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A review on: Controlled release and floating drug delivery system

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Abstract
Controlled release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ. Oral route has been the most popular route for controlled delivery of drugs because of the flexibility in the designing of dosage form than other routes. There are different aspects for design of oral controlled release drug delivery systems such as matrix, reservoir, osmotic pressure, ion exchange resin, density etc. This article contains brief review on currently existing oral controlled system and various formulation approaches for the controlled release system.

Keywords: Controlled Release, Oral, Drug Delivery System, Dissolution

Introduction
The design of oral control drug delivery system (DDS) should be primarily to achieve more predictable and increased bioavailability [1]. Nowadays most of the pharmaceutical scientist is involved in developing the ideal DDS. This ideal system should have advantage of single dose for the whole duration of treatment and it should deliver drug directly at the specific site. Scientist have succeeded to develop a system and it predictability and reproducibility to control release system. Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in body with lower and less frequent dose [2, 3].

Oral Controlled Release Dosage Form
Oral drug delivery system is the most popular route, which is due in part of ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes [4]. There is a plethora of oral controlled release products in the market place. For example, in 1998, the U.S Food and Drug administration approved 90 oral controlled release products. From 1998 to 2003, FDA approved an additional of 29 new drug application that used controlled release technologies and 12 of them were based on matrix system [5].

Advantage and Disadvantage of Oral Controlled Release Delivery System [6, 7]
Development of oral controlled release dosage forms of a given drug involves optimization of the dosage form characteristics with the inherited constrains of the gastrointestinal physiology. Controlled release delivery systems have added advantages over immediate release dosage form. These include reduction of dosing frequency by administration is reduced, patient once or twice a day. Since the frequency of drug administration is reduced, patient compliance can be improved and drug administration can be more convenient due to reduction of gastrointestinal side effects. Also causes less fluctuation of plasma drug level and leads to more uniform drug effect and lesser total dose.

On the other hand, controlled release forms have some disadvantages which include, generally higher cost, relatively poor *in vitro*/ *in vivo* correlation unpredictable and even reduced bioavailability and subjected to increased first pass metabolism for certain drugs. In order to exert control over the rate of the drug release, as well as movement of the dosage from through the GIT, a number of factors such as motility, pH, ionic strength of luminal content and differential absorption must be considered [5].

Various Approaches to Achieve Controlled Release Drug Delivery [6, 7]
Various technique have been used in the formulation of controlled release products. In general controlled release formulations can be divided into different categories based on the mechanism drug release.

Ion Exchange Resins
Are cross-linked water-insoluble polymers carrying ionized functional group? The resins have been used in various pharmaceutical applications, primarily for taste masking and controlled release systems. In tablet formulations, ion exchange resins have been used as disintegrates because of their swelling ability. It forms irreversible complex with ionizable drug upon prolonged exposure of the drug to the resin. A resin bound-drug is removed when appropriate ions are in contact with ion-exchanged groups. The area and length of diffusion pathway and the amount of cross-linked polymer in the resin moiety governs the rate of drug release.

Dissolution Controlled Release
The type of controlled release involves two process, the detachment of the drug molecules from the surface of their solid surface to the adjacent liquid interface, followed by their diffusion from the interface into the bulk liquid medium. The rate of dissolution and the amount dissolved per unit of time from this system can be calculated using Noyes- Whitney equation (1897).

Diffusion Controlled Release
In this type of controlled release system, the active ingredient diffuses through the polymeric material. There are mainly reservoir and matrix system.

Reservoir System
It consist of a core and a coating membrane. The active ingredient diffuses from the reservoir through the coating membrane. For a reservoir system where the drug depot is surrounded by a polymeric hydrogel membrane, Fick's first law of diffusion can be used to describe drug release through the membrane. The release from matrix type formulation was governed by law of diffusion.

Matrix System
A matrix system consist of active and inactive ingredient that are homogenously dispersed and mixed in dosage form. It is by far the most commonly used oral controlled release technology and the popularity of the matrix system can be attributed to several factors. The rate of drug release dissolved as solid in an inert matrix has been developed by Higuchi.

$$M=kt^{1/2}$$

Where;
k = constant,
t = time,
M = amount of drug release.

Advantages of Matrix System
Unlike reservoir and osmotic system, products based on matrix design can be manufactured using conventional processes and equipment. Secondly, development cost and time associated with the matrix system generally are viewed as variable and no additional capital investment is required. Lastly, a matrix system is capable of accommodating both low and high drug loading and active ingredient with a wide of physical and chemical properties.

Limitations of the Matrix System
As with any technology, matrix system comes with certain limitation. First, matrix system lack flexibility in adjusting to constantly changing dosage levels as required by clinical study outcome. When new dosage strength is deemed necessary, more often than not a new formulation and thus additional resources are expected. Furthermore, for some products that require unique release profiles (dual release or delayed plus extended release), more complex matrix-based technologies such as layered tablets are required.

Types of Matrix System [7]
The matrix system can be divided into two categories depending on the types of retarding agent or polymeric materials.

Hydrophobic Matrix System
This is the only system where the use of polymer is not essential to provide controlled drug release although insoluble polymers have been used. As the term suggest, the primary rate controlled components of hydrophobic matrix are water insoluble in nature. These ingredients include waxes, glycerides, fatty acid and polymeric materials such as ethyl cellulose. Methyl cellulose and acrylate copolymer. To modulate drug release, it may be necessary to incorporate soluble ingredients such as lactose into formulation. The presence of insoluble ingredient in the formulation help to maintain the physical dimension of hydrophobic matrix during drug release. As such, diffusion of active ingredient from the system in the release mechanism and the corresponding release characteristics can be described by Higuchi equation known as square root of time release kinetic [8]. The square root of time release profile is expected with a porous monolith, where the release from such system is proportional to the drug loading, hydrophobic matrix system generally are not suitable for insoluble drug because the concentration gradient is too low to render adequate drug release. As such depending on actual ingredient properties or formulation design, incomplete drug release within the gastrointestinal transit time is a potential risk and need to be delineated during the development. With the growing need for optimization of therapy, matrix system providing programmable rates of delivery become more important. Constant rate delivery always has been one of the primary target of controlled release system especially for drug with narrow therapeutic index [6].

Hydrophilic Matrix System
The primary rate limited ingredients of hydrophilic matrix are polymers that would swell on contact with aqueous solution and form a gel layer on the surface of the system. When the release medium is thermodynamically compatible with a polymer, the solvent penetrates into the free spaces between macromolecular chains. The polymer may undergo a relaxation process, due to the stress of the penetrated solvent, so that the polymer chains become more flexible and the matrix swells. This allow the encapsulated drug to diffuse more rapidly out of the matrix. On the other hand, it would take more time for drug to diffuse out of the matrix since the diffusion path is lengthened by matrix swelling. Moreover, it has been widely known that swelling and diffusion are not the only factors that determine the rate of drug release. For dissolvable polymer matrix, polymer dissolution is another important mechanism that can modulate the drug release rate. While either swelling or dissolution can be the predominant factor for a specific type of polymers, in most cases drug release kinetics is a result of a combination of these two mechanism.
The presence of water decreases the glassy rubbery temperature giving rise to transformation of glassy polymer to rubbery phase. The enhanced motility of the polymeric chain favors the transport of dissolved drug. Polymer relaxation phenomenon determine the swelling or volume increase of the matrix. Depending on the polymer characteristics, the polymer amount in rubbery phase, at the surface of the matrix, could reach the disentanglement concentration; the gel layer varies in thickness and the matrix dissolves or erodes. The concentration at which polymeric chains in the rheological properties of the gel. Bonferoni *et al* showed a relationship between rheological behavior of HPMC gel and their erosion rate, conforming that the polymer-polymer and polymer-water interaction are responsible for the gel network structure and its sensitivity to the erosion [9]. In turn, they affect drug release rate in the case of poorly soluble drugs. Swelling controlled release system are based upon these principles. Due to the viscoelastic properties of the polymer which are enhanced by the presence of cross-linked network, anomalous penetrant transport can be observed. This behavior is bound by pure Fickian diffusion and

case II transport. Therefore, transport can be reduced to three driving forces. The penetrant concentration gradient, polymer concentration gradient and osmotic force behavior are observed as a result of polymer network. Appropriate polymer can counterbalance normal Fickian diffusion by hindering the release of embedded drug, leading to an extended period of drug delivery and possibly zero order release.

Drug release from swell able matrix tables can affected by glassy rubbery transition of polymer and the various formulation variables such as polymer grade and type, drug to polymer ratios, drug solubility, drug and polymer particles sizes, compaction pressure and presence of additives or excipients in the final formulation. On the other hand, incorporation of water soluble fillers like polyethylene in the final formulation. On the other hand, incorporation of water soluble fillers like polyethylene glycol, lactose and surfactant into gel forming matrices can improve phenomenon of insufficient drug release, because these excipients can enhance the penetration of the solvent or water into the inner part of matrices, resulting in drug release from the matrices.

Polymers Used In Hydrophilic Matrix [7]

Hydrogel polymer were much investigated in literature on basis of drug release and release mechanism from hydrophilic matrix tablets as well as pellets. HPMC polymer achieve considerable attention due to their unique properties as they can display good compression characteristics, including when directly compressed.

When polymer used in hydrophilic matrix preoaration include poly ethylene oxide, hydroxypropyl cellulose, hydroxyl ethyl cellulose, xanthan gum, carbopol etc.

It is well recognized that key formulation variables are matrix dimension and shape, polymer level and molecular weight, as well as drug loading and solubility. Other factors such as tablet hardness, type of inactive ingredients and processing normally play secondary roles. The choice of manufacturing process such as direct blending or granulation typically does not affect product performance significantly, although exception does exist. In general, processing and scale up associating with hydrophilic matrices are more robust than other controlled release system.

Different Method Of Formulate Floating Dosage Form [42]

Floating system, first described by Davis in 1968, have bulk density lower than that of the gastric fluid and thus remain buoyant in stomach for prolong period.

Effervescent System

Volatile liquid containing system

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g., ether, cyclopentane, that gasifies at body temperature to cause the inflation of the chamber in the stomach. The device may also consist of a bioerodible plug made of PVA, polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable system from the stomach.

Gas generating system

These buoyant delivery system utilize effervescent reactions between carbonate salt and citric acid to liberate CO_2 which gets entrapped in the jellified hydrocolloid layer of the system thus decreasing its specific gravity and making it to float over chime.

Non-Effervescent System

Colloidal gel barrier system

Hydro dynamically balance system was first design by Sheth and Tossounian in 1975. Such system contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. These system incorporate a high level of one or more gel forming highly swell able cellulose type hydrocolloids. E.g., HEC, HPMC, NaCMC, polysaccharides and matrix forming polymer such as polycarbophil, polyacrylates, and polystyrene, incorporated either in tablets or in capsules. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and form a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms.

Microporous compartment system

This technology is based on the encapsulation of drug reservoir inside a microporous compartment with aperture along its top and bottom wall. The peripheral walls of drug reservoir compartment are completely sealed to prevent any direct contact of gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures dissolved the drug and carries the dissolve drug for continuous transport across the intestine for absorption.

Alginate beads

Multiple unit floating dosage form have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5mm in diameter can be prepared by dropping a calcium alginate solution in to aqueous solution of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen and freeze dried at 40 degree for 24 hours, leading to the formulation of porous system, which can maintain a floating force over 12 hours.

Hollow microspheres

Hollow microspheres loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion solvent diffusion method. The ethanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40 degree. The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours *in vitro.*

Factor Affecting Gastric Retention [43, 44]

Density

Density of solid dosage form should be less than the gastric contents (1.004gm/ml).

Size and Shape
Dosage form unit with a diameter of more than 7.5mm are reported to have an increased GRT competed to with a diameter of 9.9 mm. The dosage form with a shape tetrahedron and ring shape devises with a flexural modulus of 48 and 22.5 kilo pound per square inch are reported to have better GIT @90 to 100% retention at 24 hours compared with other shapes.

Fed or Unfed state
Under fasting conditions, the GI motility is characteristics by periods of strong motor activity or the migrating complexes (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be every short. However, in the fed state, MMC is delayed and GRT is considerably longer.

Nature of the meal
Feeding of indigestible polymer of fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging the drug release.

Caloric Content
GRT can be increased between 4 to 10 hours with a meal that is high in proteins and fats.

Frequency of feed
The GRT can increased by over 400 minutes when successive meals are given compared with a single meal due to the flow frequency of MMC.

Gender
Mean ambulatory GRT in males (3.4-0.4 hours) is less compared with their age and re matched female counterparts (4.6-1.2 hours), regardless of weight, height and body surface.

Age
Elderly people especially those over 70 years have a significantly longer GRT.

Advantages of Floating Drug Delivery System [45, 46]
1. The gastro retentive system are advantage for drug absorbed through the stomach. E.g., ferrous salts, antacids.
2. Acidic substances like aspirin causes irritation on the stomach wall when come in contact with it. Hence HBS formulation may be useful for the administration of aspirin and other similar drugs.
3. Administration of prolongs release floating dosage form, tablet or capsules, will result in dissolution of the drug in the gastric fluid. They dissolve in the gastric fluid would be available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed form floating dosage forms if it remains in the solution from even at the alkaline pH of the intestine.
4. The gastro retentive system are advantageous for drug meant for local action in the stomach, e.g., antacids.
5. When there is a vigorous intestinal movement and a short transit time as might occur in certain type of diarrhea, poor absorption is expected. Under such circumstances it may be advantageous to keep the drug in floating condition in stomach to get a relatively better response.

Disadvantage of Floating Drug Delivery System [47]
1. Floating system are not feasible for those drugs that have solubility or stability problem in G.I. tract.
2. These system require a high level of fluid in the stomach for drug delivery to float and work efficiently- coat, water.
3. The drug that are significantly absorbed throughout GIT, which undergo significantly first pass metabolism, are only desirable candidate.
4. Some drugs present in the floating system cause irritation to gastric mucosa.

Application of Floating Drug Delivery System [48]
Floating drug delivery offers several applications for drug having poor bioavailability because of the narrow absorption window in the upper part of GIT. It retains the dosage form at site of absorption and thus enhances the bioavailability. These are summarized as follows.

Sustained drug delivery
HBS system can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of less than 1 as a result of which they can float on the gastric contents. These systems are relatively large in size and passing form the pyloric opening is inhibited.
E.g., sustained release floating capsules of nicardipine hydrochloride were developed and were evaluated *in vivo*. The formulation compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).

Site-specific drug delivery
These systems are particularly advantageous for drug that are specifically absorbed from stomach or the proximal part of the small intestine. e.g., riboflavin and furosemide. Furosemide is primarily absorbed from the stomach followed by the duodenum. It has been reported that a monolithic floating dosage form with prolonged gastric release time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.

Absorption enhancement
Drugs that have poor bioavailability because of site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery system, thereby maximizing their absorption. E.g., a significantly increase in the bioavailability of floating dosage form could be achieved as compared with commercially available LASIX tablets and enteric coated LASIX- long product

Table 1: Commercial Gastroretentive Floating Formulations [42]

Commercial Gastroretentive Floating Formulations		
Name	**Type And Drug**	**Remarks**
Madopar HBS (Propal HBS)	Floating capsules, Levodopa and benserazide	Floating CR capsuels
Valrelease	Floating capsules, Diazepam	Floating capsules,
Topalkan	Floating antacid, aluminum and magnesium mixture	Effervescent Floating liquid alginate preparation
Amalgate Float Coat	Floating antacid floating gel	Floating dosage form
Conviron	Ferrous sulphate	Colloidal gel forming FDDS
Cifran OD	Ciprofloxacin (1gm)	Gas generating floating form
Liquid Gaviscone	Mixture of alginate	Suppress gastro esophageal reflux and alleviate the heart burn

Conclusion

The best new therapeutic entity in the world is of little value without an appropriate delivery System. Nowadays modern technologies including target concept have emerged for successful oral controlled delivery. The design of oral controlled drug delivery system depends upon various factors like, physic-chemical properties of drug, type of delivery system, disease being treated, patient condition, treatments etc. From the above discussion it is concluded that the oral controlled release drug delivery system is very helpful in increasing the efficiency of the dose. Moreover, the reasonable cost of this system has lead ease of market penetration as replacement of oral conventional drug delivery system.

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