as a controlled release dosage form (Abu-Huwaij et al., 2007); Carbopol 934 in combination with sodium carboxy methylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose served as bioadhesive material to deliver ketorolac tromethamine to the mouth: the films were produced by casting the materials from aqueous or organic solvents (Ali et al., 1998; Alanazi et al., 2007). Patches with sumatriptan succinate using chitosan were prepared by the solvent casting method. Gelatine and polyvinyl pyrrolidone were incorporated into the patches to improve their film properties (Li et al., 1998; Shidhaye et al., 2008). A bilayered buccal bioadhesive film with nicotine hydrogen tartrate for smoking cessation therapy has been proposed: the film comprises a bioadhesive drug layer (hydroxypropyl methylcellu-

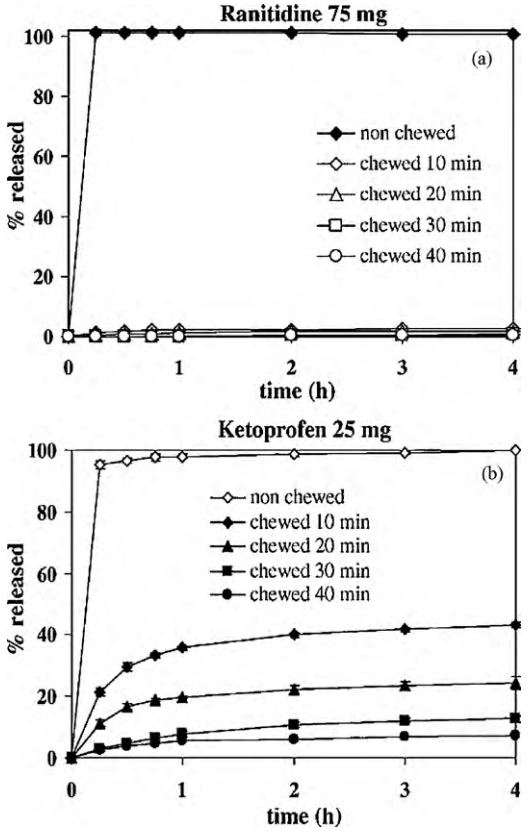

Fig. 1. Release profiles from the residual gums after different chewing times for (a) ranitidine and (b) ketoprofen (average value ± S.D., $n = 6$) (Maggi et al., 2005) (*reproduced with permission from the publisher*).

lose and polycarbophil) and a backing layer which releases the drug at a pre-determined rate for a period of 4 h (Garg and Kumar, 2007); a mucoadhesive buccal film of valdecoxib for the treatment of oral submucous fibrosis was made of chitosan and hydroxypropyl methylcellulose (Averineni et al., 2009).

Mucoadhesive patches releasing drugs in the oral cavity at a slow pre-determined rate may present advantages over mouthwashes, oral gels and lozenges. For instance, patches prepared by compressing appropriate mixtures containing drug salts complexes, lactose, gums (e.g. pectin) were tested in vitro (Burgalassi et al., 1996; Chun et al., 2003); a bioadhesive polymer patch formulation with polyisobutylene, polyisoprene and Carbopol 934P was prepared using a 2-roll milling method for the controlled release of buprenorphine (Guo, 1994). The effects of the patches backing materials (ethyl cellulose, polyvinyl pyrrolidone, cellulose acetate, poly(ethylene-co-vinyl acetate)) on their hydration and adhesion affecting the control of the drug's release were investigated (Guo and Cooklock, 1996).

The production of adhesive gels has also been considered. Piroxican in a gel had its absorption increased (by decreasing order) when formulated with hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium alginate, methyl cellulose, hydroxyethyl cellulose, Carbopol 934, sodium carboxymethyl cellulose and polyvinyl alcohol, as observed in clinical studies conducted in patients with post-operative dental pain and oedema, following maxillofacial operations (Attia et al., 2004). The hydration rate of the gels has also been addressed particularly in the presence of small water contents, as the ones observed in the mouth. Hydrogels of propranolol hydrochloride in Carbopol showed a high adhesion and elasticity to the mucosa even with small amounts of water (Blancofuente et al., 1996). Gel formulations containing 5-fluorouracil for the treatment of oropharyngeal cancer were prepared by using Poloxamer 407, hydroxypropyl methylcellulose and (poly(methylvinyl)ether-co-maleic anhydride (Gantrez) to form gels (Dhiman et al., 2008).

Tablets, as the most popular dosage form, have also been considered. Tabletting of hydroxypropyl methylcellulose with carbomer can form a complex with buccoadhesive controlled release properties for morphine sulphate (Anlar et al., 1994); the production of a composite material made of starch and Carbopol 974P by spray-drying has enabled the bioadhesion of miconazole nitrate tablets to the buccal mucosa (Ameye et al., 2005); multilayer tablets were produced to deliver acitretin: one layer contained Carbopol 934P and methyl cellulose with bioadhesive properties whereas the other layer contained a slow release matrix (hydroxypropyl methylcellulose) with acitretin (Minghetti et al., 1998). Tablet for buccal delivery of the poor soluble drug carvedilol based on poly(ethyleneoxide) as bioadhesive sustained release platform and hydroxypropyl-p-cyclodextrin as modulator of drug release (Cappello et al., 2006); Carbopol 934, together with poly(methylvinylether-co-maleic anhydride) calcium or sodium salts (Gantrez), sodium carboxymethylcellulose and poly(ethyleneglycol) 8000 were used to deliver locally sodium fluoride to the oral cavity for the prevention of caries (Owens et al., 2005). The treatment of periodontal diseases benefits from the preparation of tablets to deliver metronidazole in a matrix containing Carbopol 940 in mixtures with hydroxyethyl cellulose (Perioli et al., 2004). Double layered tablets of benzocaine as regional anaesthetic for dental procedures and in the treatment of oral mucositis pain were developed for buccal delivery (Maffei et al., 2004). Buccoadhesive erodible tablets for local delivery of clotrimazole to the oral cavity were produced with different bioadhesive polymers along with soluble excipients like mannitol and poly(ethyleneglycol) 6000 (Khanna et al., 1996). It should be pointed out that processing conditions do affect the performance of these dosage forms: the bioadhesive characteristics of thermally modified starch with polyacrylic acid tablets containing miconazole nitrate were affected by the ratio of drum-dried waxy maize starch and polyacrylic acid (Bouckaert and Remon, 1993).

Hot-melt extrusion technology (HME) was used to prepare mucoadhesive matrix films containing clotrimazole for local drug delivery applications for the oral cavity. The film formulation contained hydroxypropyl cellulose and poly(ethyleneoxide) as polymeric carriers, the bioadhesive polycarbophil, and other excipients (Repka et al., 2003).

Thiocolchicoside in two dosage forms, a bioadhesive disc and a fast dissolving disc for buccal and sublingual administration, has been given to volunteers. The fast dissolving (sublingual) form resulted in a quick uptake of 0.5 mg of thiocolchicoside within 15 min whereas with the adhesive buccal form the same dose can be absorbed over an extended period of time (Artusi et al., 2003).

Other less conventional materials have also been used for buccal adhesion. For instance, the gum from *Hakea gibbosa* (*L.*) was considered to control the release of calcitonin (Alur et al., 1999; Alur et al., 2001), beads made of either pectins or lectins were comparable to Carbopol 934P beads (Bies et al., 2004; Atyabi et al., 2007).

2.5. Alternative dosage forms

Prosthetic devices incorporating drugs are rarely used. The devices available mainly focus on the prophylaxis and the release of antibacterial agents in the mouth. Recently, as buccal delivery systems, they gained some popularity for systemic drug delivery, and prolonged well-controlled release has been identified as beneficial, especially for chronic diseases. Highly miniaturized computerized delivery systems, integrated into a dental appliance can be used for the local treatment of diseases affecting the oral cavity (e.g. periodontitis or fungal infections) or for systemic drug delivery (Scholz

et al., 2008). As an example, Jothi et al. (2009) suggested the use of a prosthetic device in the form of a biodegradable chip of chitosan to deliver chlorhexidine for the treatment of periodontitis).

3. Oesophagus

The oesophagus can be regarded as a connecting organ between the mouth and the stomach, thus it is not designed to hold any dosage form. In fact, the low permeability and transient nature of the oesophagus means that it is unsuitable for the delivery of drugs for systemic action. However, oesophageal disorders including infections, cancers, motility dysfunction and damage due to gastric reflux may be treated using locally acting agents that offer benefits or reduced dosage and decreased side effects (Batchelor, 2005). On the other hand, on designing dosage forms one should take into consideration the fact that they might be retained in the oesophagus, particularly by relaxation of the organ forming pockets in the lower portion or by reflux from the stomach.

The key limitation to the effective drug delivery to the oesophagus is sufficient retention at this location. It follows that a suitable formulation either releases the drug in a ready-to-work form at the site of action during the rapid transit through this organ or is retained at the mucosa, releasing the drug throughout time. Different approaches for targeting the oesophagus have been suggested, encompassing bioadhesive liquids and orally retained lozenges, chewing gums, gels, and films, as well as endoscopically delivered drugs (Zhang et al., 2008). Bioadhesion has been achieved with particles coated with an alginate layer (Batchelor et al., 2004). This strategy has been emphasized by combining bioadhesive polymers (e.g. a mixture of hydroxypropyl cellulose/Carbopol 934) with ultrafine ferrite (Fe_2O_3) to deliver bleomycin, an anticancer drug. Preliminary studies in rabbits have shown a high holding effect under magnetic guidance at early stages of administration. However, after removal of the magnetic field granules were not retained any more due to non-sufficient bioadhesion provided by the bioadhesive polymers (Nagano et al., 1997).

Although promising, retention of dosage forms in the oesophagus can only be fully achieved by a medical device. For instance, photodynamic therapy can be successful to treat various malignancies including oesophageal cancer, which is very much dependent on the concentration of photosensitizing drug, light energy delivered to tissue, and the presence of oxygen in the targeted tissue. To achieve this, centring balloons improve light delivery to the oesophageal mucosa, but the pressure of the balloon on oesophageal mucosa could possibly reduce mucosal blood flow and oxygenation, therefore reducing the effect of photodynamic therapy. A balance between the size and the pressure of the balloon is critical to reach the maximum therapeutic effect in oesophageal mucosal dysplasia or cancer in humans (Overholt et al., 1996).

4. Stomach

The delivery of drugs to the stomach takes advantage of several features of this organ, particularly the ones related to its physiology like the low pH, motility or gastric emptying time. By affecting the physiology, formulation variables including concomitant administration of other materials, such as food, one can retain a dosage form in the stomach or improve its displacement to the duodenum. In order to retain dosage forms in the stomach and, for that purpose different strategies can be suggested: changes on the density of the dosage forms (e.g. high porosity, swelling or expansion, super porous hydrogels) after administration, bioadhesion and changes on geometry of dosage forms (Hwang et al., 1998; Gangadharappa et al., 2007). Floating, magnetic retention or geometry changes of the dosage form can be achieved with the aim of increasing the bioavailability of the carrying drug by prolonging the gastric residence time.

4.1. Floating systems due to density

Buoyancy of a tablet can be achieved by entrapment of air in an agar gel network: the floating tablet delivered theophylline in a controlled release fashion. The tablet presented a density of 0.67 but the retention in the stomach was further emphasized by the presence of food which significantly increased the retention time and overshadowed the effect of density (Desai and Bolton, 1993). Similarly, diltiazem tablets have shown a higher hypotensive action when given to patients in a floating controlled release tablet (Gu et al., 1992). Single floating controlled drug delivery systems units have been made of polypropylene foam powder, matrix forming polymer, drug and filler. The resulting highly porous system has shown a low density enabling floating for 8 h. Polymers considered in the study were hydroxypropyl methylcellulose, polyacrylates, sodium alginate, corn starch, carrageenan, guar and arabic gums. Although all systems have shown a decrease on density, the drug was released according to different mechanisms (Streubel et al., 2003). In line with this strategy, superporous hydrogels have been synthesized (Chen et al., 2000). These hydrogels swell significantly (volume increases by two orders of magnitude) and fastly in few minutes due to water uptake by capillary wetting through interconnecting pores. The hydrogels were produced by cross-linking polymerization of various vinyl monomers, or acrylate derivatives in the presence of gas bubbles (Chen et al., 1999; Chen and Park, 2000). Pellets have also been produced as floating dosage forms and given to patients in hard gelatine capsules. Pharmacokinetic studies were carried out with verapamil (40 mg) and the parameters considered (e.g. C_{max}, t_{max}, $AUC_{0-\infty}$, $t_{1/2}$) were more favourable to pellets than to reference tablets. In vitro test has shown that pellets were able to float for 6 h (Sawicki, 2002). Microcapsules containing theophylline and sodium carboxy methylcellulose have been prepared by an emulsion phase separation method with chitosan as the matrix forming polymer. Sodium carboxy methylcellulose fraction in the microcapsules played an important role on controlling the floating property of the microcapsules (Lin and Lin, 1992).

Zou et al. (2008) suggested floating systems for chronopharmacotherapy: a floating pulsatile system was designed to increase the gastric residence time of the dosage form having a lag phase followed by a burst release of the drug: a core tablet containing the active ingredient was coated with a hydrophilic erodible polymer (responsible for a lag phase in the onset of pulsatile release) and a top buoyant cover layer (methyl cellulose, Carbopol 934P and sodium bicarbonate) which controlled the floating time. Both pharmacokinetic and scintigraphic data pointed out the ability of the system on prolonging residence times of the tablets in the stomach and releasing drugs after a programmed lag-time.

4.2. Floating systems due to gas generation

The use of a gas to decrease the density of the dosage form is an alternative to the previous strategy.

Floating of dosage forms can be achieved by the inclusion of a gas generator agent in an inert matrix (Baumgartner et al., 2000). Sustained release verapamil hydrochloride has been delivered to patients as floating tablets produced from granules containing mixtures of a forming matrix (hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethyl cellulose or Carbopol) together with sodium bicarbonate and anhydrous citric acid (Elkheshen et al., 2004).

Multi-unit tablets containing furosemide have been formulated and processed as follows: a core containing a solid dispersion of furosemide in polyvinyl pyrrolidone with other excipients prepared by direct compression; the core is then first coated with an effervescent layer (mainly sodium bicarbonate) and a second coat with polymethacrylates (Eudragit RL30D, the most promis-

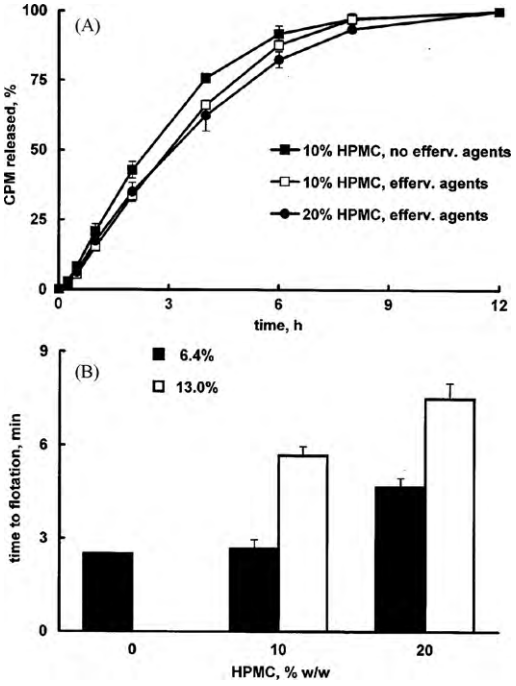

Fig. 2. Effect of the hydroxypropyl methyl cellulose and effervescent agent content on (A) the drug release (6.4%, w:w, coating level) and (B) the time to flotation of one-layer tablets (coating, Eudragit® RL:ATBC 20%, w:w, coating level of 6.4 or 13.0%, w:w) (Krogel and Bodmeier, 1999) (*reproduced with permission from the publisher*).

ing). The time to float decreased as the amount of the effervescent agent increased and the coating level of the polymer decreased. The minitablets remained in the stomach for about 6 h, as observed in radiograms (Meka et al., 2009).

Krogel and Bodmeier (1999) have designed a floating system with pulsatile drug delivery. In this example a core with the drug contained the effervescent material. The core was coated with a polymeric material either acrylic (Eudragit R, RS, RL or NE) or cellulosic (cellulose acetate, ethyl cellulose) polymers. The authors found that a coat with high elongation value and high water and low CO_2 permeabilities was preferred (e.g. Eudragit RL with acetyltributyl citrate) for the effervescent reaction (floating process), whereas, for the pulsatile drug delivery component, a weak semipermeable film which ruptured after a lag-time was the best (ethyl cellulose with dibutylsebacate). The drug was released from the first component by addition of cellulose acetate or hydroxypropyl methylcellulose. Floatation time could be controlled by the composition (type of polymer and plasticizer) or processing (thickness of the coating or hardness of the core) (Fig. 2a and b). A more complex preparation was suggested by Kawashima et al. (1992). These authors suggested the preparation of hollow microspheres loaded with drug (ibuprofen) in their outer polymer shells. The microspheres were prepared by a novel emulsion solvent diffusion method, whereby the ethanol–dichloromethane solution of a drug and an enteric acrylic polymer were poured into an agitated aqueous solution of polyvinyl alcohol at 40 °C. The gaseous phase in the dispersed polymer droplet was generated by the evaporation of the dichloromethane forming an internal cavity in the microsphere of the polymer with the drug. The microballoons floated continuously over the surface of acidic dissolution median with surfactant.

4.3. Systems acting by swelling

The swelling ability of some materials has been advantageous for the design of dosage forms to deliver drugs to the stomach. By swelling some dosage forms have their density decreased promoting floatation in water.

A gastric controlled release drug retention system made of a matrix tablet coated with a permeable membrane, when immersed in simulated gastric fluid expands for 18–20 h, allowing the release of the drug (e.g. chlopheniramine maleate or riboflavin phosphate). The coat was made of an elastic polymer (Eudragit R) whereas Carbopol acted as a strong binder to the swollen tablet, mainly due to cross-linked polyvinyl pyrrolidone. In this example the addition of carbonates provided an alkaline microenvironment (optimal pH) enabling the jellification of Carbopol providing buoyancy to the tablet (Deshpande et al., 1997). Expandable gastroretentive dosage forms have their size increased by swelling, prolonging their gastric retention times. After drug release, their dimensions are reduced with evacuation from the stomach. Gastric retention is enhanced by the combination of a substantial increase on the dimensions with a high rigidity of the dosage form to withstand the peristalsis and mechanical contractility of the stomach (Klausner et al., 2003). Gazzaniga et al. (2008) referred that swellable polymers undergo typical chain relaxation phenomena that coincide with a glassy rubbery transition. In the rubbery phase these polymers may be subject to swelling, dissolution and erosion or, alternatively form an enduring gel barrier when cross-linked networks (hydrogels) are built. Other materials have been considered. For instance, collagen can expand in the stomach after contact with the gastric fluids forming floating collagen sponges. These sponges can be produced by freeze-drying a solution of collagen containing a drug (e.g. riboflavin, captopril, acyclovir). The dried product was mixed with hydroxypropyl methylcellulose (Groning et al., 2006) and, once in the stomach, collagen hydrated and swelled.

Tablets containing hydroxypropyl cellulose, hydroxyethyl cellulose or hydroxypropyl methylcellulose have shown in gastric fluid an outer hydrated layer with a viscoelastic gel structure. This gel was able to entrap air increasing the matrix volume, thus decreasing the density (Baumgartner et al., 1998). A different work by Chueh et al. (1995) combined the effect of floating with adhesion in a device designed to prolong the residence time of a tablet containing sotalol hydrochloride in the stomach. These effects were achieved by incorporating sodium carboxymethylcellulose, hydroxypropyl methylcellulose, ethyl cellulose and cross-linked polyvinyl pyrrolidone.

4.4. Effect of adhesion

Mucoadhesion of dosage forms to the gastric mucosa has been considered to retain them in the stomach. For instance, mucoadhesion of microspheres containing acyclovir has been prepared with chitosan, thiolated chitosan, Carbopol and methyl cellulose as mucoadhesive polymers (Dhaliwal et al., 2008). The microspheres containing acyclovir were prepared by an emulsion and a chemical cross-linking technique and then placed into a hard gelatine capsule. These capsules upon dissolution released the microspheres as multiunits, which in turn, released the drug in the stomach over a period of 12 h. Another option encompassed the production of a patch (3 mm in diameter) containing three layers: a water insoluble backing, a model drug (fluorescein, fluorescein isothiocyanate) carrying adhesive layer (dextrane and gel forming polymer) and a pH sensitive enteric polymer (Fig. 3) (Eaimtrakarn et al., 2003). A more complex system has been proposed by Lele and Hoffman (2000) based on formulations containing H-bonded complexes of poly(acrylic acid) or poly(methacrylic acid) with poly(ethylene glycol)–drug (indomethacin) conjugates: the complexes were designed to dissociate as the formulation swelled in contact with the mucosal surfaces at pH 7.4, releasing the PEG-indomethacin conjugate which hydrolysed to release free indomethacin and free polyethylene glycol.

Monitoring the orally ingested gastric retentive dosage forms under physiologic conditions has been considered. For instance,

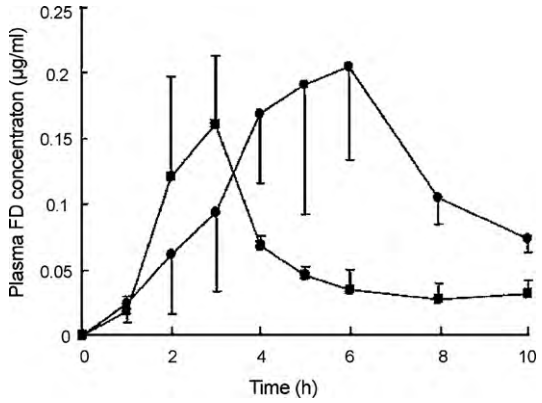

Fig. 3. Mean plasma fluorescein (FD) concentration versus time profiles obtained after oral administration of (·) tablets and (●) patch preparations to four beagle dogs at a FD dose of 30 mg (mean ± SE) (Eaimtrakarn et al., 2003) (*reproduced with permission from the publisher*).

magnetic resonance imaging with tablets loaded with magnetic Fe_3O_4 particles has been used to identify the position and residence time of such tablets in the stomach of seated human volunteers. The study also considered the use of gadolinium chelates to assess the relative position of the tablet to the intragastric meal level: the distribution was about 20% at a proximal position and 36% at a distal position (Steingoetter et al., 2003).

4.5. Alternative devices

Sakr (1999) suggested the use of a programmable, controlled release drug delivery capsule. The non-digestible oral capsule (contained levonorgestril in a slowly eroding matrix for controlled release) was designed to act by promoting an obstruction that keeps the device floating in the stomach. The capsule was made of different viscosity grades of hydroxypropyl methylcellulose promoting a built-in triggering ballooning system with predefined erosion rates, thus promoting different retention times (several days). After complete core erosion, the ballooning system is flattened off and the device returned to its normal size enabling elimination from the stomach.

5. Small intestine

The intestine is the major organ for absorption of drugs due to its long length and surface area available for absorption. Furthermore the mobility of the intestine is quite constant in comparison to other organs, thus the mobility of its contents is also constant. It is not surprising that only a few strategies have been described to control the mobility of dosage forms within the small intestine.

5.1. Effect of pH

Targeting the release of drugs for the duodenum can be achieved by enteric coating dosage forms. These coats are acidic in nature, thus start to dissolve near neutral pH values. Huang et al. (2005) have suggested a hydroxypropyl methylcellulose-acetate maleate co-polymer to deliver drugs to the duodenum only, since the polymer was dissolving at $3 < pH < 3.7$.

pH sensitive interpolymer interactions between high molecular weight poly(ethylene oxide) and poly(methacrylic acid-co-methyl methacrylate) (Eudragit L100 or S100) were used to prepare co-evaporates, physical mixtures and matrix tablets able to deliver drugs (e.g. prednisolone) to the jejunum or the ileum. With these systems, the release of the drug is inhibited at pHs lower than the threshold of Eudragit ionization, whereas at pHs exceeding such a threshold the matrix undergoes gradual erosion which controls the release (Carelli et al., 2000).

Schellekens et al. (2008) designed a capsule to deliver drugs to the ileo-colonic regions. The system was based on disintegrants in a coat which consists of a continuous matrix of a pH-responsive polymer (Eudragit S). The augmented pH-responsiveness of the new coat was related to the swelling index of the applied disintegrant, particularly sodium croscarmellose. Studies in human subjects have shown that the coat was able to resist to the environmental conditions found in the stomach and duodenum, delaying the release until the distal segments of the intestine. Other authors (Fedorak and Bistritz, 2005) managed to deliver budenoside to the ileum and proximal colon only by enteric coating cores with polymers dissolving at high pHs.

5.2. Effect of adhesion

Pellets containing caffeine were prepared by extrusion and spheronisation. Formulations included bioadhesive materials, namely polyacrylic acids (Carbopol 974P and 971P) in combination with microcrystalline cellulose. The use of electrolytes in the formulation enabled the reduction of tackiness (due to adhesion and high viscosity) throughout the pelletisation. At pH 6.2–6.6 bioadhesion of the pellets was maximised. Consequently, the pellets were able to travel through the stomach and adhere to the intestinal wall, i.e., the duodenum and jejunum, but not to the stomach or even the ileum–caecum region, releasing caffeine within 20 min (Awad et al., 2002). In a different study the intestinal residence time of solid dosage forms was increased when acrylate derivatives produced mucoadhesion. A poly(methacrylic acid)–cysteine conjugate was co-precipitated with starch at pH 3. The resulting thiolated poly(methacrylic acid)–starch composition was freeze-dried: the resulting powder did not swell at gastric pH, but upon increasing the pH it swelled and showed adhesion properties (Bernkop-Schnurch et al., 2004).

Goto et al. (2006) investigated the mucoadhesive properties of hydrogels made of poly(methacrylic acid) grafted with ethylene glycol. Particles were produced from methacrylic acid and ethylene glycol. The production of particles was by free radical synthesis. Rats were used to evaluate the adhesion to the stomach or the small intestine reflecting the adhesion kinetics.

5.3. Other systems

A more sophisticated system to deliver drugs is presented as the InteliSite® capsule. Fasudil was released at different sites using remote-controlled capsules (Hinderling et al., 2007). These capsules can deliver drugs to a defined region of the intestine after activation by application of a magnetic signal. Pithavala et al. (1998) used the capsule to deliver ranitidine to the jejunum, ileum or colon, as proved by the use of a gamma camera.

6. Colon

The colon has gained attention on the delivery of drugs not only for the treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides sensitive to the enzymes in both the stomach and small intestine. The proximal or ascendant colon is considered as the optimum site for colon-target delivery of drugs.

The successful delivery to the colon requires the exploration of a unique feature of the colonic environment: consideration of transit times in the digestive tract (e.g. formulation of timed release systems, drug with a carrier, bioadhesive system and osmotic controlled drug delivery systems), pH (e.g. coating with pH sensitive polymers) and enzymes produced by colonic bacteria (covalent

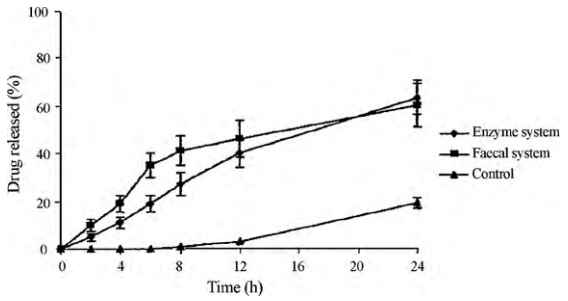

Fig. 4. 5-Aminosalicylic acid release from amylose–ethylcellulose coated pellets in batch culture fermentation systems (enzyme and faecal) and control (mean ± S.D.) (Siew et al., 2004) (*reproduced with permission from the publisher*).

linkage, i.e., exploitation of carriers that are degraded specifically by colonic bacteria) (Ashford and Fell, 1994; Basit, 2005; Asghar and Chandran, 2006). It follows that precise colon drug delivery requires that the triggering mechanism in the delivery system only respond to the physiological conditions particular to the colon (Yang et al., 2002).

6.1. Chemical modification

The chemical modification of either drugs or carriers has been attempted. For instance, prodrugs such as sulphasalazine, ipalazine, balsalazine, olsalazine or 5-amino salicylic acid for localized chemotherapy of bowl disease or for systemic absorption to act on receptors elsewhere in the body, are examples of prodrugs. The combination of a drug with a carrier has been described: dextran-nalidixic acid ester with a varied degree of substitution was synthesized as a colon-specific prodrug of nalidixic acid (Lee et al., 2001).

Carriers, have also been considered, namely bacterial degradable synthetic polymers (e.g. azo cross-linked polymers which may form hydrogels) or natural polymers (e.g. plant polysaccharides such as inulin, pectin, and guar gum) (Yang et al., 2002; Chourasia and Jain, 2003, 2004). In fact, the family of natural polymers has great appeal to drug delivery as it is comprised of polymers with a large number of derivatizable groups, a wide range of molecular weights, varying chemical compositions, and, for the most part, low toxicity and biodegradability, yet high stability (Jain and Jain, 2008).

6.2. Polymer degradation

Polysaccharides are bacterial enzymes that are available in sufficient quantity to be exploited in colon targeting (Jain et al., 2007). These polymers (e.g. pectin and galactomannan) can be used on coats applied to cores (Yang et al., 2002). To improve the specificity of drug release, certain types of polysaccharides can be used to create the dosage forms. These excipients are specifically degraded by the colonic microflora and have been used as polymer drug conjugates, coatings and matrix agents. However, some of these compounds are hydrophilic leading to premature release. For these reasons, some polysaccharides, such as inulin, amylose, guar gum and pectins, have been chemically modified to increase their hydrophobicity or have been combined with other conventional hydrophobic polymers (Vandamme et al., 2002). Amylose in combination with ethylcellulose has been used to control the delivery of drugs to the colon. Pellets produced by extrusion and spheronisation were coated with the mixture of both polymers. Release of model drugs has confirmed the ability of the coat to protect the drugs until the pellets reached the colon (Figs. 4 and 5) (Milojevic et al., 1996). Pectin has also been considered for colonic delivery. A high methoxy pectin based matrix tablet of ropivacaine in combination with ethylcellulose provided a good system for colonic delivery. Addition of ethylcellulose increased the tablet strength and provided a better dissolution control (Ahrabi et al., 1997). The coat was able to protect the core until the colon where enzymes attacked the pectin promoting the release of the drug, as confirmed by in vivo studies (Ashford et al., 1993).

6.3. pH-dependent systems

The unique pH found in the colon has been considered to target the delivery of drugs to this organ (Chourasia and Jain, 2003, 2004). Although the use of pH-dependent materials is not exclusive to deliver drugs to the colon, pH-dependent coatings make possible the design of dosage forms containing high levels of drugs, as alternatives to matrix or hydrogel systems: using polymers dissolving at pH > 7 (e.g. Eudragit FS) it is possible to prevent tablets or pellets from releasing drugs in the stomach or proximal small intestine (Vandamme et al., 2002).

6.4. Time-dependent release

Time dependency of drug delivery systems has been developed based on the principle of preventing release of drug until 3–4 h after leaving the stomach (Chourasia and Jain, 2003, 2004). Furthermore, the design of controlled release systems for optimal drug delivery to the proximal colon requires a detailed knowledge of the relationship between particle size, colonic dispersion and colonic transit rates and of the factors which influence colonic transit rates and consequent drug bioavailability (Barrow et al., 1991).

Gazzaniga et al. (1994, 1995) described a dosage form containing a core (tablet with a drug) coated with three polymeric layers: the outer layer dissolves at pH > 5, then the second layer made of hydroxypropyl methylcellulose swells providing the delay phase and finally the third layer was made of an enteric coating material. In fact, the system is resistant to acidic environment, a non-release phase ending with a rapid release of the drug.

A time-delayed oral drug delivery device was investigated in which an erodible tablet sealing the mouth of an insoluble capsule controlled the lag-time prior to drug release. Erosion rates and drug release profiles were investigated with four different excipients: calcium sulphate dihydrate, dicalcium phosphate, hydroxypropyl methylcellulose and silicified microcrystalline cellulose. Capsule integrity was confirmed to be most suitable for oral delivery when the insoluble ethyl cellulose coat was applied to a hard gelatine capsule using an organic spray coating process (Mcconville et al., 2005).

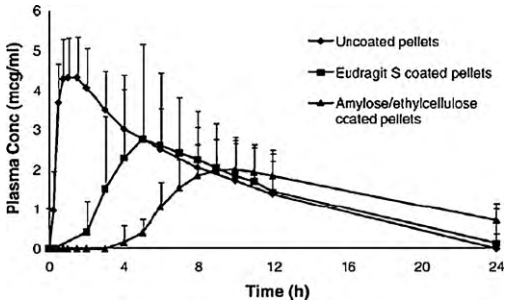

Fig. 5. Mean plasma theophylline levels after administration of uncoated pellets, or pellets coasted with Eudragit S or amylase/ethylcellulose (Mcconnell et al., 2008) (*reproduced with permission from the publisher*).

6.5. Effect of adhesion

Bioadhesive systems have also been exploited to deliver the drugs into the colon (Chourasia and Jain, 2003, 2004). Polymers described before can also be used to tailor the delivery of drugs to the colon by adhesion of the dosage forms to the mucosa.

6.6. Other systems

Other systems, such as the ones based on osmosis, have also been considered to deliver drugs to the colon. For instance, metronidazole has been delivered in a tablet having an osmotic core containing the drug, an osmotic agent and wicking agent (e.g. sodium lauryl sulphate) coated firstly with a semi-permeable membrane containing guar gum (as pore former) and secondly with an enteric coating to protect the system from the acidic environment in the stomach (Kumar et al., 2008).

Among the systems developed most recently for colon-specific delivery the pressure-controlled colon delivery capsules have shown their potential (Yang et al., 2002).

7. Conclusions

Different strategies have been summarized in the manuscript. Due to the complexity of the different organs of the digestive system, one cannot *ab initio* define the best strategy to a particular drug. It must also be pointed out very clearly that the physical and chemical properties of the drug are paramount on the selection of the delivery system.

Apart from the complex systems, not used commonly, namely the ones working under the external human body control, the most feasible strategies consider changes on pH and mobility within the different organs of the digestive system, density and adhesion characteristics of the dosage forms to the target mucosa.

References

Abu-Huwaij, R., Assaf, S., Salem, M., Sallam, A., 2007. Mucoadhesive dosage form of lidocaine hydrochloride: I. mucoadhesive and physicochemical characterization. Drug Dev. Ind. Pharm. 33, 855–864.

Ahrabi, S.F., Madsen, G., Dyrstad, K., Sande, S.A., Graffner, C., 1997. Development of pectin matrix tablets for colonic delivery of model drug ropivacaine. In: 12th Annual Meeting of the AAPS, Boston, MA, USA.

Alanazi, F.K., Rahman, A.A.A., Mahrous, G.M., Alsarra, I.A., 2007. Formulation and physicochemical characterisation of buccoadhesive films containing ketorolac. J. Drug Del. Sci. Technol. 17, 183–192.

Ali, J., Khar, R.K., Ahuja, A., 1998. Formulation and characterisation of a buccoadhesive erodible tablet for the treatment of oral lesions. Pharmazie 53, 329–334.

Alur, H.H., Beal, J.D., Pather, S.I., Mitra, A.K., Johnston, T.P., 1999. Evaluation of a novel, natural oligosaccharide gum as a sustained-release and mucoadhesive component of calcitonin buccal tablets. J. Pharm. Sci. 88, 1313–1319.

Alur, H.H., Desai, R.P., Mitra, A.K., Johnston, T.P., 2001. Inhibition of a model protease - pyroglutamate aminopeptidase by a natural oligosaccharide gum from Hakea gibbosa. Int. J. Pharm. 212, 171–176.

Ameye, D., Mus, D., Foreman, P., Remon, J.P., 2005. Spray-dried Amioca (R) starch/Carbopol (R) 974P mixtures as buccal bioadhesive carriers. Int. J. Pharm. 301, 170–180.

Anlar, S., Capan, Y., Guven, O., Gogus, A., Dalkara, T., Hincal, A.A., 1994. Formulation and in-vitro in-vivo evaluation of buccoadhesive morphine-sulphate tablets. Pharm. Res. 11, 231–236.

Artusi, M., Santi, P., Colombo, P., Junginger, H.E., 2003. Buccal delivery of thiocolchicoside: in vitro and in vivo permeation studies. Int. J. Pharm. 250, 203–213.

Asghar, L.F.A., Chandran, S., 2006. Multiparticulate formulation approach to colon specific drug delivery: current perspectives. J. Pharm. Pharm. Sci. 9, 327–338.

Ashford, M., Fell, J., Attwood, D., Sharma, H., Woodhead, P., 1993. An evaluation of pectin as a carrier for drug targeting to the colon. J. Control. Rel. 26, 213–220.

Ashford, M., Fell, J.T., 1994. Targeting drugs to the colon—delivery systems for oral-administration. J. Drug Target. 2, 241–257.

Attia, M.A., El-Gibaly, I., Shaltout, S.E., Fetih, G.N., 2004. Transbuccal permeation, anti-inflammatory activity and clinical efficacy of piroxicam formulated in different gels. Int. J. Pharm. 276, 11–28.

Atyabi, F., Majzoob, S., Dorkoosh, F., Sayyah, M., Ponchel, G., 2007. The impact of trimethyl chitosan on in vitro mucoadhesive properties of pectinate beads along different sections of gastrointestinal tract. Drug Dev. Ind. Pharm. 33, 291–300.

Averineni, R.K., Sunderajan, S.G., Mutalik, S., Nayak, U., Shavi, G., Armugam, K., Meka, S.R., Pandey, S., Nayanabhirama, U., 2009. Development of mucoadhesive buccal films for the treatment of oral sub-mucous fibrosis: a preliminary study. Pharm. Dev. Technol. 14, 199–207.

Awad, G.A.S., Charrueau, C.A.A., Allain, P., Chaumeil, J.C., 2002. Formulation and evaluation of bioadhesive pellets containing different carbomers made by extrusion-spheronization. STP Pharm. Sci. 12, 157–162.

Baldi, F., Malfertheiner, P., 2003. Lansoprazole fast disintegrating tablet: A new formulation for an established proton pump inhibitor. Digestion 67, 1–5.

Barrow, L., Spiller, R.C., Wilson, C.G., 1991. Pathological influences on colonic motility—implications for drug delivery. Adv. Drug Del. Rev. 7, 201–218.

Basit, A.W., 2005. Advances in colonic drug delivery. Drugs 65, 1991–2007.

Batchelor, H., 2005. Bioadhesive dosage forms for esophageal drug delivery. Pharm. Res. 22, 175–181.

Batchelor, H.K., Tang, M., Dettmar, P.W., Hampson, F.C., Jolliffe, I.G., Craig, D.Q.M., 2004. Feasibility of a bioadhesive drug delivery system targeted to oesophageal tissue. Eur. J. Pharm. Biopharm. 57, 295–298.

Baumgartner, S., Kristl, J., Vrecer, F., Vodopivec, P., Zorko, B., 2000. Optimisation of floating matrix tablets and evaluation of their gastric residence time. Int. J. Pharm. 195, 125–135.

Baumgartner, S., Smid-Korbar, J., Vrecer, F., Kristl, J., 1998. Physical and technological parameters influencing floating properties of matrix tablets based on cellulose ethers. STP Pharm. Sci. 8, 285–290.

Bernkop-Schnurch, A., Konig, V., Leitner, V.M., Krauland, A.H., Brodnik, I., 2004. Preparation and characterisation of thiolated poly(methacrylic acid)-starch compositions. Eur. J. Pharm. Biopharm. 57, 219–224.

Bies, C., Lehr, C.M., Woodley, J.F., 2004. Lectin-mediated drug targeting: history and applications. Adv. Drug Del. Rev. 56, 425–435.

Blancofuente, H., Anguianoigea, S., Oteroespinar, F.J., Blancomendez, J., 1996. In-vitro bioadhesion of carbopol hydrogels. Int. J. Pharm. 142, 169–174.

Blick, S.K.A., Wagstaff, A.J., 2006. Fentanyl buccal tablet—in breakthrough pain in opioid-tolerant patients with cancer. Drugs 66, 2387–2393.

Bouckaert, S., Remon, J.P., 1993. In-vitro bioadhesion of a buccal, miconazole slow-release tablet. J. Pharm. Pharmacol. 45, 504–507.

Burgalassi, S., Panichi, L., Saettone, M.F., Jacobsen, J., Rassing, M.R., 1996. Development and in vitro in vivo testing of mucoadhesive buccal patches releasing benzydamine and lidocaine. Int. J. Pharm. 133, 1–7.

Bussemer, T., Otto, I., Bodmeier, R., 2001. Pulsatile drug-delivery systems. Crit. Rev. Ther. Drug Carrier Syst. 18, 433–458.

Cappello, B., de Rosa, G., Giannini, L., la Rotonda, M.I., Mensitieri, G., Miro, A., Quaglia, F., Russo, R., 2006. Cyclodextrin-containing poly(ethyleneoxide) tablets for the delivery of poorly soluble drugs: Potential as buccal delivery system. Int. J. Pharm. 319, 63–70.

Carelli, V., di Colo, G., Nannipieri, E., Poli, B., Serafini, M.F., 2000. Polyoxyethylene-poly(methacrylic acid-co-methyl methacrylate) compounds for site-specific peroral delivery. Int. J. Pharm. 202, 103–112.

Chen, J., Blevins, W.E., Park, H., Park, K., 2000. Gastric retention properties of superporous hydrogel composites. J. Control. Rel. 64, 39–51.

Chen, J., Park, H., Park, K., 1999. Synthesis of superporous hydrogels: Hydrogels with fast swelling and superabsorbent properties. J. Biomed. Mater. Res. 44, 53–62.

Chen, J., Park, K., 2000. Synthesis of fast-swelling, superporous sucrose hydrogels. Carbohydr. Polym. 41, 259–268.

Chourasia, M.K., Jain, S.K., 2003. Pharmaceutical approaches to colon targeted drug delivery systems. J. Pharm. Pharm. Sci. 6, 33–66.

Chourasia, M.K., Jain, S.K., 2004. Polysaccharides for colon targeted drug delivery. Drug Del. 11, 129–148.

Chueh, H.R., Zia, H., Rhodes, C.T., 1995. Optimization of sotalol floating and bioadhesive extended-release tablet formulations. Drug Dev. Ind. Pharm. 21, 1725–1747.

Chun, M.K., Kwalk, B.T., Choi, H.K., 2003. Preparation of buccal patch composed of carbopol, poloxamer and hydroxypropyl methylcellulose. Arch. Pharm. Res. 26, 973–978.

Desai, S., Bolton, S., 1993. A floating controlled-release drug-delivery system—in-vitro in-vivo evaluation. Pharm. Res. 10, 1321–1325.

Deshpande, A.A., Shah, N.H., Rhodes, C.T., Malick, W., 1997. Development of a novel controlled-release system for gastric retention. Pharm. Res. 14, 815–819.

Dhaliwal, S., Jain, S., Singh, H.P., Tiwary, A.K., 2008. Mucoadhesive microspheres for gastroretentive delivery of acyclovir: In vitro and in vivo evaluation. AAPS J. 10, 322–330.

Dhiman, M., Yedurkar, P., Sawant, K.K., 2008. Formulation, characterization, and in vitro evaluation of bioadhesive gels containing 5-fluorouracil. Pharm. Dev. Technol. 13, 15–25.

Eaimtrakarn, S., Prasad, Y.V.R., Puthli, S.P., Yoshikawa, Y., Shibata, N., Takada, K., 2003. Possibility of a patch system as a new oral delivery system. Int. J. Pharm. 250, 111–117.

Elkheshen, S.A., Yassin, A.E.B., Alsuwayeh, S., Alkhaled, F.A., 2004. In vitro and in vivo evaluation of floating controlled release dosage forms of verapamil hydrochloride. Pharmazeutische Ind. 66, 1364–1372.

Fedorak, R.N., Bistritz, L., 2005. Targeted delivery, safety, and efficacy of oral enteric-coated formulations of budesonide. Adv. Drug Del. Rev. 57, 303–316.

Gangadharappa, H.V., Pramod, K.T.M., Shiva, K.H.G., 2007. Gastric floating drug delivery systems: a review. Indian J. Pharm. Ed. Res. 41, 295–305.

Garg, S., Kumar, G., 2007. Development and evaluation of a buccal bioadhesive system for smoking cessation therapy. Pharmazie 62, 266–272.

Gazzaniga, A., Busetti, C., Moro, l., Sangalli, M.E., Giordano, F., 1995. Time-dependent oral delivery systems for colon targeting. STP Pharm. Sci. 5, 83–88.

Gazzaniga, A., Iamartino, P., Maffione, G., Sangalli, M.E., 1994. Oral delayed-release system for colonic specific delivery. Int. J. Pharm. 108, 77–83.
Gazzaniga, A., Palugan, L., Foppoli, A., Sangalli, M.E., 2008. Oral pulsatile delivery systems based on swellable hydrophilic polymers. Eur. J. Pharm. Biopharm. 68, 11–18.
Giunchedi, P., Juliano, C., Gavini, E., Cossu, M., Sorrenti, M., 2002. Formulation and in vivo evaluation of chlorhexidine buccal tablets prepared using drug-loaded chitosan microspheres. Eur. J. Pharm. Biopharm. 53, 233–239.
Goswami, T., Jasti, B., Li, X.L., 2008. Sublingual drug delivery. Crit. Rev. Ther. Drug Carrier Syst. 25, 449–484.
Goto, T., Morishita, M., Kavimandan, N.J., Takayama, K., Peppas, N.A., 2006. Gastrointestinal transit and mucoadhesive characteristics of complexation hydrogels in rats. J. Pharm. Sci. 95, 462–469.
Groning, R., Cloer, C., Muller, R.S., 2006. Development and in vitro evaluation of expandable gastroretentive dosage forms based on compressed collagen sponges. Pharmazie 61, 608–612.
Gu, T.H., Chen, S.X., Zhu, J.B., Song, D.J., Guo, J.Z., Hou, H.M., 1992. Pharmacokinetics and pharmacodynamics of diltiazem floating tablets. Acta Pharmacol. Sin. 13, 527–531.
Guo, J.H., 1994. Bioadhesive polymer buccal patches for buprenorphine controlled delivery - formulation, in-vitro adhesion and release properties. Drug Dev. Ind. Pharm. 20, 2809–2821.
Guo, J.H., Cooklock, K.M., 1996. The effects of backing materials and multilayered systems on the characteristics of bioadhesive buccal patches. J. Pharm. Pharmacol. 48, 255–257.
Hinderling, P.H., Karara, A.H., Tao, B., Pawula, M., Wilding, I., Lu, M., 2007. Systemic availability of the active metabolite hydroxy-fasudil after administration of fasudil to different sites of the human gastrointestinal tract. J. Clin. Pharmacol. 47, 19–25.
Huang, Y., Zheng, L.L., Liu, J., Zhang, Z.R., 2005. Synthesis and characterization of HPMC derivatives as novel duodenum-specific coating agents. Arch. Pharmacal Res. 28, 364–369.
Hwang, S.J., Park, H., Park, K., 1998. Gastric retentive drug-delivery systems. Crit. Rev. Ther. Drug Carrier Syst. 15, 243–284.
Jacobsen, J., Bjerregaard, S., Pedersen, M., 1999. Cyclodextrin inclusion complexes of antimycotics intended to act in the oral cavity - drug supersaturation, toxicity on TR146 cells and release from a delivery system. Eur. J. Pharm. Biopharm. 48, 217–224.
Jain, A., Gupta, Y., Jain, S.K., 2007. Perspectives of biodegradable natural polysaccharides for site-specific drug delivery to the colon. J. Pharm. Pharm. Sci. 10, 86–128.
Jain, S.K., Jain, A., 2008. Target-specific drug release to the colon. Exp. Opin. Drug Del. 5, 483–498.
Jothi, M.V., Bhat, K.M., Pratibha, P.K., Bhat, G.S., 2009. The evaluation of a biodegradable dental chip containing chlorhexidine in chitosan base as a targeted drug delivery in the management of chronic periodontitis in patients. Drug Dev. Res. 70, 395–401.
Juliano, C., Cossu, M., Pigozzi, P., Rassu, Gg., Giunchedi, P., 2008. Preparation, in vitro characterization and preliminary in vivo evaluation of buccal polymeric films containing chlorhexidine. AAPS PharmSciTech 9, 1153–1158.
Kawashima, Y., Niwa, T., Takeuchi, H., Hino, T., Itoh, Y., 1992. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. J. Pharm. Sci. 81, 135–140.
Khanna, R., Agarwal, S.P., Ahuja, A., 1996. Preparation and evaluation of bioerodible buccal tablets containing clotrimazole. Int. J. Pharm. 138, 67–73.
Klausner, E.A., Lavy, E., Friedman, M., Hoffman, A., 2003. Expandable gastroretentive dosage forms. J. Control. Rel. 90, 143–162.
Krogel, I., Bodmeier, R., 1999. Floating or pulsatile drug delivery systems based on coated effervescent cores. Int. J. Pharm. 187, 175–184.
Kumar, P., Singh, S., Mishra, B., 2008. Colon targeted delivery systems of metronidazole based on osmotic technology: development and evaluation. Chem. Pharm. Bull. 56, 1234–1242.
Lee, J.S., Jung, Y.J., Doh, M.J., Kim, Y.M., 2001. Synthesis and properties of dextran-nalidixic acid ester as a colon-specific prodrug of nalidixic acid. Drug Dev. Ind. Pharm. 27, 331–336.
Lele, B.S., Hoffman, A.S., 2000. Mucoadhesive drug carriers based on complexes of poly(acrylic acid) and PEGylated drugs having hydrolysable PEG-anhydride-drug linkages. J. Control. Rel. 69, 237–248.
Li, C., Bhatt, P.P., Johnston, T.P., 1998. Evaluation of a mucoadhesive buccal patch for delivery of peptides: In vitro screening of bioadhesion. Drug Dev. Ind. Pharm. 24, 919–926.
Liang, A.C., Chen, L.I.H., 2001. Fast-dissolving intraoral drug delivery systems. Exp. Opin. Ther. Patents, 11, 981–986.
Lin, S.Y., Lin, P.C., 1992. Effect of acid type, acetic-acid and sodium carboxymethyl cellulose concentrations on the formation, micromeritic, dissolution and floating properties of theophylline chitosan microcapsules. Chem. Pharm. Bull. 40, 2491–2497.
Maffei, P., Borgia, S.L., Sforzini, A., Yasin, A., Ronchi, C., Ceschel, G.C., 2004. Design and in vitro–in vivo evaluation of a bi-layered tablet containing benzocaine for local buccal administration. J. Drug Del. Sci. Technol. 14, 363–372.
Maggi, L., Segale, L., Conti, S., Machiste, E.O., Salini, A., Conte, U., 2005. Preparation and evaluation of release characteristics of 3TabGum, a novel chewing device. Eur. J. Pharm. Sci. 24, 487–493.
Mannila, J., Jarvinen, T., Jarvinen, K., Jarho, P., 2007. Precipitation complexation method produces cannabidiol/beta-cyclodextrin inclusion complex suitable for sublingual administration of cannabidiol. J. Pharm. Sci. 96, 312–319.
Mashru, R.C., Sutariya, V.B., Sankalia, M.G., Parikh, P.P., 2005. Development and evaluation of fast-dissolving film of salbutamol sulphate. Drug Dev. Ind. Pharm. 31, 25–34.
Mcconnell, E.L., Short, M.D., Basit, A.W., 2008. An in vivo comparison of intestinal pH and bacteria as physiological trigger mechanisms for colonic targeting in man. J. Control. Rel. 130, 154–160.
Mcconville, J.T., Ross, A.C., Florence, A.J., Stevens, H.N.E., 2005. Erosion characteristics of an erodible tablet incorporated in a time-delayed capsule device. Drug Dev. Ind. Pharm. 31, 79–89.
Meka, l., Kesavan, B., Kalamata, V.N., Eaga, C.M., Bandari, S., Vobalaboina, V., Yamsani, M.R., 2009. Design and evaluation of polymeric coated minitablets as multiple unit gastroretentive floating drug delivery systems for furosemide. J. Pharm. Sci. 98, 2122–2132.
Messina, J., Darwish, M., Fine, P.G., 2008. Fentanyl buccal tablet. Drugs Today 44, 41–54.
Milojevic, S., Newton, J.M., Cummings, J.H., Gibson, G.R., Botham, R.L., Ring, S.G., Stockham, M., Allwood, M.C., 1996. Amylose as a coating for drug delivery to the colon: Preparation and in vitro evaluation using glucose pellets. J. Control. Rel. 38, 85–94.
Minghetti, P., Colombo, A., Montanari, L., Gaeta, G.M., Gombos, F., 1998. Buccoadhesive slow-release tablets of acitretin: design and 'in vivo' evaluation. Int. J. Pharm. 169, 195–202.
Nagano, H., Machida, Y., Iwata, M., Imada, T., Noguchi, Y., Matsumoto, A., Nagai, T., 1997. Preparation of magnetic granules containing bleomycin and its evaluation using model esophageal cancer. Int. J. Pharm. 147, 119–125.
Overholt, B.F., Panjehpour, M., deNovo, R.C., Peterson, M.G., Jenkins, C., 1996. Balloon photodynamic therapy of esophageal cancer: effect of increasing balloon size. Lasers Surg. Med. 18, 248–252.
Owens, T.S., Dansereau, R.J., Sakr, A., 2005. Development and evaluation of extended release bioadhesive sodium fluoride tablets. Int. J. Pharm. 288, 109–122.
Perioli, l., Ambrogi, A., Angelici, F., Ricci, M., Giovagnoli, S., Capuccella, M., Rossi, C., 2004. Development of mucoadhesive patches for buccal administration of ibuprofen. J. Control. Rel. 99, 73–82.
Pithavala, Y.K., Heizer, W.D., Parr, A.F., OïConnor-Semmes, R.L., Brouwer, K.L.R., 1998. Use of the InteliSite (R) capsule to study ranitidine absorption from various sites within the human intestinal tract. Pharm. Res. 15, 1869–1875.
Repka, M.A., Prodduturi, S., Stodghill, S.P., 2003. Production and characterization of hot-melt extruded films containing clotrimazole. Drug Dev. Ind. Pharm. 29, 757–765.
Sakr, F.M., 1999. A programmable drug delivery system for oral administration. Int. J. Pharm. 184, 131–139.
Sawicki, W., 2002. Pharmacokinetics of verapamil and norverapamil from controlled release floating pellets in humans. Eur. J. Pharm. Biopharm. 53, 29–35.
Schellekens, R.C.A., Stellaard, F., Mitrovic, D., Stuurman, F.E., Kosterink, J.G.W., Frijlink, H.W., 2008. Pulsatile drug delivery to ileo-colonic segments by structured incorporation of disintegrants in pH-responsive polymer coatings. J. Control. Rel. 132, 91–98.
Scholz, O.A., Wolff, A., Schumacher, A., Giannola, l., Campisi, I., Ciach, G., Velten, T.T., 2008. Drug delivery from the oral cavity: focus on a novel mechatronic delivery device. Drug Discov. Today 13, 247–253.
Seager, H., 1998. Drug-delivery products and the Zydis fast-dissolving dosage form. In: British Pharmaceutical Conference, Eastbourne, England.
Segale, L., Maggi, L., Machiste, E.O., Conti, S., Conte, U., Grenier, A., Besse, C., 2007. Formulation design and development to produce orodispersible tablets by direct compression. J. Drug Del. Sci. Technol. 17, 199–203.
Shidhaye, S.S., Saindane, N.S., Sutar, S., Kadam, V., 2008. Mucoadhesive bilayered patches for administration of sumatriptan succinate. AAPS PharmSciTech 9, 909–916.
Siepmann, F., Siepmann, J., Walther, M., Macrae, R.J., Bodmeier, R., 2008. Polymer blends for controlled release coatings. J. Control. Rel. 125, 1–15.
Siew, L.F., Man, S.M., Newton, J.M., Basit, A.W., 2004. Amylose formulations for drug delivery to the colon: a comparison of two fermentation models to assess colonic targeting performance in vitro. Int. J. Pharm. 273, 129–134.
Steingoetter, A., Weishaupt, D., Kunz, P., Mader, K., Lengsfeld, H., Thumshirn, M., Boesiger, P., Fried, M., Schwizer, W., 2003. Magnetic resonance imaging for the in vivo evaluation of gastric-retentive tablets. Pharm. Res. 20, 2001–2007.
Streubel, A., Siepmann, J., Bodmeier, R., 2003. Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. Eur. J. Pharm. Sci. 18, 37–45.
Tagarro, I., Vauzelle-Kervroedan, F., Diez, M.C., 2004. Pharmacokinetic assessment of a fast-release orodispersible tramadol tablet compared to a conventional tramadol capsule. Arzneimittel-Forschung-Drug Res. 54, 293–297.
Vandamme, T.F., Lenourry, A., Charrueau, C., Chaumeil, J., 2002. The use of polysaccharides to target drugs to the colon. Carbohydr. Pol. 48, 219–231.
Yang, L.B., Chu, J.S., Fix, J.A., 2002. Colon-specific drug delivery: new approaches and in vitro/in vivo evaluation. Int. J. Pharm. 235, 1–15.
Zhang, l., Russell, D., Conway, B.R., Batchelor, H., 2008. Strategies and therapeutic opportunities for the delivery of drugs to the esophagus. Crit. Rev. Ther. Drug Carrier Syst. 25, 259–304.
Zou, H., Jiang, X.T., Kong, L.S., Gao, S., 2008. Design and evaluation of a dry coated drug delivery system with floating-pulsatile release. J. Pharm. Sci. 97, 263–273.