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# Recent Trends and Progress in Sustained or Controlled Oral Delivery of Some Water Soluble Drugs: Morphine Salts, Diltiazem and Captopril

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## ABSTRACT

The development of oral controlled release systems has been a challenge to formulation scientists due to their inability to restrain and localise the system at targeted areas of the gastrointestinal (GI) tract. Controlled/sustained release preparations using alternative routes have been formulated but the oral route still remains the most desirable. For obvious reason, water soluble drugs are more difficult to deliver orally in sustained or controlled release manner than lipophilic drugs. Attempts have been made to regulate the release process by incorporating hydrophobic fillers

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within the system or by coating the drug with poorly soluble, swollen or non-swollen polymers or other substances. Others used the so called 'hydrodynamically balanced systems' which float in the gastric fluid at the stomach thereby increase the residence time for the device in the GI tract. A new approach has been the use of mucoadhesive systems to increase the residence time of the device within the GI tract. This review focuses on the progress made in the design of controlled/sustained release delivery systems for some water soluble drugs. Highly/freely water soluble diltiazem, captopril and morphine salts have been selected as model drugs due to the leading role they play in their respective field of therapy and their widespread use in treating chronic patients. Particular emphasis is given to delivery systems designed to achieve their once a day dose treatment.



## INTRODUCTION

In order to develop sustained or controlled release oral delivery systems the formulation scientists face the difficulties of restraining and localising the system at targeted areas of the gastrointestinal (GI) tract. Water soluble drugs are considered difficult to deliver in the form of sustained or controlled release preparation due to their susceptibility to "dose dumping" phenomenon [1]. Drugs like captopril, diltiazem and morphine salts which are freely/highly water soluble play leading roles in their respective field of therapy. These drugs are usually prescribed to patients who are chronically ill and require long-term use for their therapeutical benefits. Their mean plasma elimination half-lives are relatively short ranging from 2 to 4.5 hours requiring 3-4 divided doses in a day. For better patient compliance and minimisation of side-effects, attempts have been made to design long acting devices in the form of sustained or controlled release preparations to deliver these drugs. Currently, there are

oral sustained release preparations for some water soluble drugs (e.g., diltiazem SR capsules, USP) on the market for commercial use, but most of these preparations are effective for a maximum period of 12 hours following oral administration and require at least twice a day dose treatment. An obvious therapeutic advantage could be realised if delivery systems capable of extending the release profile of these drugs could be designed for once a day dose treatment.

Despite significant interest and numerous reports about the design of sustained or controlled release delivery systems for various water soluble drugs, very few have been successful, and most of the proclaimed successful formulations are the results of research work carried out in laboratories of commercial organisations. Not surprisingly, almost all these formulations have been patented and clinical supportive data regarding their efficacies are not always available. Due to the nature of publications, most patented formulations are not freely accessible to all readers which sometime might contribute to reinventing the formulations. The main objective of this review is to focus on the technologies used in recent years in designing oral sustained/controlled release delivery systems for various water soluble drugs with particular emphasis on those systems having the potential for use as once a day dose treatment. Three highly/freely water soluble drugs, diltiazem, captopril and morphine salts, were selected as model drugs due to the leading role they play in their respective field of therapy and their widespread use in treating chronic patients. Table I summarises and compares the various dosage forms proclaimed to be suitable for once a day administration. The dosage forms have been broadly categorised here as either single unit dosage form or multiple unit dosage form on the basis of their structural and physical appearance. Much publicised mucoadhesive systems which fall among either of these two

Table I. Comparison of Various Oral Dosage Forms Designed to Achieve Once-a-Day Administration of Some Water Soluble Drugs Like Morphine Salts, Captopril and Diltiazem

| Dosage form | Factor(s) responsible for controlled release mechanism | Type of experiment/ Drug used | Remarks | Reference |
|---|---|---|---|---|
| Hydrophobic/ Swellable tablets | Hydrophobicity of filler(s) (ethylcellulose) | *In vitro*/Diltiazem | A release of 86% of the drug was obtained after 20 hours | 15 |
| | Hydrophobicity of fillers (hydrogenated castor oil and stearic acid) | *In vitro*/Diltiazem | The tablets, recommended for once a day administration, released >60% of the drug after 5 hours | 16 |
| | Hydrophobicity of filler(s) (glyceryl monostearate) | *In vitro*/Diltiazem | A dissolution rate of 96% of the drug was obtained after 24 hours | 17 |
| | Complexation of the drug with the carrier (diethyl- or triethyl-β-cyclodextrin) | *In vitro* and in rats/ Diltiazem | An increased AUC compared to conventional tablets for up to 48 hours was obtained | 20 |
| | As above | *In vitro* and in dogs/ Diltiazem | A sustained and prolonged AUC for the drug was obtained | 21 |
| | Complexation of the drug with carboxymethyl-ethyl-β-cyclodextrin | *In vitro* and in dogs/ Diltiazem | A pH-dependent release of the drug and 2-fold higher AUC up to 24 hours compared to conventional tablets were obtained | 22 |

| | | | | |
|---|---|---|---|---|
| Osmotic devices | Control over the thixotropic activity of the drug carrier by osmotic means | *In vitro*/Diltiazem, nifedipine | A controlled release of the drug over about 24 hours was claimed | 35 |
| | Dual osmotic mechanism of the drug carrier and the pushing compartment of the device | *In vitro* and in dogs/ Calcium antagonist | A controlled release of the drug over 24-30 hours was obtained with good *in vitro* and *in vivo* correlation | 40 |
| | Permeability of the semipermeable wall which is controlled by its composition and surface area, and osmotic gradient across the wall | *In vitro*/Diltiazem | A sustained release profile of the drug over 20 hours with 50% release in 6-7.5 hours was obtained | 42 |
| | Permeability of the semipermeable wall which is controlled by its composition and surface area, osmotic gradient across the wall and viscosity of drug solution within the drug compartment | *In vitro* and in humans/ Diltiazem | An once a day administration of the device was found adequate in a study involving four male volunteers | 41 |

*(continued)*

Table 1. Continued

| Dosage form | Factor(s) responsible for controlled release mechanism | Type of experiment/ Drug used | Remarks | Reference |
|---|---|---|---|---|
| Microgranules/ Spheroids | Permeability of coatings applied to the granules | *In vivo*/Diltiazem | High bioavailability of the drug over >24 hours was obtained | 45 |
| | Amount of coatings applied to the granules | In humans/Diltiazem | A 300 mg single dose was found to provide effective concentration of the drug over 24 hours | 49 |
| | Amount and permeability of coatings applied to the spheroids | *In vitro*/Diltiazem | A sustained release of the drug over 20 hours could be obtained | 50 |
| Beads | Wetability of the core beads and permeability of the microporous membrane used to coat the beads | *In vitro* and in humans/Diltiazem | About 84% of the drug was released in 12 hours in a buffer (pH 5,8) and optimum bioavailability over 24 hours was obtained after single administration | 51 |
| | Different mixing ratios of water soluble and water insoluble polymers used for coating the beads | *In vitro* and in humans/Diltiazem | Rapid release and slow release beads, prepared by adjusting the mixing ratios, filled in capsules gave optimum bioavailability of the drug over 24 hours postadministration period | 52 |

| | | | | |
|---|---|---|---|---|
| Beads (continued) | Amount and selection of the polymer used to coat the beads and the position of the drug in the beads | *In vitro* and *in vivo*/ Diltiazem | The beads were recommended for once a day administration after studies in dogs and in humans | 43,54 |
| Pellets | The number of layers and mixing ratios of the water soluble (Eudragit RL) and water insoluble (Eudragit RS) polymers used to coat the pellets | *In vitro* and in humans/Diltiazem | The bioavailability and other pharmacokinetic parameters of the drug after single oral administration were consistent with once a day requirement | 59-61 |
| | Amount and mixing ratios of polymers (with different solubilities in different regions of the GI tract) used to coat the pellets | *In vitro* and in humans/Morphine salt | The pellets showed typical slow and prolonged release characteristics and were recommended for single daily dose treatment | 1 |
| Mucoadhesive tablets | Mucoadhesive and gelling properties of Carbopol 934P | Not specified/ Captopril | A sustained release of the drug over 16 hours was claimed | 74 |

categories are discussed separately due to the importance and emphasis given to them.

## SINGLE UNIT DOSAGE FORMS

The single unit dosage forms usually refer to diffusion-controlled systems where the drug is uniformly distributed (dissolved or dispersed) throughout a solid matrix and the release of the drug is controlled or sustained either by incorporating hydrophobic filler (or fillers) within the matrix or by coating the drug matrix with swellable or non-swellable polymer film (or films). In the former instance, the delivery system is known as monolithic device where diffusion of the drug through the matrix is the rate-limiting step. From such devices usually the rate of release of drug is not constant and follows a square root of time dependency [2]. Some monolithic devices use hydrophilic polymers where drug release is governed by the swelling rate of the polymer matrix. A zero-order release kinetics from these devices can be maintained if the polymer swells at a constant rate maintaining a constant surface area and the diffusion of the drug is comparatively rapid [2]. In the second case, which is commonly known as complex reservoir system or multilayered matrix system, diffusion of the drug through the polymer coating(s) or external layer(s) of the system is the rate-limiting step.

### Monolithic devices

The simplest technique to prepare sustained release monolithic device for water soluble drugs is to mix the powdered drug(s) with excipients those exhibit sustained/controlled release properties in physiological fluids and deliver the powder mixture in the form of capsules.

Dennis et al. [3] obtained a sustained release powder formulation for water soluble drugs by mixing the drug with a pH-dependent polymer (Na alginate) and a pH-independent hydrocolloid gelling agent, hydroxypropyl methyl cellulose (HPMC).

The monolithic devices include such systems as tablets with hydrophobic or swellable properties, floating tablets (or capsules), semisolid matrix systems and some mucoadhesive matrix systems.

*Floating tablets or capsules*

The architecture of designing floating tablets or capsules or the so called 'hydrodynamically balanced drug delivery system' (HBS$^{TM}$) is based on the principle that devices with specific gravity lesser than that of the gastric juice will float in the gastric juice at the stomach and retain the drug in the stomach for an extended period thereby increasing the total residence time or residence time in the proximal region of the GI tract. This approach is particularly suitable for drugs which are either liable to degradation at higher pH conditions of the intestine or are poorly absorbed from the distal parts of the GI tract. Captopril falls into this category of drugs [4]. Morphine was reported to be poorly absorbed or not to be absorbed from the colon [5], but Cole et al. [6] found comparable plasma concentration of morphine delivered via rectal route in the form of a controlled release suppository with those reported for the same dose given orally over the same period.

The reduction of specific gravity of these systems is attained by incorporating fillers of low density within the system. Hard gelatin capsule shells filled with captopril mixed and blended with hydroxypropyl cellulose, lactose and microcrystalline cellulose were found to act as floating devices in artificial gastric fluid and retard the *in vitro* dissolution rate of the drug

as a function of viscosity and concentration of the polymer used [4]. Tossounian et al. [7] demonstrated that HBS™-based capsules or tablets containing vitamins and minerals significantly prolonged the release pattern of these substances in the stomach when compared with conventional dosage forms or standard solutions.

Intragastric floating tablets based on chitosan and its HCl salt [8] and polyvinyl alcohol (PVA) and polyvinylpyrolidone (PVP) [9] containing diltiazem HCl produced a sustained plateau of the drug when tested in dogs. Apart from floating characteristic, chitosan is also known to posses mucoadhesive properties [10] which might have also influenced the residence time of the chitosan based tablets in the stomach. The tablets were demonstrated to float and gradually swell in acid medium at pH 1.2 [8].

An alternative method of preparing floating tablets was described by Bolton and Desai [11]. They prepared noncompressed tablets with numerous air holes and internal passages within the matrix to keep the density of the tablets <1. An emulsion prepared from the drug, inert oil and water heated to 70°C was poured into a tablet mold, cooled and air-dried to get the tablets. The tablets had sustained release properties in acid medium at pH 1.2.

Most of the systems described above show *in vitro* sustained release pattern only for a short period of only up to 8 hours and their *in vivo* release pattern is not well investigated. These facts make it difficult to consider them as effective sustained release devices. However, Gu et al. [12] reported efficacy of floating tablets of diltiazem in humans for up to a period of 12 hours with recommendation for twice a day dose treatment.

*Hydrophobic/swellable tablets*

Tablets prepared by mixing the water soluble drug with hydrophobic filler(s) appear to extend the release time of the drug from the devices

within the GI tract after oral administration. Opium alkaloids such as morphine salts homogenised with a fatty acid or its salt and an ethylene vinyl acetate copolymer, and then compressed into tablets was reported to give sustained release pattern of the drug during *in vitro* studies [13].

Yoshida et al. [14] used hydrogenated oils or polymeric substances as controlling agents to formulate long acting tablets for diltiazem and other water soluble drugs. Diltiazem tablets prepared from HPMC phthalate, a hydrogenated oil, lactose, hydroxypropyl cellulose and magnesium stearate gave sustained release dissolution pattern of the drug when tested *in vitro*. Tablets prepared from diltiazem HCl, lactose, HPMC, ethylcellulose and magnesium stearate gave a dissolution of 86% of the drug after 20 hours when tested *in vitro* [15].

Altevogt et al. [16] proclaimed an once a day dose tablet formulation for diltiazem HCl using hydrogenated castor oil and stearic acid as hydrophobic fillers to control the release pattern of the tablets. Diltiazem HCl mixed with lactose, hydrogenated castor oil and stearic acid and heated to 60°C and then cooled and granulated (with Na-CMC) produced tablets with >60% dissolution of the drug after 5 hours during *in vitro* studies. A diltiazem hydrophobic tablet comprising of glyceryl monostearate, confectioner's sugar, microcrystalline cellulose, povidone and magnesium stearate gave an *in vitro* dissolution rate of 96% after 24 hours [17]. The release rate could be further delayed by coating the tablets with water insoluble polymers (e.g., ethylcellulose) or enteric polymers (e.g., cellulose acetate phthalate) or combination thereof.

A tablet formulation consisting of a pH-independent hydrocolloid gelling agent (or agents), a pH-dependent polymer (e.g., Na alginate) and a binder was found to control the release of incorporated basic drugs independently of pH of the dissolution media [18]. Thakur and Jain [19]

described a chitosan-based tablet formulation for captopril which comprises of chitosan, lactose, magnesium stearate and the drug. The tablets gave a zero-order release of the drug continuously over 8 hours in neutral and acidic environment.

Sustained release properties of hydrophobic tablets can be improved if the drug can be incorporated within the matrix in the form of a hydrophobic complex with the carrier. Diltiazem HCl, complexed with ethylated β-cyclodextrins and compressed into tablets showed sustain release pattern and a considerable increase in area under the plasma concentration curve (AUC) (up to 48 hours) when compared to conventional diltiazem tablets (with starch as diluent) following an oral administration in rats [20]. In a follow up study, the authors reported that tablets containing diethyl-β-cyclodextrin complex produced a sustained release pattern of the drug for a longer period than those containing noncomplexed diltiazem without decrease in AUC following oral administration in dogs [21]. The rate of release of the drug could be controlled by combining ethylated β-cyclodextrin complexes of diltiazem with β-cyclodextrin (hydrophilic) complexes of the drug in different mixing ratios. The *in vitro* release pattern of diltiazem from tablets prepared from ethylated β-cyclodextrin complexes was virtually unaffected by the pH of the dissolution media. In another study, the authors were able to prepare sustained release tablets using carboxymethyl-ethyl-β-cyclodextrin as a complex forming material with diltiazem HCl [22]. The rate of release of the drug from these tablets was pH-dependant. After oral administration in dogs, the tablets passed the stomach without significant release and rapidly released the drug in the intestine as judged by the plasma concentration. The AUC for the drug was 2-fold greater up to 24 hours postadministration period when compared with diltiazem HCl tablets prepared using starch as diluent.

Sulphonic type cation exchange resins which produce salts with diltiazem can be utilised to sustain the delivery of the drug. A salt of diltiazem and Dowex$^{R}$ 50W-x4 ($H^{+}$) showed sustain release properties during *in vitro* studies and the release characteristics of the complex was not influenced by the pH of the dissolution media [23].

*Semisolid matrix systems*

As with hydrophobic matrix tablets, the semisolid matrix systems are also prepared by dispersing the water soluble drugs in a hydrophobic medium. The difference is however, in selection of the hydrophobic material. In these systems, the hydrophobic carrier occurs in an oily 'semisolid' state where the drug is incorporated, and the final mass is usually filled into gelatin capsules to prepare the dosage form. A group of Japanese workers has reported the use of a mixture of soybean oil and glyceryl monostearate as a semisolid base to deliver captopril [24-26]. Captopril suspended into soybean oil-glyceryl monostearate mixture and filled into hard gelatin capsules gave better bioavailability than other controlled release systems (e.g., coated granules) when orally administered into dogs [24]. The authors hypothesised that the content of these capsules easily adhered to the surface of the GI tract due to oily base which resulted in a slower transition rate. The capsules were pharmacologically effective for over 8.5 hours following single dose administration while the conventional tablets were effective to the same level only for 2.5 hours [25]. However, studies in humans revealed that this semisolid matrix system (in slightly modified form) is efficient only for 12 hours and require twice a day doses for maintaining the optimum level of therapy [26].

Coated tablets and similar multilayered systems

Multilayered systems are designed in such a way that the drug has to cross barrier(s) or membrane(s) on its way from the device to the

physiological environment. The release process is controlled by the nature and number of barriers. To design appropriate barriers, the formulation scientists have been relying on polymers from the very beginning of the emergence of controlled release technology. This is perhaps attributable to the fact that these substances can be fabricated according to the needs of the system and most of them are inert and biocompatible.

In their simplest form, coated tablets comprise a core containing the drug and a coating layer which surrounds the core. The core is usually the drug either alone or loaded onto an inert material (hydrophilic or hydrophobic), and the coating layer is a hydrophobic or slightly water permeable polymeric film or a mixture of both hydrophobic and hydrophilic films of which the ratio being optimised according the needs of the system. Drugs like captopril or diltiazem HCl or ranitidine HCl, blended with HPMC, microcrystalline cellulose, PVP and magnesium stearate, and wetted with anhydrous ethanol, then dried and compressed into tablets showed a sustained release profile of the drug during *in vivo* studies when coated with a semi-permeable membrane prepared from a mixture of microcrystalline cellulose acetate, PVP and tri-propyl citrate [27]. A hydrophilic matrix of a water soluble diltiazem salt composed of hydroxyethyl cellulose, dicalcium phosphate, polyvidone, hydrogenated castor oil and magnesium stearate was shown to have controlled release properties when coated with a film composed of Eudragit L 30D, polyethyleneglycol (PEG)-6000 and HPMC [28]. Addition of anionic surfactants like sodium lauryl sulfate to the coat can improve the sustain release properties of tablets coated with Eudragit RL or RS [29].

In order to extend the release profile of drug from coated tablets more complex systems have been introduced. The common approach is to use multiple coatings with polymers of different physico-chemical properties

or polymers in combination with other hydrophobic materials. Other attempts to extend the release of the drug from coated tablets include modification of the core by using hydrophobic matrices or by complex formation of the drug with a carrier in the matrix which result in prolongation of the drug release. Complexation of ionic drug with ion-exchange resin of opposite polarity and then coating the complex with an ionic polymer of polarity opposite to that of the resin can modulate the drug release from the device [30]. Various substances such as an acid, base, water soluble salt, surfactant, have been used to modulate the solubility of the core of coated tablets [31].

Multilayered systems having the drug in both outer layers and within the core have also been described in literature. The rationale behind this type of formulations is that a rapid release of the drug followed by a controlled release as required for prolong action can be achieved using these devices. Abramowitz et al. [32] described such a multilayered formulation for captopril. They prepared pH-stabilised core tablets of the drug to protect it until release in the colon and coated the tablets with a mixture of methacrylic acid copolymer, plasticiser (e.g., acetyltri-n-butyl citrate) and glidant (e.g.,talc). An overcoat containing the drug and a water soluble polymer (e.g., hydroxypropyl cellulose) was then applied for immediate release of the drug after administration. The coating material for the innercoat could be selected as either enteric coating (e.g., Eudragit L) or delayed release coating (e.g., Eudragit RS) so as to release the drug at the lower part of the intestine or throughout the GI tract. Apart from captopril, the core contained chelating agent (e.g., $Na_2EDTA$), antioxidant (e.g., ascorbic acid), binding agent (e.g., microcrystalline cellulose), lubricant (e.g., stearic acid) and other optional ingredient(s) (e.g., corn starch).

Multilayered tablets having two or more distinct (separate) layers usually prepared by dry coating techniques have also been used to formulate

sustained or controlled release preparations for water soluble drugs. In this case, the core tablet containing the drug is covered only partially by coating(s) which controls the release process. Conte et al. [33] described a two-layered tablet with a core containing the drug and polymer(s) with swelling or gelling properties, and a support layer covering one surface of the core tablets. The support layer was made from slowly soluble plasticising substances which remains intact until the complete release of the drug. Core granules, prepared from diltiazem HCl, HPMC, mannitol, ethyl cellulose, magnesium stearate, colloidal $SiO_2$ and ethanol, and support granules prepared from HPMC, hydrogenated castor oil, ethyl cellulose, yellow iron oxide, colloidal $SiO_2$ and magnesium stearate, were then compressed together into two-layered tablets. The tablets gave zero-order release kinetics when tested *in vitro* using USP XXI method up to 4 hours. A similar multilayered tablet for diltiazem HCl was prepared by Ishino et al. [34] to obtain a pulsatile release formulation. They prepared the tablets using dry-coating technique and covered both the horizontal surfaces of the core tablets with outer shells prepared from a polyvinyl chloride-hydrogenated castor oil-PEG mixture. The core tablets were prepared from diltiazem HCl, calcium carboxymethyl cellulose (disintegrant) and magnesium stearate. The tablets gave a pulsatile release of the drug after 7 hours of administration in dogs, and a good correlation existed between *in vivo* and *in vitro* dissolution rates. Following the lag time, a very fast release of the drug within 15 minutes was observed. However, fed conditions of the dogs were found to play a role in *in vivo* disintegration of the tablets. This type of delivery system seems to be useful when time-controlled or site specific delivery is required, and is not suitable without modification for once a day administration.

Osmotic devices

In osmotic systems usually an osmotic agent (often with an osmotic adjuvant) is contained within a rigid compartment at least one wall of which is a semipermeable membrane. The drug is dispersed in another compartment which is separated from the osmotic compartment by a partition. In the physiological environment the aqueous fluid penetrates across the membrane and the increased volume within the osmotic compartment pushes the drug out of the device through a delivery orifice. These devices suffer the draw back of complex manufacturing techniques involved in fabricating and placing the movable semipermeable membrane in the system. There is also a danger of high local concentration of the drug due to its exit from particular orifice(s) and in case of rupture of the membrane. In some cases, the osmotic adjuvant (often used with the osmotic agent) is unable to imbibe sufficient fluid for its maximum expansion as required to push the total drug content out of the device [35]. In simpler devices, the drug itself serves as the osmotic agent or is dispersed in an osmotically active carrier and is surrounded by a semipermeable membrane. Penetration of water causes the drug to be driven out through the orifice or the perforated membrane. Diltiazem HCl granulated with an water insoluble nondiffusable resin (e.g., Dowex-1), bearing the same charge as the drug, and other optional ingredients, then tableted and coated with a semipermeable membrane made of cellulose acetate, PEG-400 and sorbitol (pore forming additive), showed a constant sustain release pattern of the drug after a brief lag period irrespective of the pH of the dissolution media (1.2 or 8.0) over 12 hours when tested *in vitro* [36]. In the absence of the charged resin, the drug release was found to be pH dependent. In osmotic devices, the rate of release of drug is primarily controlled by the permeability of the semipermeable wall. The formulation

scientist usually manipulates the permeability of the wall by selecting appropriate membranes, adjusting their thickness [37] and by introducing pore-forming substances (water soluble) within the wall [37,38].

An osmotic controlled release bilayer tablet for water soluble drugs was described by Wright et al. [35]. In their device, the drug compartment containing the drug and an osmopolymer, a low molecular weight CMC (as thixotropic transport means), was placed together side by side with the osmotic compartment which had a higher molecular weight CMC as osmotic agent preferably with another osmotically active compound. The contacting drug compartment and the pushing compartment were coated with a semipermeable wall (made of a cellulose ester and a flux enhancer) which had an exit orifice for the drug to be pushed out. Both low and high molecular weight CMC in the device cooperated to exhibit a high level of hydrodynamic and osmotic activity adequate for controlled delivery of the drug over time with minimum (as little as 3.7%) residual drug left in the device. In a similar device, Wong et al. [39] used various poly (ethylene oxides) and other hydrophilic polymers as osmotic adjuvants which they dispersed in both drug and osmotic compartments to obtain a controlled release of the drug from the device. For example, for controlled delivery of a calcium antagonist, they prepared granules separately both from the drug, poly (ethylene oxide) (mol. wt., 200,000), HPMC and KCl, and from poly (ethylene oxide) (mol. wt., 5,000,000) and NaCl, and made two layered cores from the granules, followed by coating the cores with a semipermeable wall made from cellulose acetate (95%) and HPMC (5%). The device showed controlled release of the drug over 24-30 hours when studied both *in vitro* and in dogs. In another report [40] the authors described a similar system proclaimed to give 'time varied pattern' delivery of the drug. The device gives a drug free interval after administration prior

to delivery of the drug. In this case, they used poly (ethylene oxide) only in one compartment in combination with HPMC, $Fe_2O_3$ and magnesium stearate. The other compartment had the drug, mannitol, KCl, crosslinked PVP, noncrosslinked PVP and magnesium stearate.

A drug core containing diltiazem HCl, polyvinyl alcohol, $K_2SO_4$ and magnesium stearate, coated by an outer shell (semipermeable) made from cellulose-2,5-acetate and PEG-600 was found to give controlled release pattern of the drug (*in vitro* and in humans) which was adequate for single daily dose treatment [41]. A similar pump device where the drug core containing diltiazem L-malate, Na-bitartrate and povidone was coated with cellulose acetate, sorbitol and PEG-400, released 50% of the drug after 6-7.5 hours when tested *in vitro* in dissolution media with pH 1.2 to 7.5 [42]. McClelland and Zentner [31] used controlled release source of osmagents, coated and uncoated NaCl, to regulate the swelling behaviours of swellable adjuvants used in preparing osmotic devices. The controlled release source of osmagents offers an advantage of continuous availability of the osmagent in the device.

## MULTIPLE UNIT DOSAGE FORMS

As the name implies, an unit of 'multiple unit dosage forms' represents a combination of subunits of the dosage form the source of which may either be unique (homogeneous) or different (heterogeneous). These systems offer the advantage of much diversity in achieving dissolution profiles by combining various types of subunits in a single system. Most chronic diseases like hypertension require combination therapy. In these circumstances, for good patient compliance it is desirable to deliver two or more drugs via a single dosage form. Immediate release of one of the drugs (or part of the same drug) is often required for various

reasons while the remaining drug(s) (or part of the same drug) would require controlled delivery. Multiple unit dosage forms are easy to design to meet this criteria. They are also useful where drug-excipient or drug-drug physico-chemical interaction is inevitable in a single unit dosage form. Multiple unit dosage forms are also known to have less variance in transit time through the GI tract than single unit dosage forms [43]. A recent review [44] dealt with biopharmaceutical characteristerisation of both multiple unit and single unit sustained release oral dosage forms. While multilayered tablets or tablets with multiple coatings require complex manufacturing techniques, the multiple unit dosage forms can be prepared by simply combining the different types of subunits of the dosage form prepared separately. These dosage forms usually are based on such subunits as granules or spheroids, beads or beadlets, pellets, microcapsules. Usually, the subunits are delivered in hard gelatin capsules.



Microgranules/spheroids

Drugs wet granulated alone or incorporated into inert granules, and then coated to control the release pattern have become a common approach in preparing controlled release oral preparations. Delivery systems containing drugs like griseofulvin, diltiazem HCl loaded onto particles of crosslinked water insoluble but swellable nonionic polymer (e.g., crosslinked β-cyclodextrin, crosspovidone) and coated with an water insoluble but slightly water permeable polymer (e.g., Eudragit RS) could prolong the release of the drug over >24 hours maintaining high bioavailability in biological studies [45]. The coating plurality can be as complex as tablets with multiple coatings. Capsules containing microgranules prepared from diltiazem HCl, sugar and povidone, and alternatively coated with methacrylic acid copolymer, ethylcellulose, di-

ethyl phthalate and talc showed prolonged release characteristics [46]. Barry et al. [47] prepared granules of water soluble drugs and coated the granules with wax or wax-like substances such as cetostearyl alcohol to prepare sustained release preparations. An additional coating with Eudragit NE 30D applied to the granules further prolonged the release profile. A mixture of both types of granules (pellets) filled into capsules gave 100% dissolution of the drug at 12 hours. A similar system where uncoated and coated granules were delivered together was described by Applegren et al. [48].

An once a day formulation for diltiazem using microgranules has been proclaimed by Thiercelin et al. [49]. The authors used polymers to coat the granules, the permeability of which affected the dissolution pattern of the drug. The rate of release of the drug could be manipulated by varying the amount of coatings applied to the granules. Their pharmacokinetic studies in young male volunteers suggested that the formulation was equally bioavailable when compared to conventional tablets and a 300 mg single dose of this formulation would provide effective concentration of the drug over 24 hours.

Microgranules filled capsules designed for combined delivery of diltiazem HCl and hydrochlorothiazide, where hydrochlorothiazide was available for immediate release and diltiazem was meant for controlled release, were prepared by Buxton et al. [50]. Initially they made spheroids from diltiazem HCl and microcrystalline cellulose (spheronising agent) by wet granulation and coated the spheroids with a film forming water insoluble material (e.g., ethylcellulose) for controlling the release of the drug. The permeability of the coating could be regulated by adding appropriate amount of water soluble substances to the film forming material. The controlled release diltiazem spheroids obtained were then coated with a dispersion of hydrochlorothiazide and HPMC. Capsules filled with these

spheroids released hydrochlorothiazide in 10 minutes while diltiazem HCl was release slowly over 20 hours when tested *in vitro*.



Beads

Beads prepared from various polymers and other inert materials have been used as carriers to deliver water soluble drugs orally in the form of sustained/controlled release preparations. Beads made from diltiazem HCl, lactose, microcrystalline cellulose and povidone K-30 (binder), and then coated with a suspension containing Eudragit NE 30D, povidone K-30, magnesium stearate, $TiO_2$, simethicone, talc and Tween 80, gave 84% dissolution of the drug in 12 hours in phosphate buffer (pH 5,8) [51]. The beads (in slightly modified form) provided optimum bioavailability of the drug after once a day administration. The meth(acrylate) polymers in the coating membrane played the dominant role in controlling the release rate of the drug. Hendrickson et al. [52] also used coated beads to obtain a controlled release formulation for diltiazem for once a day oral administration. Central cores of the beads prepared from diltiazem HCl attached to solid carriers (sugar) coated differently with various amounts of Eudragit RS 30D and Eudragit RL 30D resulted in rapid release and slow release characteristics of the beads. A mixture of these two types of beads filled into capsules was found suitable for once a day administration in antihypertensive treatment. Beadlets prepared from captopril, an organic carboxylic acid (e.g., citric acid) and a non-lipophilic binder (e.g., microcrystalline cellulose), and filled into hard shell capsules released the drug slowly but continuously for up to 6 hours during *in vitro* studies [53]. The release pattern of the beadlets could be further modified by coating them using conventional coating polymers. Beads, prepared from nonpareil layered with diltiazem powder by spraying PVP solution and coated with

Eudragit RS, Ca stearate (or talc) and triethylcitrate, gave sigmoidal release pattern of the drug with a burst release of about 60% at 7-8 hours and maintained the high plasma level over 24-30 hours following single administration in dogs [43,54]. The lag time could be controlled by varying the amount of coatings and the selection of appropriate powder material could regulate the release pattern of the membrane where Ca stearate offered the advantage of having a pH-independent drug release characteristic. In human studies, these preparations were found adequate as once a day dosage forms [43]. A layer of the drug provided around the coating layer would start the immediate release of the drug as required for once a day administration [54]. A similar formulation having nonpareil sucrose particles coated with diltiazem HCl, talc and PVP, as the core and coated with an inner layer of ethylcellulose and talc followed by application of more diltiazem HCl on the coat, was described by Samejima et al. [55]. Their *in vitro* studies suggested that the dissolution rate of the drug could be manipulated by adjusting the coating amounts of the inner layer. In another report, Noda et al. [56] used hydrogenated castor oil as binder and coating material to control the release rate of the drug from the beads.

Pellets

Sustained release diltiazem HCl pellets were prepared by Vasilevska et al. [57,58] simply by coating inert diltiazem HCl pellets with soluble Eudragit L and S film forming polymers, the drug release being dependent on the coating composition of the polymers and the amounts of coating. A similar diltiazem formulation (pellets) capable of controlling the drug release over 24 hours was reported earlier by Geoghegan et al. [59]. To prepare the pellet core, diltiazem HCl, fumeric acid (or adipic acid), and talc were blended, mixed and applied to nonpareil using a coating solution

of PVP (or other water soluble polymer or a combination of water soluble and a minor proportion of water insoluble polymer). The core was then coated by spraying solutions of Eudragit RS and Eudragit RL. The ratio of the two polymers could be optimised in order to get a controlled release profile over 24 hours. The prepared pellets could be compressed into tablets using a binder (e.g., microcrystalline cellulose) maintaining the same release pattern or filled into capsules. An initial rapid release of diltiazem could be obtained by combining rapid release pellets (prepared similarly without coating) with the coated pellets. The same authors also reported other similar formulations with minor changes for diltiazem [60,61].

Morella and Fisher [1] developed an once a day pellet formulation for morphine salts and other highly water soluble drugs. To prepare the pellets, cores prepared from the drug, core seeds, HPMC and ethanol, were coated with a so called hybrid coating compound made primarily from polymers with different solubilities in different regions of the GI tract. The amount of coatings and mixing ratios of various polymers used to coat the pellets were utilised to regulate the rate of release of the drug from the pellets. Their clinical pharmacokinetic studies suggested that the pellets can be used for single daily dose treatment.

To avoid the complexity involved in coatings, Follonier et al. [62] described a hot-melt screw extrusion process to prepare pellets for sustained delivery of diltiazem. utilising various polymer properties (e.g., solubility), their mixing ratios with the drug and the pellets sizes to regulate the release pattern of the drug from the device. But the manufacturing technique for this type of pellets would require special instrumentation.

## MUCOADHESIVE DELIVERY SYSTEMS

In recent years considerable attention has been focused on developing delivery systems which utilise the principle of bioadhesion for

optimum delivery of drug from the device. Bioadhesion is defined as the occurrence in which a biological substance is adhered to another substance which may either be of biological or nonbiological origin. However, the term 'bioadhesion' is commonly used to describe the adhesion phenomenon between two biological objects [63,64]. If the substrate is a mucosal membrane, the phenomenon is known as 'mucoadhesion'. Leung and Robinson [65] described mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer. Mucoadhesive delivery systems have been demonstrated as effective dosage forms for controlled delivery of various drugs using buccal, ocular, rectal, vaginal, nasal, sublingual and oral routes of administration [63,66]. These systems can be utilised to optimise either the systematic or local delivery of drug. Although the conventional controlled release dosage forms described above can prolong the duration of action of drugs to some extent, their suitability for once a day peroral administration is doubtful. This is attributable to their inability to restrain and localise in selected regions of the GI tract. An optimism to this aspect was raised with the recent emergence of mucoadhesive drug delivery systems. The mucoadhesive systems were proven to be suitable for the purpose of reducing the transit rate of the dosage form through the GI tract, increasing the intimacy and duration of contact of the drug with absorbing membrane, and localisation of delivery of the drug at targeted sites [63,67]. In a comparative study with a slightly water soluble drug (chlorthiazide), Longer et al. [67] demonstrated that the bioavailability and duration of action of the drug was significantly improved when it was orally administered in rats in the form of a mucoadhesive sustained release system (polycarbophil-albumin beads) when compared to a conventional sustained release dosage form (albumin beads). This was explained as due to delay in stomach emptying caused by mucoadhesion of the system to the gastric mucus membrane.

The process 'mucoadhesion' involves three regions [64]: (i) the surface of the mucoadhesive substance, (ii) the mucosal surface and (iii) the interfacial layer between the two surfaces which primarily consists of mucus (at least initially). An intimate contact between the mucus and the adhesive substance initiates the process which is followed by interdiffusion (entanglement) or interpenetration of both phases (mucus and the adhesive substance) forming various bonds comprising electrostatic and hydrophobic interactions, hydrogen bonds and van der Waals interactions [63,64,68].

Various synthetic polymers (e.g., carbophil) and natural substances (e.g., chitosan) have been used as mucoadhesive carriers. To design optimum mucoadhesive systems for controlled delivery of drug, several properties of the adhesive substance are required to be considered during its selection: the molecular weight of the adhesive, its mobility and viscosity, the abundance of hydrophilic functional groups in the molecules (swelling properties) and their surface energy properties. The presence of hydrophilic functional groups that can form hydrogen bonds (e.g., carboxyl, hydroxyl, amide and sulphate groups) in the molecules appears to be very crucial for mucoadhesion. Factors like molecular weight and their mobility determine the strength of mucoadhesive bonds and the depth of interpenetration of mucus and the adhesive substance. The presence of sufficient amount of water is a prerequisite for mucoadhesion for the adhesive substance to hydrate, expand and to expose all binding sites and to facilitate interdiffusion or interpenetration of the substances [65]. Among various polymers investigated, CMC, hyaluronic acid, carbopol and polycarbophil are regarded as substances with strong muco-binding properties [66]. Polycarbophil is also known to work as a penetration enhancer [69]. Natural substances like tomato lectin [70] and chitosan [10] have also been used as mucoadhesive drug carriers.

The mucoadhesive technology is relatively new in the area of controlled release drug delivery systems. There is some evidence that mucoadhesive systems can prolong the duration of action of drug and improve its bioavailability when delivered through the so called alternative routes such as buccal, nasal, ocular, rectal and vaginal. Particularly encouraging are the experimental results obtained using the nasal route for delivering these systems [71,72]. But studies comparing their efficacies with the conventional controlled release systems have rarely been reported making it difficult to claim their superiority to conventional controlled release systems. Some mucoadhesive formulations (e.g., AFTACH$^{R}$, a double layered buccal tablet of triamcinolone acetionide) which use alternative routes have already been marketed for commercial use.

There are also a very few reports about the use of mucoadhesive systems for controlled oral delivery of water soluble drugs like morphine and captopril. Aiache [73] mixed morphine sulphate with a natural protein, Prosobel L85 (>50%) and a hydrophilic polymer, HPMC (0.5-10%), then wet granulated and compressed the dry granules (with lubricants and other excipients) into tablets to prepare a sustained release mucoadhesive dosage form. DeCrosta et al. [74] used carbopol 934P as mucoadhesive substance to prepare captopril sustained release tablets. Captopril mixed with carbopol 934P and stearic acid (as lubricant) and tableted, could sustain the release of the drug for up to 16 hours or more. However, in explaining the controlled release mechanism of the tablets, the authors overlooked the mucoadhesive properties of carbopol and interpreted the slow release mechanism as solely due to gelling properties of carbopol which caused a diffusional barrier to the drug release. Matharu and Sanghavi [4] also used carbopol 934P and another bioadhesive polymer, poly (acrylic acid) crosslinked with 0.001% ethylene glycol, to prepare mucoadhesive tablets for captopril.

Despite early optimism about the possibility of prolonging the gastrointestinal transit time of drug delivered through mucoadhesive system [67], the follow up studies suggested that the effects found in one species of animals could not be reproduced in another species or in humans [63]. There are also difficulties in prolonging the residence time of the dosage form sufficiently to produce once a day dosage forms. Several reasons have been postulated to this effect [63,70]:

(i) surface properties of both the mucus and the adhesive substance of the dosage form may change in response to the composition of the gastrointestinal fluid which is variable in normal and pathological conditions,

(ii) the mucoadhesive delivery system can also adhere to other contents of the GI tract (e.g., food) because of nonselective adhering properties of the mucoadhesive substance, and

(iii) the high turnover rate of mucus can deactivate the mucoadhesive surface resulting in sloughing away the device which is capable of being anchored only once.

Further attempts have been made to use mucoadhesive substances like tomato lectin considered to be capable of adhering directly onto the mucosal cell surface rather than onto mucus, but the results of preliminary investigations were not very promising [70].

## CONCLUSIONS

The ultimate goal of controlled release formulations is to optimise the drug delivery. "Optimisation of drug delivery aims at supplying drug in a predictable and reproducible manner to the required site, at the required rate, for the required time, with minimum inconvenience to the patient"

[75]. Here arises the question, how many of the formulations reviewed here comply with all these requirements of optimisation of drug delivery? Most of the claims are based on *in vitro* data only, while other formulations were studied in single groups of animals or humans. The reproducibility of reported data have not been examined. The general tendency appears to be protecting the formulations in the form of patents. In some cases, where bioavailability studies were carried out, the formulations have not been revealed which makes it difficult to reproduce the work. Nevertheless, the commercial availability of some controlled release formulations of the mentioned drugs is encouraging and the proven efficacies of some of the reviewed formulations in humans over 24 hours after single administration suggest that the 'once a day' proposition is feasible.

The concept of once a day oral dosage form is really challenging. The conventional controlled release formulations can simply delay the release process to some extent, but are unable to restrain and localise the system in required area of the GI tract for the required time. The mucoadhesive systems can delay the gastric emptying of the device thereby increasing the residence time, but for how long? As discussed above, the system also has its shortcomings. Perhaps, further modulation of mucoadhesive system which will provide site specific and receptor mediated mucoadhesion and prolong the residence time will bring an end to this problem. But this will require extensive investigation.

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