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Controlled Release Oral Dosage Forms: Some Recent Advances in Matrix Type Drug Delivery Systems

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An appropriately designed controlled release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery to the target sites. The development of oral controlled release systems has been a challenge to formulation scientists due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract. Matrix type drug delivery systems are an interesting and promising option when developing an oral controlled release system. This review focuses on the progress made in the design of controlled release dosage forms employing various types of matrices as carriers for the active ingredients.

Key words: Controlled release, drug delivery systems, matrices, recent advances

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Introduction

Controlled release (CR) systems provide drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, with the release profiles of predominantly controlled by the special technological construction and design of the system itself. The release of the active constituent is therefore, ideally independent of exterior factors. In case of sustained release (SR) dosage forms the release of the active agent, although, is lower than in the conventional formulations, however, it is still substantially affected by the external environments into which it is going to be released. Extended release (ER) dosage forms are those which due to special technology of preparation provides, soon after a single dose administration, therapeutic drug levels maintained for 8-12 hours; while Long or Prolong action products are dosage forms containing chemically modified therapeutic substances in order to prolong biological half-live (Lee and Robinson, 1987).

The use of controlled release technology in the formulation of pharmaceutical product has become increasingly important during the last few years. Despite significant interest and numerous reports about the design of CR delivery systems for various types of drugs, very few have been successful and most of the proclaimed successful formulations are the result work carried out in laboratories of commercial organizations. Not surprisingly, almost all of these formulations have been patented and clinical supportive data regarding their efficacy are not always available. Due to the nature of publications, most patented formulations are not freely accessible to all readers, which some times might contribute to renovating the formulations.

In particular, the interest awakened by matrix type deliveries is completely justified in view of their biopharmaceutical and pharmacokinetics advantages over the conventional dosage forms (Longer and Robinson, 1990). These are release systems for delay and control of the release of a drug that is dissolved or dispersed in a resistant support to disintegration. However, the release behavior is inherently non-linear in nature, with continuously diminishing release rate due to diffusional resistance and/or a decrease in effective area at the diffusion front. With the growing need for optimization therapy, matrix system providing programmable rate of delivery other than the typical first-order delivery, are becoming more important (Qiu *et al.*, 1998). For this reason, constant rate delivery has been one of the primary targets of CR systems, especially for drugs with a narrow therapeutic index. Considerable efforts have been made and are being continued to develop new drug concepts in order to achieve zero-order or near zero-order release kinetics. To alter the kinetics of drug release from inherent non-linear behavior, we have exploited the use of some matrices with erosion, diffusion and swelling controlled mechanisms, as well as matrix membrane combination concepts, during our research work (Khan and Zhu, 1998; 1998a; 1998b; 1999; 2001; 2001a).

Drug release mechanism from matrices: From time to time, various authors have proposed different types of drug release mechanisms from matrices. It has been proposed that drug release from matrices usually implies water penetration in the matrix, hydration, swelling, diffusion of the dissolved drug (polymer hydro fusion), and/or the erosion of the gelatinous layer. Several Kinetics models relating to the drug release from matrices, selected from the most important mathematical models, are described over here. However, it is worth mention that the release mechanism of a drug would depend on the dosage from selected, pH, nature of the drug and, of course, the polymer used.

Zero-Order Kinetics (Xu and Sunada, 1995)

$$W = k_1 t \quad (1)$$

First-Order Kinetics (Singla and Medirata, 1988; Xu and Sunada, 1995)

$$\ln (100 - W) = \ln 100 - k_2 t \quad (2)$$

Hixon-Crowel's Cube-Root Equation (Erosion Model) (Singla and Medirata, 1988)

$$(100 - W)^{1/3} = 100^{1/3} - k_3 t \quad (3)$$

Higuchi's Square Root of Time Equarion (Diffusion Model) (Higuchi, 1963)

$$W = k_4 t^{1/2} \quad (4)$$

Power Law Equation (Diffusion/Relaxation Model) (Ritger and Peppa, 1987)

$$Mt / M_\infty = k_5 t^n \quad (5)$$

Where W is % drug release at time t and $k_1 - k_4$ are release rate constants, depending on the kinetic model used. Mt / M_∞ is the fractional drug release into the dissolution medium and k_5 is a constant incorporating the structural and geometric characteristics of the tablet. The term 'n' is the diffusional constant that characterizes the drug release transport mechanism. When $n = 0.5$, the drug diffuses through and is release from the polymeric matrix with a quasi-Fickian diffusion mechanism, For $n > 0.5$, an anomalous, non-Fickian drug diffusion occurs. When $n = 1$, a non-Fickian, Case II or Zero-Order release kinetics could be observed.

Single unit dosage forms: The single unit dosage forms include

(a) monolithic devices where diffusion of the drug through the matrix is rate-limiting step and
(b) complex reservoir system or multilayered matrix system where diffusion of the drug through the polymer coating(s) or external layer of the system is the rate-limiting step. The monolithic devices include such systems as tablets with hydrophobic or swellable characteristics, floating formulations, semisolid matrix systems and some mucoadhesive matrix systems.

Hydrophobic Matrix Tablets: Ethylcellulose has been evaluated as a hydrophobic matrix to prolong the release of water-soluble drugs, acetaminophen and theophylline (Shaikh *et al.*, 1987) and water-insoluble drugs, ibuprofen and indomethacin (Khan and Zhu 1998b; 2001; Shaikh *et al.*, 1987b). Polymer's concentration, drug-to-polymer ratio and to some extent the viscosity grade of the polymer were found to be responsible for the changes in the release rates of the drugs.

Very recently, Khan *et al.* (unpublished data) investigated

(a) the potential use of Ethocel® Standard Premium and Ethocel® Standard FP Premium as direct compression CR matrices forming materials and
(b) the effects of different viscosity grades and drug-to-polymer ratios (D:P) of Ethocel® Standard Premium vs. Ethocel® Standard FP Premium polymers on the tablet characteristics, drug release rate, and release kinetics from directly compressed CR matrix tablets. It was found that both types of the Ethocel® Polymers could be used successfully in manufacturing directly compressed CR tablets containing sparingly soluble drugs. The Ethocel® polymers with lower viscosity grades were more compressible than their counterparts with higher viscosity grades. Moreover, particle size and concentration of the polymer, rather than viscosity grades were found to be the

rate determining factors in controlling the release of the drug from the tablets. Ethocel® Standard FP Premium polymers extended the release rates of the drug more efficiently than the conventional granular forms of the Ethocel®. The release mechanism of the drug from the tablets was changeable, depending mainly on the particle size and amount of the polymer used in the formulations.

Hydrophilic Swellable Matrix Tablets: Hydrophilic matrix tablet using hydroxypropyl methylcellulose (HPMC) were prepared and evaluated by Xu and Sunada (1995). They found that the type and amount of HPMC could effect the release rates as well as kinetics from the swellable matrices. Several investigators (Huang and Schwards, 1995; Khan and Zhu, 1998, 1998a, 1999, 2001a; Sen *et al*., 2001) investigated the drug release rates and release kinetics from carbomer matrix tablets. Tablets exhibiting zero-order release mechanisms could be obtained at several different levels of concentration of different carbomers, such as Cabopol® 934P, 971P and 974P. The results indicated that drug release from the carbomer matrix tablets could occur, both by diffusion through low microviscosity pores (polymer hydro fusion) and by a swelling-controlled mechanism. Among the carbomers used in this investigation, Cabopol® 971P was found to have a tremendous capability of controlling the release of drug from the matrix tablets, even at a very small amount of the polymer. As the amount of the carbomers in their respective formulations increased, drug release rate decreased and the release mechanism gradually changed from anomalous type of release to the Casell (zero-order) transport mechanism. Other factors responsible for the reduction in the number and/or size of low microviscosity pores, such as higher pH that increased polymer swelling and decreased drug release, tended to shift the release profiles towards the swelling controlled, Case II type release mechanism. Moreover, factors such as the presence of monovalent cations, like potassium, (K) tended to reduce polymer swelling and increase the rate of drug release from the matrix tablets (Khan and Zhu, 2001a).

Floating Type Drug Delivery Systems: The architecture of designing floating tablets or the so called 'hydronamically balanced drug delivery system' (HBS) is based on the principle that devices with specific gravity less than that of the gastric juice will float in the stomach and retain the drug over there for an extended period thereby increasing the total residence time in the GIT. The reduction of specific gravity of the system can be obtained by incorporating fillers of low density within the system.

Intra-gastric floating tablets based on chitosan and its HCl salt, polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) containing diltiazem HCl produced a sustained release plateau of the drug when tested in dogs (Hou *et al*., 1991). Through an alternative method (Bolton and Desai, 1992) noncompressed tablets were prepared with numerous air holes and internal passage within the matrix to keep the density of the tablets <1. An emulsion prepared from the drug, oil and water heated to 70 °C was poured into a tablet mold, cooled and air-dried to get the tablets. In another research work (Desai and Boston, 1993) a theophylline floating CR delivery system was prepared by using agar gel. The tablets could maintain constant drug levels for 24 hours, which was contributed to the release from the agar gel matrix and the buoyancy of the tablet in the stomach. Recently (Whitehead *et al*., 1998; 2000) methods have been described to produce a floating, multiparticulate systems based on calcium alginate. These systems exhibited considerable gastric retention compared to other similar systems.

Complex Reservoir or Multilayered Matrix Systems: Multi layer 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 environments. The release process is controlled by the nature and number of barriers. Inert and biocompatible type of polymers could be fabricated according to the need of the particular system. Partially coated three layered delayed release ibuprofen (IBF) tablets were prepared (Conte *et al*., 1992) with barriers of different polymeric compositions. The system could be considered a prototype for the development of tablets in which a delayed (one-pulsed) drug release is dependent on the gelation process of dry coating made of water gelling polymers. Prolonged release tablets of IBF base on sodium alginate were developed and investigated (Sirkia *et al*., 1994). The dose was divided between the core and the coat in the ratio of 2:1 and different chemical types, viscosity grades and amount of sodium alginate were used to control drug release rates. The release of ibuprofen from a unique core-in-cup tablet was study (Danskwerts, 1994) to determine their time exponent vs. release profiles. The tablet released drug at zero-order kinetics for 8-23 hrs. The effect of various polymers on formulation of CR multi-layered tablets by fluid bed technique wereinvestigated (Tehrani and Shobeiri, 1995) and the release patterns of first order kinetics were analyzed. Qiu *et al*. (1998) designed a layered system for zero-order sustained release with a hydrophobic middle layer and press-coated hydrophilic and/or hydrophobic barrier layer(s). The system overcome the inherent disadvantage of non-linear release associated with diffusion-controlled matrix devices and was claimed to have potentials for scaling up to commercial production. Sustained release bilayer caplets with an immediate release portion and a prolonged release portion, containing hydroxypropyl methylcellulose matrix, were formulated and evaluated for their dissolution characteristics (Ohmori and Makino, 2000). The dissolution profiles were independent of pH and were not affected by mechanical shear.

Bioadhessive or Mucoadhesive Drug Delivery Systems: Bioadhesion is the attachment of synthetic or biological macromolecules to a biological tissue. When applied to a mucosal epithelium, bioadhesion occurs primarily with the mucus layer and the phenomenon is referred to as mucoadhesion. Such types of dosage forms have the potentials to prolong the residence time within a specified region of the body and create an intimate contact with the absorbing membrane. These would decrease the diffusion path of the drug and could protect it from the enzymatic activities or luminal degradation (Ben *et al*., 1994; 1996). It has been found (Longer *et al*., 1985) that the bioavailability and duration of action was significantly improved when drug were orally administered in the form of mucoadhesive CR dosage forms as compared to the conventional CR dosage forms. Mucoadhesive SR tablets were prepared, using wet granulation method, by mixing morphine sulfate with a natural protein (Aiache, 1992). Several attempts have been made (Ben *et al*., 1996; Tobyn *et al*., 1996) to sufficiently prolong the residence time by exploiting the potentials of mucoadhesion, in order to produce once-a-day dosage forms. The ability of polymers to produce a large increase in the resistance to deformation when incorporated into a mucus gel has been investigated (Madsen *et al*., 1998). This phenomenon, termed as rheological synergism, could be used as a measure of the strength of the mucoadhesive interaction.

Multiple unit dosage forms: Multiple unit dosage forms represent a combination of sub-units of the dosage form the source of which may either be homogeneous or

heterogeneous. These are usually based on such sub-units as microspheres, granules or spheroids, pellets, beads, microcapsules, microtablets, etc.

Microspheres: Microspheres are one of the most important and successful controlled drug delivery devices. It has been known that spherical particles can be uniformly covered with polymer film and the specific surface area of such particles is a main factor to control the drug release rate. In a research work (Adeyeye and price, 1994) SR drug-wax microspheres were developed and the effect of formulation variables on physical characteristics and *in vitro* dissolution rate were investigated. It was found that formulation variables such as wax modifiers, modifier concentration, emulsification dispersant concentration and nature of the wax affected the particle size distribution. It was found that with appropriate modifiers, wax microsphere formulations of the drug could offer a starting basis for predictable SR dosage forms. Hollow microspheres (microbaloons) loaded with drug in an outer enteric acrylic polymer shell and prepared by a novel emulsion-solvent diffusion method were studied for their physico-chemical properties (Kawashima *et al.*, 1992). The drug incorporated in the solidified shells of the polymer was found to be partially or completely amorphous. The microspheres floated continuously over the surface of acidic dissolution medium containing surfactant, for more than 2 hours. The drug release rates were drastically reduced at pH 6.8, in a polymer concentration dependent method. The microspheres were able to provide prolonged release dosage form with an improved bioavailability. To evaluate the kinetics of wax and fat embedded microspheres of drug, paraffin, acetyl alcohol and stearic acid microspheres were prepared using methyl cellulose, sodium alginate and Tween-80, emulsifying agents in all cases (Nath and Reddy, 1995). The drug release was found to be erosion controlled and the type of emulsifying agent used influenced the release kinetics.
Microspheres of poly(2-hydroxyethylmthacryate - PHEM) crosslinked with ethylene glycol dimethacrylate (EGD) were prepared and evaluated (Orienti *et al.*, 1995). The release rates were slower, approaching zero-order release kinetics. Eudragit-RSPM, ethyl cellulose, HPMC, HPMC-Phtalate and silicondioxide colloidal (Aerosil-200, Aerosil R-972) were evaluated as possible carriers to sustain the release rates of the drugs (Samy, 1995). Granules peppered with ethyl cellulose, Eudragit and Aerosil R-972 gave slower release rates of the drug than those prepared with the other polymers. Moreover, by increasing the particle size of the granules the release rate of the drug could be reduced.

Pellets: Sustained release pellets of the drug and cetosteryl alcohol using an emulsion melt-cool method were prepared and evaluated (Alkhassas *et al.*, 1993). The release rates were found to decrease with increasing the cooling time during the preparation. Pallets containing 80% of the drug and 20% (w/w) of microcrystalline cellulose or other polymers were prepared and the effect of drying techniques, polymer type, drug loading and other variables on the release rate of the drug from the pellets was investigated (Dyer *et al.*, 1995). The results showed that drying techniques and polymer type had quantitative effect on the release rates of the drug from the pellets. Drug release was diffusion controlled with First-order release kinetics. However, above a defined polymer level, drug release was membrane controlled having Zero-order release kinetics. The presence of plasticizers in the polymer film imparted a hydrophilic component to the otherwise hydrophobic membrane and increased the drug release rate. Chou *et al.* (1996) developed a versatile matrix pellet formulation based on the combination of hydrophobic material and starch derivatives. They used the melt pelletization technique and matrix pellets containing a combination of 25-45% microcrystalline waxes, pregelatinized starch and maltose dextrin with 15-70% of the drug were prepared and evaluated for dissolution and swelling, undertaking porosimetric analysis. The release rate of the drug was controlled by pore matrix diffusion. Ethylcellulose-coated tablets were evaluated for the optimization process, using Tauguchi approach (Palmieri and Wehrle, 1997). They found that the coated pellets could provide a Zero-order release of the drug but after the compression step the ethyl cellulose film was damaged and there occurred an immediate drug release.

Beads: Sustained release beads were prepared in capsule and tablet dosage forms and were evaluated for *in vitro* release (Kurumaddeh *et al.*, 1994). The beads disintegrated in simulated gastric fluid (SGF) but not in simulated intestinal fluid (SIF). Beads containing sorbitan mono-oleate (Span 80) and HPMC showed gave SR preparations. However, beads containing polysorbate 80 (Tween 80) and HPMC showed no SR properties, with over 90 % of the drug released in 2 hour. Beads in tablet form yielded a slow dissolution profiles than those in capsule form, which in turn has slower release profiles than did the beads alone. Release from tablets was much slower after one year of storage than immediately after manufacturing. It was concluded that such beads might be used to produce SR capsule and tablet formulations. Beads coated with experimental CR latex comprised of ethyl-acrylate and metyl-acrylate were formulated, evaluated and compared with commercially available dispersions (Singh, *et al.*, 1995). The optimum pellet preparations based on the predicted levels yielded response values that were close to the predicted values. Comparative evaluation with commercial preparation indicated that the experimental latex provides a more efficient release of the drug.

Microcapsules and Microtablets: Kagadis (1985) studied the preparation and dissolution rates of drug microcapsules of various sizes. They found that the size of the microcapsules correlated the release time. Later on, SR polymer microcapsules containing drugs with various solubility characteristics were prepared with colloidal polymer dispersion in a completely aqueous environment, as an alternative to the conventional microencapsulating technique (Bodmeier and Wang, 1993). Microcapsules were prepared by spraying; dropping sodium alginate solution containing drug and colloidal polymer into a calcium chloride solution. Actual drug contents of approximately 50% and encapsulating efficiency of 80-98% were achieved for all drugs. The drug release was a function of drug solubility, drug loading and the type colloidal polymer dispersion used in the investigation. Weiss *et al.* (1995) studied the microencapsulation of drugs with HPMC phthate through simple coasevation by addition of 20% sodium sulfate (Na_2SO_4) solution. The coaservates enveloped the suspended drug that had no effect on the phase separation of the polymer due to low solubility of the drug in the polymer solution. The preparation of calcium (Ca) induced free flowing, smooth-surfaced dispersion of sodium alginate and the drug in mineral oil (liquid paraffin) followed by cooling process with calcium chloride as the curing agent has been described (Kakkar, 1995). Sodium alginate levels influenced the mean diameter, recover, encapsulation efficiency, wall thickness, size distribution and release characteristics of the microcapsules. Choudary *et al.* (1995) described the microencapsulation of the drug by a complex coasevation technique in an attempt to incorporate a maximum amount of the drug in SR microcapsules by using a minimum amount of economic devices. The mean particle size of this coasevate was approximately 6.8μm. The microcapsules thus obtained were stable up to 6 months after the addition of cross-linking agents. Mini-matrix tablets containing S(+)-ibuprofen have been prepared (Cox *et al.*, 1999) using the wet granulation method. The hydrophilic matrix was formed with xanthin gum, karaya gum or HPMC, together with a choice of additives from

lactose, Encompress®, Avicel® PH101, talc and Lubritab®. Multi-unit dosage forms were subsequently obtained by encapsulating the mini-matrix tablets into hard gelatin capsules. Xanthan gum produced a greater sustaining effect than karaya gum. Xanthan gum and HPMC were particularly suitable with release exponents approaching Zero-order (constant) release over 12 hours periods *in vitro*.

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