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American Journal of Life Science Researches
www.worldofresearches.com

Am. J. Life. Sci. Res.
Vol. 2, Issue 1, 27-35, 2014

Oral Drug Delivery System: A Review

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Abstract: Oral administration of drug in one of the preferred route and widely used formulation for new existing and new drugs. It might be due to its ease of administration and most impotently patient compliance. A recent report by new England health care institute stated that the cost of non- compliance alone in us was around $ 290 billion, 13% of total annual health care expenditure. More over oral medications improved patient compliance and results in affective treatment which resulted in innovation in oral drug delivery system.
Key Words: Drug, Oral Drug Delivery System, Review study

INTRODUCTION

Modified oral release drug delivery system has been developed to extend the drug release for several hours (by combining drug with release-retardant material to form matrix core or by applying release modifying film coat over the core drug material). The MR system offers reduction in dosing frequency. Low incidence of side effects and better therapeutic effect and enhancement of bioavailability.

Physiological and physicochemical factors affecting Modified release Technology:

The human GI tract is a complex organ. The physiological factors that control absorption of drug include Gsatric and intestinal transent time. Fluid and food intake, gastric and intestinal secretion, absorptive mechanism. pH metabolism. The physicochemical factors include solubility, stability, ionisation and lipophilicity. By controlling both physiological and physicochemical factors we can successfully design modified release drug delivery system. The greatest challenge in the design modified release formulations is changing the nature of immediate release of the small intestine and extended release preparation throughout the small intestine and sometime colon[1].

Transit time in GI tract is also one of the major factors that affect the effectiveness of MR dosage form as it directly influences the site of drug release. Different the site of drug release require change in pH and water content on subsequent drug absorption[2].

Approximate Fluid Flux, pH, and Residence Time within the gastrointestinal tract

Section	Fluid	input/day (ml)	Output/day(ml)	pH	Residence time (h)
Mouth	Water Saliva	1200_1500			
Stomach	Gastric Fluid	2000		1-3.5	0.5-12
	Pancreatic juice	1500			
Duodenum				4-6.5	
	Bile	500			3-4
Jejunum				5-7	
	Intestinal secretions	1500	8500		
Ileum				6-8	
Colon	Fluid transfer	500	350	6-8	10[d]

The rate of gastric empting depends on state and size of dosage form and the presence and composition of food, intestinal transit time etc. hence there must be interplay between GI physiology and formulation design for the success of modified release drug product[3].

Factor influencing performance of modified drugs formulation:

Food:

The influence of food on the bioavailability of drug must be investigated for safety and efficacy. If any food effects are found then a justified dose with respect to the product intake in relation to meals is given[4].

Gastro- Intestinal function:

By the modified release formulation is co- administrated with drug affecting GI tract physiology then investigation related to MR dosage form must be done.

Diurnal Rhythms:

Plasma concentration profile measured for 24 hrs at steady state of any difference occurs in view of Day/ night.

Site of application:

The absorption of drug at different site must be investigated of the application site in not limited to one body area.

Dose dumping :

The chances of unexpected release of drug resulting in unacceptable higher exposure occur when the MR formulation contains higher compared to immediate release product.

Classification :

A successful formulation of MR device requires understanding of mechanism of drug release form microscopic effect of size, shape, structure and molecular interactions.

Multiparticulated dosage forms are less prone to food effects hence it is preferred dosage form for extended or delayed release[5].

Film coated is an ideal process for multiparticulated extended release dosage form in which the permeability property of film coating is essential.

Ethyl cellulose is a water insoluble polymer widely used in extended release coating due to its properties like tough, flexible, coating, tasteless and odorless characteristics[6] .

Major of enteric coating rely on polymers containing carboxylic acid groups as a functional moiety. These groups remain unionized at low pH and ionse at higher pH. As the pH level raise above the point of dissolution the polymer ionized & drug is released for monolithic matrix approach cellulose, ether HPMC are most widely used polymers.

Time Rx technology:

Penwest phaemaceuticals introduced time Rx based on slowly eroding matrix platform technology to prior Time Rx the predominant systems available are hydrophilic matrices, oral osmotic pumps a multiparticulates (beades). The conventional matrix tablet even though they are simple but possess many drawbacks such as polymer variability, difficulty in achieving zero order release, extended release of drug etc. to over conc. This problem Time Rx technology was developed. The Time Rx tablet formulation consists of drug, lubricant and bulk Time Rx.

It mainly consist of two polysaccharides namely xantha gum which as a homodisperse system produces helical or double helical molecular conformation that produces high viscosity without gel formulation and locust bean gum which is slow soluble and ungelled at low temperature . on prolonged exposure to the dissolution fluid promotes solubilization. Which in turn allows molecules to associate and undergo gelation value to inter molecular cross linking in helical smooth region? The xanthan gum swell in the presence of water whereas locust bean gum retards water penetration into the dosage form and as a result controls the release of active ingredient.

Molecular confirmation of a heterodisperse polysaccharide system in the presence of saccharine, drug and cation[7].

Advantage:

It forms a hydrophilic matrix in aqueous medium and controls drug release for 24 hrs .

It is cost effective and easy to manufacture.

Improves patient compliance.

Suitable for wide variety of drug with different drug loading and drug solubility.

It shows different drug release profile such as zero order, first order and burst release.

The pewest pharmaceutical and Mylan laboratories have developed an oral controlled release dosage form of nifedipine using Time Rx technology[8].

MAS Rx Technology:

In matrix controlled release drug delivery system, hydrocolloids are often used in the formulation to modified or sustain the drug release. The major problem

associated with high viscosity water soluble polymers is their ability to hydrate. Tablets with high viscosity polysaccharides begin to gel and hydrate cause stop at certain point which leads to drying of tablets core and not all the drug is released.

Guargum a naturally occurring highly viscous water soluble polysaccharide is used as sustain release excipients due to its high viscosity, low cost and availability[9].

The objective was to assess factor affecting drug release form guargum based once daily matrix sustained release formulations (MASRx tm). The tablets were designed to hydrate completely into the tablet core. In the process the tablet core expanded and released the drug in a sustained release manner. To evaluate the effect of varying losta of guargum on dissolution formula A was manufactured with their lots of guargum obtained from the same manufacturer. The resulting dissolution release rate constant was insignificantly different. The variability was evaluated and it shown that guargum source did not affect diltiazem release . the difference in drug release is possible due to greater percentage of fines in the granules which cause the tablet to hydrate faster leading to gelling of the polymer[10].

Summary of the Clinical Trial Formulations Based on MASRx Technology

	Formulation				
Ingredients	**A**	**B**	**C**	**D**	**E**
Diltiazem Hcl, USP	**31.00%**	**31.00%**	**31.00%**	**31.60%**	**31.60%**
Guargum (Supercol G3-NF)	**62.00**		**62.00**	**64.60**	**57.15**
Purified guargum (Supercol G3-NF)			**67.00**		
Methocel K100LV	**5.0**			**2.50**	**10.00**
Polyethylene oxide (Polyox, MW_8000000)				**5.00**	
Povidone				**0.25**	**0.25**
Stearic Acid		**2.0**	**2.0**	**2.0**	
Magnesium Stearate, NF				**2.0**	**2.0**
Total Weight	**785mg**	**785mg**	**785mg**	**785mg**	**785mg**

Cos Rx Technology:

Formulation based on constant sustained release matrix (COSRxtm) technology can also be developed using guargum as a major rate-controlling polymeric material. Depending on the solubility of drug, low or high viscosity of guargum can be used**.**

The formulation involves a guargum based tablet and a combination of water-soluble and water and water insoluble polymeric tablet core. When the tablet is placed in a dissolution medium, there is slow diffusion water through the polymeric wall leading to swelling and gelling of guargum drug core. As the

hydration progress, the tablet continuous to swell until the wall breaks, forming a sandwich like structure. The release of drug processed primarily out of the side of the tablet as it passes through the intestinal tract. The tablet provides a nearly zero order drug release following a programmed period of delayed drug release**.**

To achieved a constant zero order matrix sustained release formulation (COS Rx) for a poorly water soluble drug such as nifedipine (< 10ugml-1) a low mol.wt guargum was used. Channeling agents such as water-insoluble silicon dioxide water soluble lactose were used to enhance the porosity of the matrix aiding in the dissolution of drug. A combination of water soluble (Eudragit RLPO) and water insoluble polymer (Eudragit RSPO) in the ratio 1:9 (RL:RS) was used as coating material (2%w/w). the combination produced a lag time in drug release of 2 hrs**.**

Capsule (Ring cap technology):

Ring cap technology is on oral controlled release drug delivery system in which several insoluble rings are incorporated around a tablet. These ring control erosion of tablet and modified the drug release in GIT[11]. MR . in general the drug release from ring cap tablet is proportional to the area exposed to the dissolution media. This surface area changes over time as the area round the rings become hydrated and erode creating new surface area which can be decreased, remain constant or even increase with time. The exposed surface area is controlled by number, width and placement of ring of insoluble polymers applied to the tablet**.**

Madopar DR is a three- layer gastro retentive matrix tablet of 1-dopa is used for the treatment of parkinson's disease. The inner layer is sustained in action made up of hydrophilic water sellable polymer (HPMC) and the outer layer release 1-dopa in higher concentration for quick onset of action. HPMC swell in presence of water and increase gastric retension time and the swelled tablet release the drug slowly at a maintenance dose up to 6 hrs**.**

ADVANTAGE:

Two different drugs with different release profile can be achieving a single tablet**.**

It is meant for controlled release and abuse resistant drug delivery system**.**

Ring CAPtm system can deliver the total dose evenly over an extended period of time**.**

Drugs can be formulated ring cap technology include calcium channel blocker, ACE inhibitors, NSAIDS & Vitamins**.**

Multilayered Tablet:

The multilayered tablet approached is a convenient method in which the loading dose is sandwiched two outer matrix layers. The central layer releases the dose for immediate onset of action whereas the matrix layer for sustained release of drug. This helps in maintaining the blood level. The multilayered tablets are prepared by direct compression or wet granulation or tablet compression. The polymer used is ethyl cellulose, Eudragit RS 100. The challenges faced during multilayered tabletting include cross contamination from one layer to other.

Example : if the first layer is red and second is white any granulation bypass the first feeder and contaminate leading to pink color**.**

Uses :

Two incompatible actives or excipients are compressed into one to make a high weight tablet**.**

Control release and time release**.**

Imprinting (molecular):

Molecular imprinting provides lithography system and technology for application in the manufacturing, areas such as Nano- devices, advanced packaging, microstructure, bio devices, semiconducting devices and optical components[9,10]**.**

The concept behind the technology is to mold a material around individual molecules. When the molecular templates are removed, one is left template molecule. This shows that molecular imprinting is applicable to that material that can selectively bind to molecules of interest**.**

Working of molecular imprinting:

Three basic ingredients are required namely templates molecule, functional monomers and a cross linker**.**

The templates molecules may range from small organic molecules to large biopolymers. The templates must be purified, catalyzed or detected with the final product. These behave similar to high energy intermediates in the chemical reaction**.**

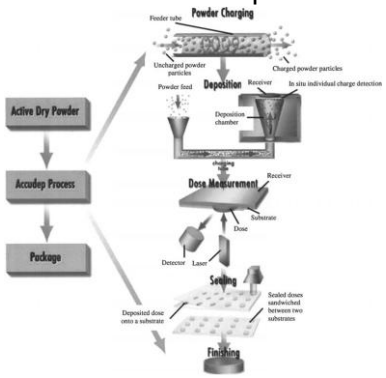
Functional monomer should have two functional group each one end they should interact with templates with weak interaction (non-covalent) with the cross linkier**.**

Cross linkers is a molecule that can be polymerized around the templates, binding covalently to the functional monomers and holding them in place after the templates in removed porous cross linkers or those which can be broken into small pieces are used typically[5,8]**.**

Accudep technology:

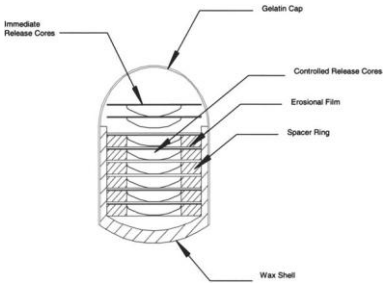
Accudep technology has been developed for products for immediate release dosage form, super generic products ment, novel controlled release formulations. The main goal of this technology is to identify highly flexible delivery design that will accommodate many drugs of diverse physicochemical characteristics and dose facilitate engineering of immediate as well as control release of active pharmaceutical powder. This process excludes processer such as mixing blending, granulation, drying, compression etc. and uses active ingredient in pure form and achieves control release by the use of polymeric films**.**

In the process, the pharmaceutical powders acting as a toner are charged, then transported to a chamber where in dispersion and disposition takes place.



Technology:

For preparation of oral dose unit i.e. Accudep core is separated by erosional polymer films.



Illustrates It contains 6 layers each contains and each layer contains accudep core which in turn contained by a polymer core the layers are separated by rate controlling films and an impermeable coating is applied to the dosage form.

The variables that affected drug release include rate controlling film composition, amount of drug per layer, number of layers, immediate release elements, extend of coverage by on co permeable coating. Rate controlling films was prepared with cellulosic material, polyethylene oxide film[1,10].

Osmotically CDDS:

Osmotically Crdds is unique delivery system in which the activating agent is osmotic pressure the release. The drug at a zero order rate. It contain tablet core with water soluble drug and osmotic agent such as Nacl, Mannitol, PEG, Carbopol etc. the tablet core is coated with the semipermeable polymer (cellulose acetate) which is unpermeable to water. A laser drilled hole, 100-250 um is size is created as delivery orifice. The osmotic pressure of OROS tab is around 130-140 atm and that of body fluid is 7.4 atm. Hence aqueous fluid present in GIT enters into OROS tablet through semipermeable membrane and pushes the drug through orifice. This type of delivery system required highly water soluble drug and poor water soluble drug causes insufficient pressure as a result complete drug release is prevented.

To overcome this problem Alza corporation come up with a technology called " OROS pull-push technology" in which tablet is made of multiple drug layer and a push layer at the bottom. This layer contains water swellable polymer, osmotic

agent and other excipients. Water permeates in to the tablets, polymers swells due to intake of water and the swelled and layer push solution form upper dry layer through the orifice5.

It is mainly developed for highly insoluble drug, hormones steroid etc. few example like glucotrol XL formulation of glipizide, procardia XL of nifedipine.

Multiparticulated system:

Multiparticulated system is made up of natural biodegradable polymer which is ment for controlled and sustained release of drug. Oral multiunit dosage form such as microspheres, microcapsule are ment for such delivery. It mainly provides an intimate contact with the absorbing membrane. This is achieved by coupling bio adhesive characteristic to microcapsules. Alginates (polysaccharides) are used as a polymer. Sodium alginate as matrix material to a control release, chitosan as polymers in preparation of micro adhesive microcapsule.

The multipartuculate system gained popularity due to advances such as capsule filling, better flow property of spherical beads, each of coating, site specific action, even distribution of drug in GIT and less GIT irritation. It can be prepared by several techniques such as spray congealing hot melt extrusion. Sphernization of low melting materials, spray coating etc. Beads can be coated with rate-limiting polymers or it might be directly compressed into tablet. More over beads with two incompatible bioactive agent can also be prepared.

Elan's multiparticulate technologies such as spheroidal oral drug absorption system (SODAS), programmable oral drug absorption system (PRODAS), chromo therapeutic oral drug absorption system are designed based on the need of individual drug. For example controlled release formulation of naproxen (naprelan) uses intestinal protective drug absorption system (IPDAS) which disintegrates into multiparticulate beads and distributes throughout GIT and prevent dosage dumping of naproxen.

Research had found that certain disease like heart attach are affected by rhythmic changes of human body i.e. risk is more during morning than evening. Hence CODAS drug delivery system is designed to give drug release according to circadian pattern of disease.

DISCUSSION

Oral modified drug delivery system has been developed to extend the drug release for several hours. It offers reduction in dosing frequency, low incidences of side effect and better therapeutic effect and enhances the bioavailability hence it is more prefer than conventional dosage form [4,9,11].

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