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Review Article

Oral controlled release drug delivery system and Characterization of oral tablets; A review

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ABSTRACT

Oral route of drug administration is considered as the safest and easiest route of drug administration. Control release drug delivery system is used as emerging tool in the development of pharmaceuticals. The oral route is most suitable for such kind of drug delivery system due to its convenience for all age groups including both pediatric and geriatrics. There are various systems which are adopted to deliver drug in a controlled manner to different target sites through oral route. It includes diffusion controlled drug delivery systems; dissolution controlled drug delivery systems, osmotically controlled drug delivery systems, ion-exchange controlled drug delivery systems, hydrodynamically balanced systems, multi-Particulate drug delivery systems and microencapsulated drug delivery system. The systems are formulated using different natural, semi-synthetic and synthetic polymers. The purpose of the review is to provide information about the orally controlled drug delivery system, polymers which are used to formulate these systems and characterizations of one of the most convenient tablet dosage form.

Keywords: Oral route, Controlled release drug delivery system, Tablets characterizations

INTRODUCTION:

One of the most satisfactory and secure means for administration of the drugs because of its appropriateness and simplicity of administration, is the oral drug delivery system. Conventional dosage form can partially achieve the goal of delivering the therapeutic response over the time of dose interval. Recent technological development and advances in oral drug delivery has guided the pharmaceutical industry towards the improvement of dosage forms. Many unique features are now being efficiently used for gaining most favorable results with fewer disadvantages. Novel drug delivery system (NDDS) is much vital. This system has remedial efficiency, little prevalence of toxicity and better stability profile.

Oral drug delivery system can be categorized into (1) targeted release formulations (2) sustained release formulations and (3) immediate release formulations. The immediate release formulations are typically superior to attain rapid onset of action for some drugs like analgesics, antipyretics and vasodilators. Sustained release (SR) drug delivery system has gained more significance in the field of pharmaceutical science. SR drug delivery system has following major advantages than the usual solid oral dosage forms. (1) Serum concentration is maintained in therapeutic range for longer duration. (2) Drug release rate can be predicted and controlled for distinct time period. (3) Drugs with shorter half-life can be consecutively designed to enhance their duration of action. (4) Lesser frequency of drug

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administration and hence better level of patient compliance with minimum wastage of drug. To distribute the contents to preferred area, targeted drug delivery system has been formulated (Neau *et al*., 1996). Conventional tablets can be coated by pH sensitive polymers and site specific binding legends for active targeting (Allen and Ansel, 2013).

Now a days, site specific delivery of the active pharmaceutical ingredients (API), especially at the desired location is attaining more and more popularity (Banker *et al*., 2002). Oral route for such kind of drugs is not used generally because the aim is to deliver the drug at the target site, avoiding major side effects. The prime focusing areas, related with active drug targeting are chemotherapy and other genetic abnormalities.

Active agent and the system, based on the mechanism along with the associated technologies are typically directed to molecular pathways to cure the basic cause of the disease. Liposomal preparations (Pattni *et al*., 2015), nanoparticles preparations(Singh *et al*, 2009), resealed red blood cells, and pro-drugs are generally used for satisfying these stated objectives.

CLASSIFICATION OF ORAL CONTROL RELEASE DRUG DELIVERY SYSTEMS

It can be classified on the basis of drug released pattern. Generally the oral sustained release formulations are categorized as given below:

- Diffusion controlled drug delivery systems
- Dissolution controlled drug delivery systems
- Osmotically controlled drug delivery systems
- Ion-exchange controlled drug delivery systems
- Hydrodynamically balanced systems
- Multi-Particulate drug delivery systems
- Microencapsulated drug delivery system

Diffusion controlled drug delivery system

The system is termed as diffusion controlled, when the released of drug is controlled by the diffusion process (De Robertis *et al*., 2015). Diffusion occurs through the non-reactive immobile membrane that provides the barrier(Zaman *et al*., 2014) which is of non-soluble polymeric contents. Furthermore this system can also be classified into:

i. Matrix system

ii. Reservoir system

i. Matrix system

In such a dosage form drug is distributed homogeneously in polymeric matrix as described in Figure. 1. In these systems the active agent in external surface layer, that is in touch with dip medium, is first dissolved and then released by diffusion through the matrix system(Malik *et al*., 2014, Zaman *et al., 2013).* Arithmetical model discussing these systems have following focal assumptions.

(a) During release of the drug particles, quasi stable state is usually sustained, (Singh *et al*, 2009) (b) Thickness of particulate dosage form is smaller than the average space travelled by the ingredients during course of diffusion through matrix is greater than the diameter of that dosage form, (Pattni *et al*., 2015) (c) Section that received the solution provides comprehensive sink condition, and (d) In matrix system diffusion coefficient of the diffusion remains unchanged and no variation is possible in polymeric membrane functions and in its strength (De Robertis *et al*., 2015). The matrix system is shown in figure 1.

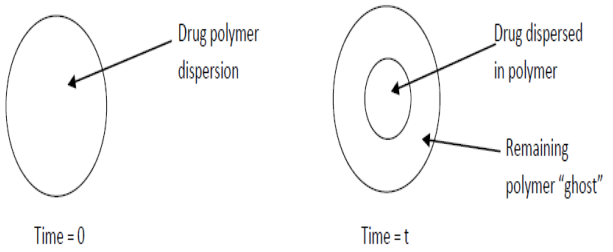


Figure 1: Matrix diffusion system (Amass *et al*., 1988)

Release of the drug can be controlled by changing the parameters given below:

- Initial concentration of drug in the matrix
- Aperture size of the inert membrane
- Combination of the polymers used in the matrix
- Drug solubility

This system offers a number of advantages. These advantages include ease of formulation, ability to use high molecular weight substances and dose dumping from unintentional seepage is avoided in these systems. There are some drawbacks in this system. An ideal zero order release is not achievable. In case of implant systems, unsolvable matrix remains intact after the drug is released. It must be removed. Matrix system is simple to formulate and can be used efficiently for drugs with high molecular weight to be delivered to the desire target site. In the matrix system drug is equally distributed and rapid elimination of the contents is avoided (Modi *et al*., 2011).

Main disadvantages are:

- The elimination of exhausted polymeric material from body is difficult
- Zero order release in typically difficult to attain

ii. Reservoir system

In reservoir system a core of drug is enclosed in a polymeric membrane that is responsible for controlling the release pattern of the drug from matrix device(Stevenson *et al*., 2012). Reservoir systems have some feature like:

- Different polymeric membranes can be used to achieve various release rates of the drug
- Using reservoir type system Zero order release can be attain
- By altering membrane character drug release pattern can be controlled

These systems have few drawbacks such as;

- The implanted systems should be detached physically
- It's too difficult to add in drugs with high molecular weight in these system because membrane aperture size restricts the size of the active substances
- Can be the cause of increased toxicity in case of system collapse
- High production cost

Continuous release can be achieved from diffusion control matrix device at steady state, but there are chances of variability in release pattern of the drug initially, either greater or lesser amount of the drug release can be observed depending upon nature of the device. The device that is used almost immediately after its development will observably show slow release primarily due to extended lag period for drug to reach and penetrate in-to membrane. This membrane is responsible for the control of the rate and if a reservoir device is stored for a longer period of time then there is possibility that drug may saturate the membrane through this time and immediate release can also be occur.

Dissolution controlled drug delivery systems

Drugs having slow rate of dissolution will exhibit sustaining properties, as the rate of dissolution restricts the drug release from the formulation; hence it looks possible to develop the sustained released formulation by decreasing the rate of dissolution of hydrophilic drugs (Kumar *et al*., 2012, Nokhodchi *et al.*, 2012).

It can be made possible by;

- Preparation of suitable salt derivatives
- Coating with slowly dissolving coating materials
- Distribute the drug in a system having slow dissolving carrier i.e. dissolution control matrix system

Osmotically controlled drug delivery system

In the osmotic system an osmotic agent is used in the formulation. Drug that is soluble in water is packed together with an osmotic agent like sodium chloride, covered by a selectively permeable layer. Usually semi-permeable film is composed of cellulose derivatives such as cellulose acetate. The system containing osmotic agent and covered by an impermeable membrane can also be used to deliver the drug. Mechanical or laser drill is used to make small single or multiple openings on the tablet using. Water diffuses through the semi-permeable membrane to gain access to the drug to dissolves the drug. Dissolved drug can only release from the orifice. The osmotic pressure gradient between the inner and outer medium can cause the drug efflux.(Srinkonda *et al*., 2006, Verma *et al*., 2000)

Osmotic systems have the advantage over the other drug delivery systems because zero order release is attainable. Incompatible drugs can also be incorporated and dispensed in a single dosage form. Food content or pH of the GIT has no effect on drug release. Although, the quality control of osmotic systems is very difficult therefore the system is relatively expensive (Pu *et al*., 2011, Sharma *et al*., 2011).

Ion-exchange controlled drug delivery system

These systems involved the resin in which water insoluble polymers are cross linked. In the polymer chains salt forming functional groups are present in repeating manner. When the dosage form exposed to the ion exchange resin in the dissolution media or gut, the exchange of properly charged ions e.g., Na^+, H^+, Cl^-or OH resulting in the release of resin bounded drug that then efflux out from the resin. The drug-resin complex can be prepared either by prolonged contact of drug and resin in solution or by exposing them to the drug repeatedly in a chromatogram. The rate of drug efflux from such dosage form depends upon the site, distance to be travelled and the stiffness of the system that depends upon concentration of the substance involve in the formulation of resin(Malinovskaja *et al., 2013,* Nitanan *et al., 2013).*

This system is advantageous as the drugs that are highly liable to enzymatic degradation integrated in this type of system (Raghunathan *et al*., 1981).

Hydro-dynamically balanced drug delivery system

In various controlled delivery systems short duration of the gastric residence is very problematic. Various techniques can use for the reduction of gastric emptying for a dosage form, like floating drug delivery system. The system has less bulk density as compared to the gastric fluids. Floating systems floats over the gastric fluid for longer period that enhance the bioavailability of therapeutic agents(Jha *et al*., 2015).

The long-term intra gastric buoyancy of this system might also offer an appropriate method to continually release the drug locally into the stomach and thus attain a sustained targeted therapeutic effect. Drug is layered over the shells filled with air that makes the system lighter than the gastric contents(Strübing *et al*., 2008).

Multi-Particulate drug delivery systems

In these dosage forms, therapeutic substance is distributed onto beads, pellets(Kim *et al*., 2006), granules or other particulate systems are used to deliver the drug. The drug is dispersed into this system. Sugar and starch or microcrystalline cellulose spheres are used and solution of the drug is coated on them by conventional pan coating air suspension methods. The size of nonpareil seeds particles ranges from 425 to 850 µm and that of the microcrystalline cellulose spheres is from 170 to 600 µm. The microcrystalline spheres are considered to be the more durable during formulation as compared to the sugar beads .Small spheroid-shaped compressed tablets having 3 to 4 mm in diameter are prepared by compressing these small particles having different drug release pattern. For the desired behavior of drug, these released, mini tablets can be filled in the gelatin capsules. 8 to 10 mini tablets are present in the capsule. There are some uncoated tablets that give instant release and others coated for sustained release(Dey *et al*., 2008, Nutan *et al*., 2005).

Microencapsulated drug delivery system

Solids, liquids, or gases can be entrapped by this technique. A thin layer formation takes place around the material to be encapsulated. Gelatin is used commonly for encapsulation but synthetic polymers such as polyvinyl alcohol, ethyl cellulose, polyvinyl chloride, and other materials can be used(Wang *et al*., 2006). Various proteins, lipids, and other drugs can be encapsulated by these materials (Ma, 2014).

RELEASE CONTROL POLYMERS USED IN SUSTAINED RELEASE ORAL CONTROL DRUG DELIVERY SYSTEM

A wide variety of Polymers can be used in formulating the sustained release oral control drug delivery system. Classification of the polymers is usually based on the features of the matrix system. Polymers can be classified in the following classes.

Natural polymers

Natural polymers such as xanthan gum, pectin, guar gum, gum acacia, tragacanth etc. are extensively used in pharmaceutical preparation for formulation of various dosage forms like oral and topical preparations.

They have different advantages when these are used in formulating the matrix system to develop the sustained release dosage form. Usually they have hydrophilic character. Normally in the physiological conditions these are nontoxic, more over they can be a very good source of food ingredient (Rajesh *et al*., 2009,Varshosaz *et al*., 2006, Bhardwaj *et al*., 2000).

Xanthan gum

Xanthan gum is a cream- or white fine powder having no colour or odor with excellent flow properties. Its chemical name is Xanthan gum. Molecular weight of xanthan varies from 4 to 12 $\times 10^6$ g/mol. It also called as, Xantural, E415, keltrol, polysaccharide B-1459, rhodigel, corn sugar gum, vanzan NF. Its pH ranges from 6.0–8.0 for a 1% w/v aqueous solution. Practically it is insoluble in ether and ethanol but soluble in water(Rowe *et al*., 2009). Structural formula of Xanthan gum is represented in figure 2.

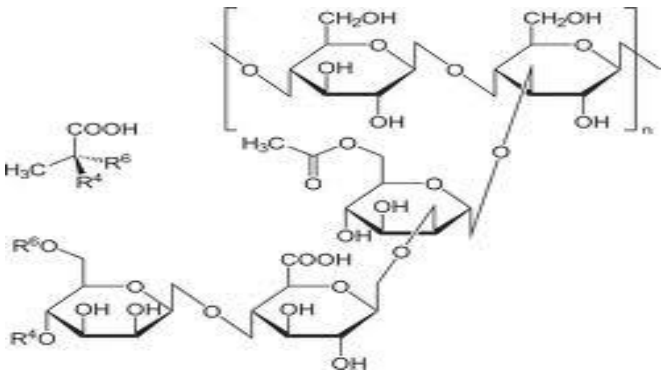


Figure 2: Structural formula of Xanthan

Pectin

Its particle size is coarse or fine. It is an odorless coarser or fine powder with yellow to white appearance with a mucilaginous taste and chemical name is pectin. Molecular weight of the pectin is 30000–100000. Synonyms that can be used are citrus pectin, E440, methopectin, methyl pectin, methylpectinate, mexpectin, pectin, pectinic acid. Its pH ranges 6.0–7.2. It is soluble in water and insoluble in ethanol (95%) and other organic solvents (Rowe et al., 2009). The Structural formula of Pectin is represented in figure 3.

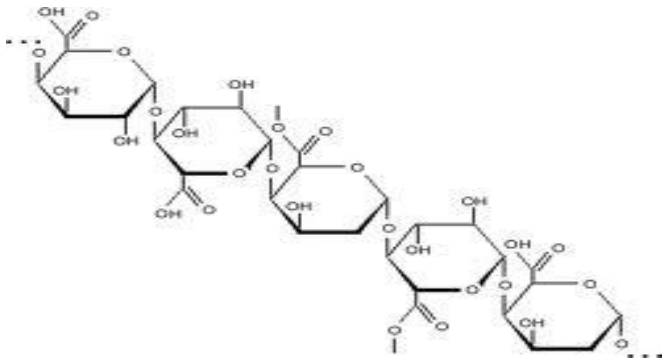


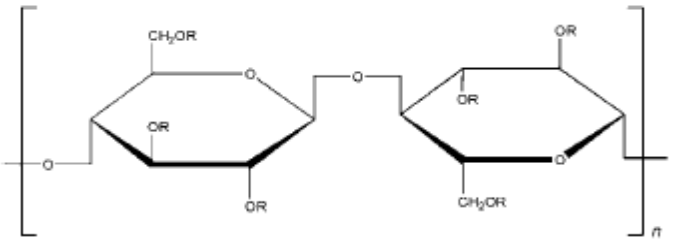
Figure 3: Structural formula of Pectin

Semi synthetic polymers

Semi synthetic polymeric materials are used extensively in formulating oral control drug delivery system. These polymers swell when they come in contact with the water. Examples of such polymers are HPMC (Hydroxy propyl methyl cellulose), Hydroxy ethyl cellulose (HEC),Galactomannoe,sodiumcarboxymethylcell ulose, carboxypolymethylene, Methyl cellulose, Sodium alginate. Upon the hydration of these materials gel layer formation occurs (Zaman *et al.*, 2014).This gel layer acts as barrier to drug release all the way through inflamed matrix. In this type of system erosion of the barrier formed by the gel layer also play a role in controlling the drug release(Zaman *et al.*, 2014). Drug to polymer ratio and character of the polymeric material determines the intensity to which diffusion and /or erosion acts as a release monitoring feature. Low molecular weight polymer, methyl cellulose can cause the release of the drug by erosion because appropriate hydrated film is not maintained for greater duration of time. Carboxy methylcellulose is an anionic polymer in nature that can cause hindrances with cationic drugs causing to higher dissolution in intestinal tract.

HPMC (Hydroxyl Propyl Methyl Cellulose)

It is a white to creamy white granular powder having no odor and taste. Its chemical name is Cellulose hydroxyl propyl methyl ether and its molecular weight is 10 000 -1 500 000. It is also called as HPMC (hydroxyl propylmethyl cellulose), methocel, methylcellulose propylene glycol ether, methyl hydroxyl propyl cellulose, metolose, tylopur. Its pH ranges from 5.5–8.0 for a 1% w/w aqueous solution. Its bulk density is 0.341 g/cm3, tap density is 0.557 g/cm3 and true density is 1.326 g/cm^3. Its glass transition temperature is 170–1808C^0 (Rowe *et al.*, 2009). The structural formula for HMPC is shown in figure 4.



where R is H, CH_3, or $CH_3CH(OH)CH_2$

Figure 4: Structural formula of HPMC

Insoluble inert matrix forming (non-biodegradable) polymers

Matrix system can be formulated by inert insoluble polymers. Ethyl cellulose, Polyethylene, Polyvinyl chloride, Methylacrylate-methacrylate copolymer can be used for this purpose. These polymers are swelled intact and stay unbroken inside the GIT. These polymers have suitable compression properties and usually compressed by direct compression method and occasionally

wet granulation can also be used before compression. Generally release of the drug depends on liquid penetration into the matrix system. Incorporation of wetting and pore forming agent can increase the liquid penetration in the matrix system causing diffusion and/ or dissolution to be the process that will control the rate of the drug release from the matrix systems (Fu and Kao, 2010, Roth and Herman, 1999).

Insoluble erodible matrix forming polymers

When lipids, waxes and related hydrophobic substances are used for the preparation of matrix system than diffusion and erosion processes adequately control the release of the drug from the matrix (Ilium, 1998). Different waxes like Castor wax (polyethylene glycol mono stearate), Carnauba wax (stearyl alcohol, stearic acid, polyethylene glycol) and Triglycerides are included in these polymers. Lipid core covers some of the drug that's why it is impossible for drug to be released completely from the matrix system form by lipid waxes (Mehta *et al*., 2001). Water penetration into the system can be increase by surfactants that will in result can enhance the released of the drug erosion of the matrix(Mehta *et al*., 2001, Ilium, 1998).

Bio degradable polymers

Cyclic lactones are subjected to polymerization, which occurs after opening of the ring structure and then they are changed into biodegradable polyesters such as Polylactic acid. Poly lactic-co-glycolic acids (PLGA) consist of copolymers of glycolic acid and lactic acid. When individual polymers and co polymeric materials are mixed together it decrease the crystalinity and increase their rate of degradation. Generally homopolymers can be used in the ratio of 50:50 to form the matrix system but by varying the concentration required results can be obtained. In case of internal injuries these polymers are commonly used as suturing materials for stitching of the wounds in preliminary stage because these polymers have the ability to degrade in body. Some water insoluble polymers like Polycaprolactone can be used to improve the life period of these polymers as these hydrophobic material blocks the influx of the water into the system and results in decrease in the degradation of these polymers (Pillai and Panchagnula, 2001, Amass *et al*., 1998).

CHARACTERIZATIONS OF ORAL CONTROLLED RELEASE TABLETS

Weight variation

It is the parameter that suggests that variation in the weight of an individual tablet is a suitable indication of the related variation in drug content. 20 tablets are taken randomly and then average weight of the tablets is calculated (Zaman *et al*., 2014 ,Qureshi *et al*., 2014).

Hardness test

The test is used to find out, under given conditions, the hardness of tablets, calculated by force required to destroy the tablets by crushing. Hardness of the tablet is also known as crushing strength of the tablet. Generally it is considered as a useful parameter of controlling a tablet manufacturing process. It can effect the friability and disintegration time of the tablet. Typically, it affects dissolution, release, bioavailability of the drug (Qureshi *et al*., 2014, Akhtar *et al*., 2011).

In this method 20 tablets are taken randomly then hardness of the each tablet is determined individually with the help of hardness tester. Mean of these values is calculated for all tablets. All the formulations are analyzed by the same method.

Thickness test

Thickness of tablet is measured by the quantity of fill allowed to enter the die and total pressure applied during compression. Without changing the weight, thickness can vary due to the differences in density of the material and applied pressure along with the speed of the compression(Qureshi *et al*., 2014). Vernier caliper

is used to measure thickness of the 20 tablets taken randomly and then average of these values is calculated. Same method is used for all formulations.

Friability test

Friability test can also be used to measure the strength of the tablet. It is used to observe the ability of the tablets to hold up both shock and abrasion without collapsing by handling during the manufacturing, packaging, transportation and consumer use. Friability test of the tablet is performed on 20 tablets chosen randomly. Revolution speed is adjusted at 25 rpm for 4 minutes using friabilator. The percentage of friability is measured based on the weight lost after the test(Qureshi *et al.*, 2014)

20 tablets are taken randomly and dust is removed by using a soft brush. After weighing the tablets accurately, placed in a friabilator. The apparatus is set to 25 rpm and run for 4 minutes. After that again dust is removed from the tablets and then they are weighed again. According to compendia only 1.0% or less than 1.0% decrease in weight is acceptable.

Content uniformity test

Ten tablets of each formulation are subjected to assay determination method. The amount of the powdered material equivalent to active drug is taken and then extracted using suitable volume of solvent. Water bath is used to heat this solution for 15 minutes at the temperature of 40 C^0. Residual material is diluted up to the suitable final volume and then filtered. The Absorbance of the finally filtered solution is measured using spectrophotometric method.
Absorbance of reference solution of same concentration is used to measure the percentage drug contents. Graph of concentration against time is plotted and the curve is chosen, up to as high concentrations as it remain linear(Qureshi *et al.*, 2014, Akhtar et al., 2011).

Drug release studies

Dissolution studies of oral control drug delivery system of various formulations are performed using dissolution apparatus (USP apparatus-II, paddle method) (Watson Marlo, Stockholm, Sweden). 900ml of dissolution media at a constant temperature of 37 ^{0}C (±5.0^{0}C) at the rotation speed of 50 rpm. Samples of suitable volume are taken at recommended time intervals. Samples are analyzed by Spectrophotometric method and release profiles are assessed by using software. Time for 50% drug release is determined by using dissolution data through cubic spline interpolation technique with software (graph pad software)(Zaman *et al*., 2014).

Release kinetics models

Different kinetic models can be applied to evaluate the different release pattern of the drug from the orally controlled drug delivery system. These models are utilized in the prediction of drug behavior and release kinetics (Zaman *et al*., 2014,Shah *et al*., 2009).

These are given as:

Zero order models

$$Q_1 = Q_0 + k_o t \quad \text{..... (i)}$$

Where k_0 is the release rate constant Q_t is the amount of drug released at any time interval

1st order model

$$\log Q_t = \log Q_0 + K_1 t/2.303 \quad \text{..... (ii)}$$

k_1, is the 1st order release rate constant Q_t, is the amount of drug released at any time interval

Higuchi model

$$F_t = K_H t^{1/2} \quad \text{..... (iii)}$$

K_H, is release rate constant for Higuchi model

Korsmeyer Peppas model

$$M^t/M^0 = kKPtn \quad \text{..... (iv)}$$

Kkp, is release rate constant for Korsmeyerpeppas model M^t/M^0, is the amount of drug release at time t and infinity n, is the diffusional constant

Hixon-crowell model

$W_0^{1/3} - W_t^{1/3} = K_S t$ ..... (v)

Ks, is release rate constant for Hixon-crowell model

CONCLUSION

Oral control drug delivery system is one of the safe, effective and convenient route of drug administration. Various systems and techniques are available that can deliver the drug in a controlled manner increasing the bioavailability of the drugs through Trans GIT. It can be effectively used to enhance the patient compliance.

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