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Research Article

CONTROLLED RELEASE APPROACH TO NOVEL MULTIPARTICULATE DRUG DELIVERY SYSTEM

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ABSTRACT

Pharmaceutical research is always on inventing drug delivery systems that can enhance patient compliance by obtaining desired therapeutic effect and reducing side effect along with lowering dosing frequency. In the treatment of some diseases polypharmacy is always applied but by designing a drug delivery system that have the entire various active pharmaceutical ingredient in one capsule can be always beneficial which deliver the drug at right time and in proper amount according to body's circadian rhythm. According to recent pharmaceutical applications involving pulsatile delivery the multiparticulate dosage forms are getting much favor over single unit dosage form because of their smaller particle size these systems have capacity for passing through the G.I. tract easily, leading to less inter as well as intra subject variability.

Keywords: PRODAS, CODAS, OROS, Chronotherapeutics, DIFFUCAPS.

INTRODUCTION

Pharmaceutical invention and research are gradually more focusing on delivery systems which enhance desired therapeutic objectives while lowering side effects. Recent trends specify that multiparticulate drug delivery systems are specifically suitable for achieving controlled or delayed release oral formulations with smallest amount risk of dose dumping, flexibility of combination to achieve different release patterns with reproducible and little gastric residence time. The drug release pattern from these systems depends on a carrier which is used in the formation of multiparticulates and the amount of drug enclosed in them. Thus multiparticulate drug delivery systems provide incredible opportunities for designing novel controlled and delayed release oral formulations. The oral route is most frequently used route for oral administration of drugs. A tablet forms considerably the majority of oral dosage form due to their convenience of application and ease of preparation on an industrial scale.

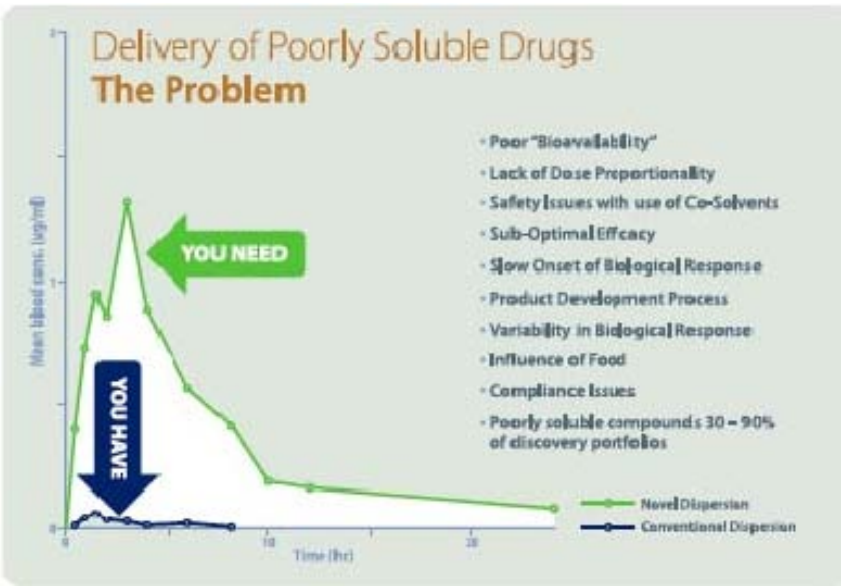

Fig. 1: Delivery of poorly soluble drugs: the problem[1]

A major percentage of active pharmaceutical ingredients predicted through discovery screening programs are poorly soluble in water. These molecules are complex to formulate using conventional approaches and are linked with immeasurable formulation-related performance issues: poor oral bioavailability; lack of dose proportionality; and slow onset of action. Using the conventional dosage form, drugs are on occasion unable to achieve steady-state plasma concentrations so the difficulty of over or under medication may take place. The risk of adverse effects due to poor patient compliance rises. These challenges can be minimized by the use of controlled drug delivery systems that give several benefits, like the drug being delivered at a programmed rate for exact period of time and at definite site, reduced frequency of administration, reduced side effects, and enhanced patient compliance, amplified safety margin of highly potent drugs, lowered healthcare costs, and enhanced therapy. The pathophysiology of some diseases are influenced by body's circadian rhythm like, in peptic ulcer acid secretion is high in the afternoon and at the night or early at the morning hour.[2] In cardiovascular diseases B.P. is at its lowest during the sleep cycle and rises steeply during the early morning period. In the diabetic patient the blood sugar level increases after meal. So the drug delivery system should deliver the drug at the accurate time at proper place in controlled manner and thus increasing patient compliance.[22]

Multiparticulate Drug Delivery System

Oral dosage form can be broadly classified into two categories: Single-unit and Multiple-unit dosage forms. The single-unit dosage forms include matrix tablet or coated/uncoated tablet or capsules. The multiple-unit dosage forms consist of pellets or microencapsulated drug filled in a capsule or compressed into a tablet. The basic concept of multiple-unit systems is that the dose of the active ingredient is released by the individual subunits like pellets, and the functionality of the entire dose depends on the quality of the subunits. The idea behind designing multiparticulate dosage forms is to build up a reliable formulation which has all the advantages of single unit formulations without danger of modification in drug release profile and formulation behavior owing to unit to unit variation.

These delivery systems are mainly reservoir type of oral dosage forms having multiplicity of small distinct units, each having some preferred characteristics. In these types of drug delivery systems, the dosage of the drug substances is separated on a plurality of subunit. Multiparticulate dosage form is pharmaceutical formulations where the active substance is in the form of number of small independent subunits. They give many advantages over single-unit systems due to their small size. Drug safety may also be augmented by using multiparticulate dosage forms, mainly for modified release systems. To deliver the projected entire dose, these subunits are packed into a capsule or compressed with added excipients to form a tablet. Conventional IR dosage forms have to be administered numerous times a day as to maintain a therapeutically effective plasma level of the drug which is major drawback in terms of patient compliance. Oral controlled release formulations overcome many of the drawbacks of conventional IR dosage form. Dissimilar to conventional IR dosage forms CR tablets are not associated with alternating periods of toxic levels and sub therapeutic concentration thereby improving the therapeutic efficacy and avoiding toxic side effect. In order to improve the therapeutic efficacy of oral drug administration and to overcome many of the drawbacks of conventional IR dosage forms, R&D of academia & industry has to focus on development of oral controlled release technologies & novel release controlling excipients. The reduced side effects and lower frequency of administration of Controlled Release tablets represents increased comfort and more reliable tablet intake, which is especially important for patients which are subject to a chronic medication regimen.

The drug can be formulated as a multiparticulate system because of many reason for example, to aid disintegration in the stomach, or to offer a suitable, fast disintegrating tablet which dissolves in water before swallowing and which can relieve compliance in aged patients and children. Multiparticulate systems give superior reproducible pharmacokinetic behavior in comparison to conventional (monolithic) formulations. Upon disintegration which occurs within a hardly any minutes frequently even within seconds, the individual subunit particles pass quickly through the GI tract. If these subunits have diameters of less than 2mm, they are able to depart the stomach constantly, yet if the pylorus is closed. These result in lower intra and inter individual variability in plasma levels and bioavailability. Safety of drug may also be improved by using multiparticulate dosage forms, mostly in case of customized release systems. For example, if the film coat of a single-unit (monolithic) enteric coated tablet is damaged, the entire dose will be discharged into the stomach where it may cause pain or ulceration or lowered efficacy, depending on the reason for choosing the protection of the enteric coating. Similarly, if there is damage to the film coating of a monolithic tablet with a sustained release formulation, it may lead to "dose dumping" resulting into spectacular side effects. But in multiparticulate formulation, the release individuality are included into every sole subunit and any damage merely affects the release pattern of the subunit involved, representing a little part of the total dose, lowering the likelihood of safety problems.

For colonic delivery multiparticulate approaches tried due to their smaller particle size compared to single unit dosage forms so these systems have ability of passing through the GI tract without difficulty, resulting in low inter as well as intra subject variability. In addition, multiparticulate systems are to be more homogeneously dispersed in the GI tract and also make sure more uniform drug absorption [3]. Multiparticulate approaches also tried for Chronotherapy and in case of certain diseases whose pathophysiology influenced by circadian rhythm. These delivery systems provide remarkable opportunities for scheming new controlled and delayed release oral formulations.

Advantages and Drawbacks of Multiparticulate Drug Delivery Systems [4]

Advantages

Predictable, reproducible and short gastric residence time

Less inter- and intra-subject variability

Improve bioavailability

Reduced adverse effects and improved tolerability

Limited risk of local irritation

No risk of dose dumping

Flexibility in design

Ease of combining pellets with unlike compositions or release patterns.

Improve stability

Improve patient comfort and compliance

Achieve a unique release pattern

Extend patent protection, globalize product and overcome competition

Drawbacks

Low drug loading

Proportionally higher need for excipients

Lack of manufacturing reproducibility and efficacy

Large number of process variables

Multiple formulation steps

Higher cost of production

Need of advanced technology

Trained/skilled personal needed for manufacturing

Mechanism of Drug Release from Multi-Particulates[5]

The Multiparticulate's drug release mechanism can be occurring in the following ways:

Diffusion

Upon contact with aqueous fluid of the gastrointestinal tract (GIT), water gets diffused into the core of the particle. Drug dissolution get occurs and the drug solutions disperse across the release coat to the exterior.

Osmosis

Under the right circumstances when water is allowed to enter, an osmotic pressure can be created inside the interior of the particle. Due to this the drug is expelled out of the particle into the outside through the coating [6].

Erosion

In some cases coatings can be designed to wear away gradually with time, thus delivering the drug contained within the particle.

Types of Multiparticulate Systems:

Pulsatile Release by Rupturing of Membrane

The drug is coated on sugar beads and then the beads are further coated with insoluble and swellable top layer [7, 8]. The swelling agent

includes superdisintegrants like carboxy methyl cellulose, sodium starch glycollate, etc. polymers like polyacrylic acid, PEG etc. are used. Water ingress to the system leads the coating to swell, rupture, and release of drug takes place. Release of drug is not dependent on pH or solubility of drug. Lag-time can be changed by variable thickness of coating or by altering amount of plasticizers in the outermost layer [9].

Pulsatile Release by Osmotic Rupture of Membrane

Here, the core contains the drug, a lipid material and disintegrant. Core is coated with CAP, upon immersion in aqueous medium; water penetrates the core, and displaces the lipid material. After displacement of the lipid material, internal pressure rises until a critical pressure is reached, which causes crack of the coating. This system is used for anti-hypertensive drug Diltiazem [9].

Design of Multiparticulate Drug Delivery Systems

The idea behind scheming multiparticulate dosage form is to produce a responsible formulation which has all the benefits of single unit formulations and devoid of the danger of modification in drug release pattern and formulation behavior owing to unit to unit variation, change in gastro luminal pH and enzyme population. Generally it is accepted that multiparticulate systems perform superior in compare to single unit system, as they reach out throughout the area of the intestine cause minimum irritation, enjoy a slower transit through the colon and provide a more reproducible drug release. Also in the case of single unit dosage forms, for the reason of the scheming multiparticulate colon specific drug delivery system, the existence of precise bacterial populations in the colon and rising pH gradient have been broadly explored as triggering mechanism so as to begin colon specific drug release [5].

Some Novel Multiparticulate Drug Technologies

PRODAS® Technology [10]

Fig. 2: PRODAS

Programmable Oral Drug Absorption System (PRODAS® Technology) delivery system is Elan Drug Technologies' multiparticulate minitablet technology which is presented as a number of controlled-release minitablets gathered in a hard gelatin capsule means it is distinctive as it combines the advantages of tabletting technology within a capsule[12]. PRODAS technology is representative of combination of both multiparticulate and hydrophilic matrix tablet technologies and therefore provides the benefits of both these drug delivery systems in single dosage form. Generally controlled-release minitablets lies in the size range of 1.5 to 4 mm in diameter. Minitablets with different release rates can be combined and formed into a single dosage form to give the desired release rates. These combinations may consist of immediate-release, delayed-release, and/or controlled-release minitablets and show the distinctiveness of a number of different conventional dosage forms.

Immediate release component will take off the conventional formulation which ensures that the once daily formulation is as fast acting.

Sustained release component provides supplementary controlled release/ protection.

Delayed release can present site / regional release and food resistance.

It is possible to include different minitablets, each one formulated independently and intended to release drug at various sites in order that superior dose loading is possible inside the gastrointestinal tract. Equally also possible to incorporate minitablets of various sizes so that much more drug loading is possible. Very flexible, the PRODAS® technology can be used to object the profile of a candidate drug. Furthermore to controlled absorption over a particular period, PRODAS technologies also enable targeted delivery of drug to particular sites of absorption right through the GI tract. Combination products also are achievable by the use of minitablets manufactured with different active ingredients.

PRODAS involves the production of individual minitablets by direct compression of an immediate release granulate that contain active ingredients according to the formulation. These mini tablets are afterward included into hard gels and capsules which result into the final dosage form. A more valuable use of this technology is in the manufacture of controlled release formulations. In this, by the addition of various polymer combinations within granulates may delay the release rate of drugs from every individual mini tablets. These mini tablets may consequently be coated with controlled release polymer solutions to offer supplementary delayed release properties. The supplementary coating may be essential in the case of highly water soluble drugs or drugs causing gastro irritation where drug release can be delayed until the formulation reaches more distal regions of the gastrointestinal tract. Significance of PRODAS technology lies in the intrinsic flexibility to formulation whereby combinations of mini tablets, each of which is with different release rates, are included into single dosage form. In addition to potentially permitting controlled absorption over a specific period, this also may permit targeted delivery of drug to particular sites of absorption throughout the gastrointestinal tract.

OROS® Technology[16]

OROS technology is based on osmotic mechanism to give pre-programmed, controlled drug delivery to the gastrointestinal tract. Osmotic systems employ the principle of osmotic pressure for the delivery of drugs. Drug release pattern of these systems is independent of pH and other physiological parameter to a large extent and it is possible to adjust the release characteristic by optimizing the properties of drug and system Chronoset™ is proprietary OROS® (Osmotic-controlled Release Oral delivery System) developed by Alza Corporation (now part of Johnson and Johnson).

The system is composed of two compartments—the drug vessel and the osmotic engine cap. When the system is open to the elements to an aqueous medium, water permeates into the osmotic engine cap via a rate-controlling membrane. Hydration of the osmotic engine leads to its expansion, which exerts a driving force against the ridge of the drug vessel. The two compartments separate from each other by sliding apart. After disengaging, the open mouth of the drug vessel is exposed to the fluid environment. The Chronoset® can deliver essentially the entire dose and minimizes the drug residue in the drug vessel after the operation. The vessel is made of water-impermeable ethylene-co-vinyl acetate copolymer (EVA), while the cap is made of proprietary water-permeable blends of polycaprolactone (TONE) and flux enhancers.

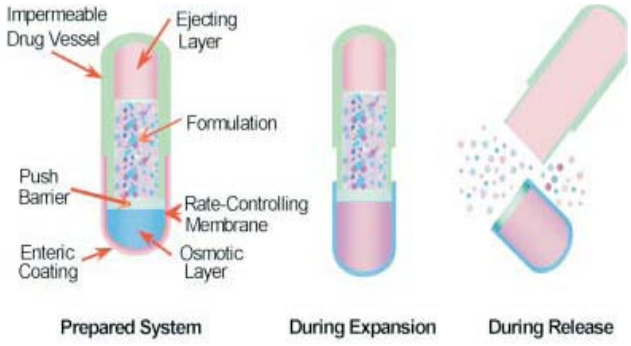

Fig. 3: OROS Technology

OROS® push pull technology

This system consist of mainly two or three layer among which the one or more layer are essential of the drug and other layer are consist of push layer. The drug layer mainly consists of drug along with two or more different agents. So this drug layer comprises of drug which is in poorly soluble form. There is further addition of suspending agent and osmotic agent. A semi permeable membrane surrounds the tablet core

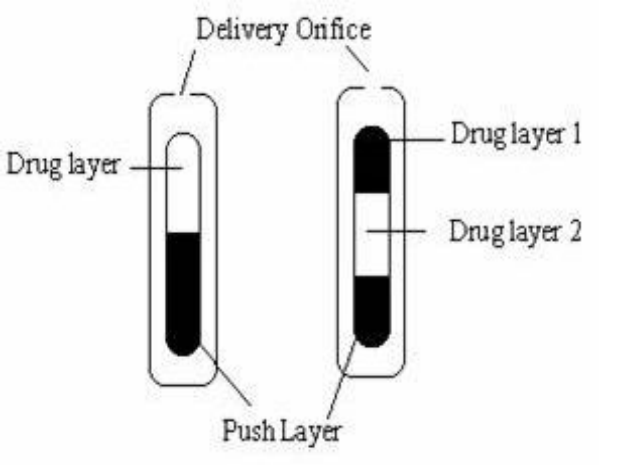

Fig. 4: OROS® push pull technology

Available marketed products

- Alpress™ LP (prazosin)
- Cardura® XL (doxazosin mesylate)
- Concerta® (methylphenidate HCl) CII
- Covera-HS® (verapamil)
- Ditropan XL® (oxybutynin chloride)
- DynaCirc CR® (isradipine)
- Efidac 24® (chlorpheniramine)
- Glucotrol XL® (glipizide)
- Sudafed® 24 Hour (pseudoephedrine)
- Procardia XL® (nifedipine)
- Volmax® (albuterol)

CODOS®[17]

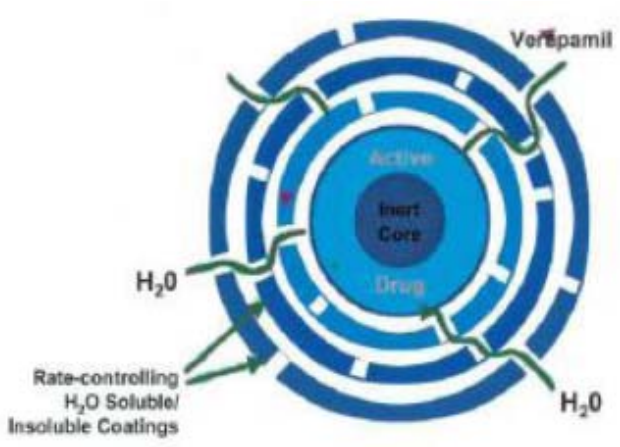

Fig. 5: CODAS[20]

In Chronotherapy drug release may be planned to occur after a prolonged interval next to administration. Elan Drug Technologies' Chronotherapeutic Oral Drug Absorption System (CODAS® Technology) was developed to accomplish this prolonged interval[10]. The CODAS is a multiparticulate system which meant for bedtime drug dosing, incorporating a 4–5 hr delay in drug delivery. This delay is occurred due to non-enteric release-controlling polymer applied to drug loaded beads. The release controlling polymer is a blend of water soluble and water insoluble polymers. When water from the gastrointestinal tract get in touch with the polymer coated beads, the water soluble polymer gradually dissolves and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier maintaining the controlled release of drug. The rate of release is basically independent of pH, posture and food. The nighttime dosing regimen of (CODAS-Verapamil) was not associated with excessive BP reductions during the sleeping hours. The CODAS-verapamil extended release capsules (Verelan PM) as chronotropic dug delivery systems actually provided enhanced BP reduction during the morning period in compare to other time intervals of the 24-h dosing period[13]. This technology can be customized to release drug following a predetermined delay. The CODAS® drug delivery system allows delayed onset of drug release, resulting in a drug release profile that more accurately compliments circadian patterns[22].

Benefits given by the CODAS® technology are delivery profile designed to compliment circadian pattern, rate of release basically free from pH, posture and food, controlled onset, extended release delivery system, decrease in effective every day dose and drug exposure, "sprinkle" dosing by just opening the capsule and sprinkling the contents on food, gastrointestinal tract targeting for local effect, reduced systemic exposure to achieve a target profile.

Marketed Preparation[4]

Verelan® PM XL capsule **API-** Verapamil HCl

DIFFUCAPS® TECHNOLOGY[14]

DIFFUCAPS technology is the most popular and versatile approach for chronotherapy for delivering drugs into the body in a circadian release manner. It is made up of multiparticulate one or more populations of drug-containing particles.

Diffucaps® technology in its simplistic form involves the preparation of:

(1) Drug-containing cores by drug-layering on inert particles

(2) Customized release (CR) beads by coating immediate release (IR) particles with one or more functional dissolution rate controlling polymers or waxes.

(3) Combining one or more functional polymer coated Diffucaps® bead populations into hard gelatin or Hydroxypropyl Methylcellulose (HPMC) capsules[15].

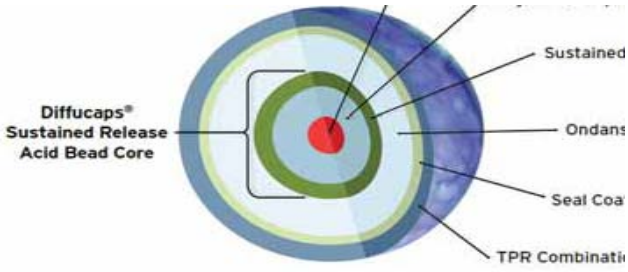

Fig. 6: DIFFUCAPS® TECHNOLOGY

Diffucaps is type of multiparticulate bead system containing several layers of drug, excipients, and release-controlling polymers. The beads contain a layer of organic acid or alkaline buffer to direct the solubility of a drug by creating an optimal pH microenvironment for drugs showing poor solubility in intestinal pH, in environments with pH greater than 8.0, or in physiological fluids. On the other hand, the beads consist of a solid-solution of drug and crystallization inhibitor in respect to improve bioavailability by maintaining the drug in its amorphous state. The active core may be produced by granulating

and milling and/or by extrusion and spheronization of API. Such a chronotropic drug delivery system is intended to provide a plasma concentration–time profile, which changes according to physiological need during the day, i.e. mimicking the circadian rhythm and severity/manifestation of a cardiovascular disease, predicted based on pharmacokinetic and pharmacodynamic considerations and in vitro / in vivo correlations. This type technology has been used to prepare the first and recently FDA approved propranolol containing chronotropic system (***InnopranR XL***) for the management of hypertension.

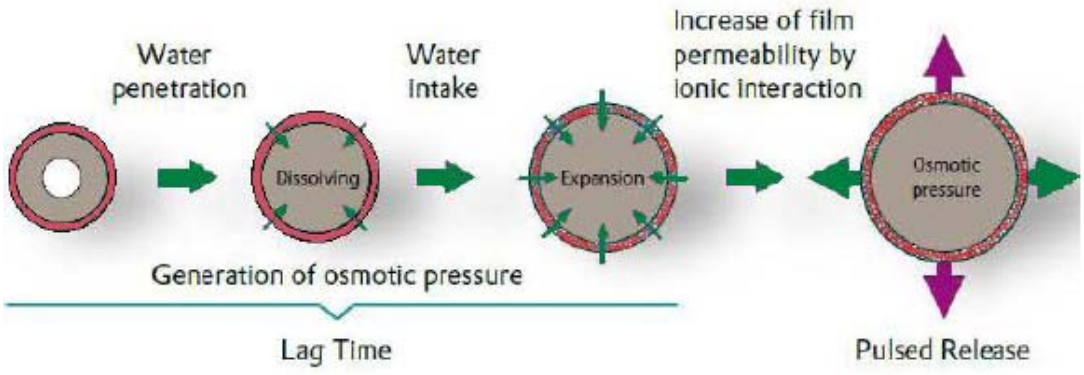

Fig. 7: Drug Release Mechanism in Diffucaps Technology

Diffucaps technology is particularly suitable for drugs that conventionally need multiple daily doses or drugs require customized release formulations. Every Diffucaps bead has an inert core enclosed by drug as well as coated with a functional polymer membrane to control the rate of drug release. Diffucaps can also be combined with other proprietary Aptalis Pharmaceutical Technologies to optimize drug delivery. Diffucaps beads are less than 1.5mm in diameter and can be filled into capsules or compressed into orally disintegrating tablets. As well a multi-particulate system, Diffucaps products produced in capsules allow for the capsules to be opened and the contents used as a sprinkle on foods, offering a flexible dosage form for patients who has difficulty in swallowing tablets or capsules.

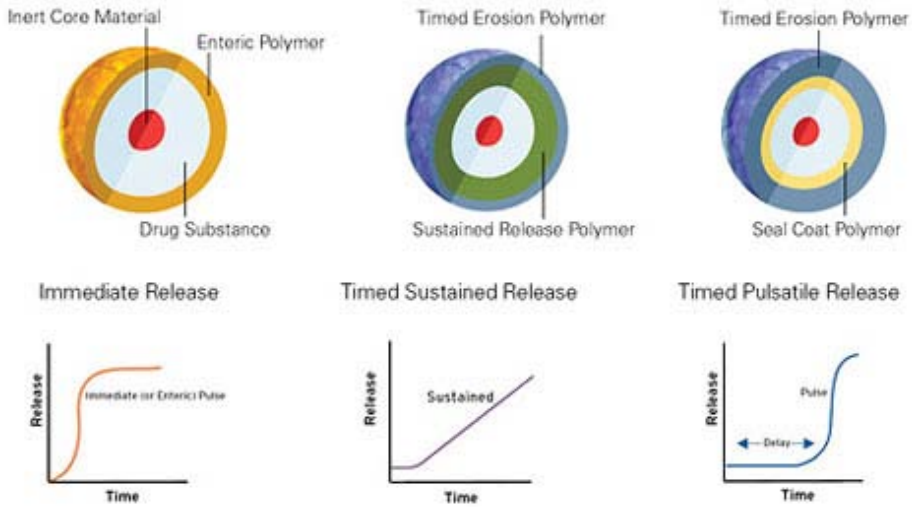

Fig 8: Diffucaps Technology

The versatility of the Diffucaps system helps in simple modification of the release profile and dosing strength to attain targeted in vivo results. For drug development partners concerned in clinical testing, this versatility simplifies dose-ranging studies since the beads can be encapsulated individually to create separate study arms. Aptalis Pharmaceutical Technologies' Diffucaps technology is now used in many currently marketed products and in novel products in clinical development.

Advantages of CR Diffucaps® Drug Delivery Systems

Controlled-release drug delivery systems consisting of coated multiparticulates, particularly based on *Diffucaps*® technology, which typically have a particle size in the range of 200-600 µm, exhibit characteristic target *in vitro* profiles, as well as target plasma concentration time profiles to be suitable for a once-daily dosing regimen. Multiparticulate drug delivery systems, such as *Diffucaps*®, offer the following advantages over conventional controlled-release monolithic dosage forms such as matrix or coated tablets including osmotic delivery systems:

- Dispersed along the GI Tract for more effective delivery
- Predictable and consistent GI transit time thereby minimising food effect
- Low probability of dose dumping
- Reduced inter- and intra-subject variability

- Easy adjustment of multiple dose strengths

In addition, the *Diffucaps*® technology offers incremental advantages:

- Easy adjustment of target plasma profiles including combining bead populations exhibiting differing release profiles
- Ability to make combination products of incompatible actives or actives requiring differing target plasma profiles
- Capability to create micro-environments:

Create a sustainable acidic pH micro-environment in coated bead to solubilise the weakly basic drug (which is practically insoluble at pH 6.0 or above) in order to extend its release into the GI tract

Create a sustainable alkaline pH microenvironment inside coated bead to moderate the solubility of a weakly basic drug (which is extremely soluble in the entire physiologically relevant pH range of 1.0 to 8.0) to avoid dose dumping

- Improve patient adherence due to reduced frequency of dosing, ease of oral administration, reduction in incidence of adverse events, and/ or improved safety profile
- Additional product patent protection
  - **Marketed preparation**
  - Innopran® XL Tablets Verapamil HCl[4]
  - Zofran® Tablets Ondansetron HCl dihydrate

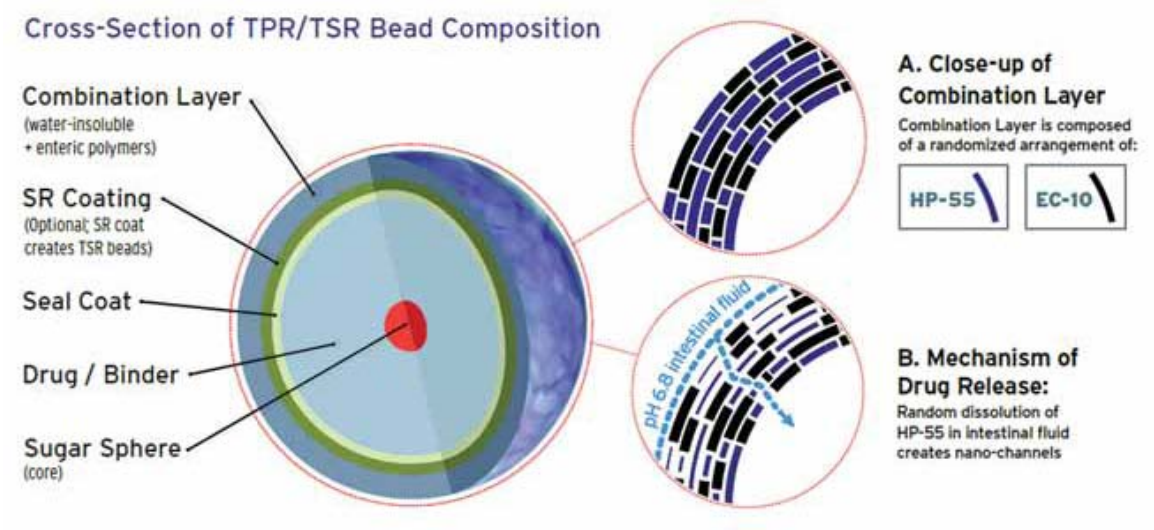

Fig. 9: Diffucaps®– Customised Drug Release Bead

CONCLUSION

Now days, there is urge for dosage forms with pulsatile drug release because of circadian rhythm have been extensively responsible for many of diseases which leads to inventing drug delivery systems adjusted to patients requirements in terms of therapeutic efficacy as well as compliance. Novel multiparticulate technologies having the smart formulations specially suited to satisfy these needs. But lack of manufacturing reproducibility and efficacy and large number of manufacturing reproducibility and efficacy also large number of manufacturing variables due to multiple formulation steps still limits the number of marketed products of these kinds. Still increase in technological advancement and better design parameters these hurdles can be overcome in near future.

REFERENCES

1. Dr Gurvinder Singh Rekhi. advances in solid dose oral drug delivery. Frederick Furness Publishing 2010.
2. Parul B. Patel, Avinash S. Dhake. Multiparticulate approach: an emerging trend in colon specific drug delivery for Chronotherapy. Journal of Applied Pharmaceutical Science 01 (05); 2011: 59-63.
3. Laila F. A.A., Chandran S. Multiparticulate Formulation approach to colon specific drug delivery current perspectives. J. Pharm Pharm Sci, 2006, 9(3): 327-338.
4. Pallab Roy a, Aliasgar Shahiwala. Multiparticulate formulation approach to pulsatile drug delivery: Current perspectives. Journal of Controlled Release 134 (2009) 74–80.
5. NS Dey, S Majumdar, MEB Rao. Multiparticulate Drug Delivery Systems for Controlled Release. Trop J Pharm Res, September 2008.
6. Shaji J., Chadawar V.,Talwalkar P. Multiparticulate Drug Delivery System. The Indian Pharmacist, June 2007, 6(60): 21-28.
7. Dvane, John G, Stark, Paul, Fanning, Niall MM. Multiparticulate modified release composition. US Patent No. 4863742 2009.
8. Ueda Y, Hata T, Yamaguchi H, Kotani M, Ueda S. Development of a novel drug release system, time-controlled explosion system (TES). Part 1: concept and design. J Drug Targeting 1994; 2: 35-44.
9. Devane, john G. Sark, Paul, fanning, Niall M.M. Multiparticulate modified release composition. US Patent 6228398.
10. Programmable oral drug absorption system, Elan Corporation, U.S.Patent 75283262, Jun27, 2000.
11. Multiparticulate crystalline drug compositions having controlled release profiles. United States Patent 20050181062, www.freepatentsonline.com.
12. US Patent 6,110,494, Article Butler. Pharm. Tech. 1998, 22(3), 122-138.
13. White WB, Mehrotra DV, Black HR, Fakouhi TD. Effects of controlled onset extended release Verapamil on nocturnal blood pressure (dippers versus nondipprs)-verapamil study group. Am J Cardiol 1997; 80:469-474.
14. 14 Murugesh Shivashankar, Dhandayuthapani Mani. A Brief Overview of Diabetes. Int J Pharm Pharm Sci, Vol 3, Suppl 4, 22-27
15. G. Venkatesh, “Diffucaps® technology for controlled release drug delivery”, In. Chronotherapeutics”. B.-B.C.Youan (Ed.), John Wiley & Sons, New York (2009) 121-144.
16. Theeuwes F. Push pull OROS system technology. Pharma Tech. 1984; 259.

17. Elan drug technology -CODAS® Technology: http://www.elandrugtechnologies.com/oral_controlled release/codas
18. Shidhaye S.S., Lotlikar V.M., Ghule A.M., Phutane P.K., Kadam V.J. Pulsatile delivery system: An approach for Chronotherapeutic diseases. Sys Rev Pharm. 2010; 1(1): 55-61.
19. Lida E. Kalantzi. Recent Advances in Oral Pulsatile Drug Delivery, Bentham Science Publishers Ltd 2009.
20. Divya .A, K. Kavitha, M. Rupesh Kumar, Dakshayani S, Jagadeesh Singh SD. Bilayer tablet technology: An overview. Journal of Applied Pharmaceutical Science 01 (08); 2011: 43-47
21. Sadhna Khatry, Sirish, Nalini Shastri, Sadanandam.M. Novel drug delivery systems for antifungal therapy. Int j pharm pharm sci, vol 2, issue 4, 6-9.
22. Diffucaps in multiparticulate drug delivery, Eurand S.P.A. Corporation, U.S. Patent 72329344, Feb29, 1972.