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Review Article

A REVIEW ON EXTENDED RELEASE DOSAGE FORM OF NSAIDS USED IN COLON TARGETED DRUG DELIVERY

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ABSTRACT

The oral route plays an important role in the administration of drugs. It is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorb from these regions of the GIT depends upon the physicochemical properties of the drug, pharmaceutics factors and the patients related factors etc. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. Dosage forms that deliver drugs into the colon rather than upper GIT prefers number of advantages. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Crohn's disease, carcinomas and infections) where by high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption.

Keywords: Extended Release dosage form, NSAIDS, Colon Targeted Drug Delivery

INTRODUCTION

The oral route plays an important role in the administration of drugs. It is considered to be most convenient for administration of drugs to patients. Oral administration of conventional dosage forms normally dissolves in the stomach fluid or intestinal fluid and absorb from these regions of the GIT depends upon the physicochemical properties of the drug, pharmaceutics factors and the patients related factors etc. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions

where a drug needs to be protected from the hostile environment of upper GIT. Dosage forms that deliver drugs into the colon rather than upper GIT prefers number of advantages. Oral delivery of drugs to the colon is valuable in the treatment of diseases of colon (ulcerative colitis, Crohn's disease, carcinomas and infections) where by high local concentration can be achieved while minimizing side effects that occur because of release of drugs in the upper GIT or unnecessary systemic absorption.

Anatomy and Physiology of colon

The colon forms the lower part of the gastrointestinal tract and extends from ileoceaclal junction to the anus divided in to three parts colon, rectum and anal–canal. The colon is made up of caecum, the ascending colon, the hepatic flexure, the transverse colon, the splenic flexure, the descending colon, and the sigmoid colon. It is about 1.5 m long. The transverse colon is the lowest and the most mobile part with average diameter of about 65 cm. However, it varies in diameter from approx. 9.0. cm. in caecum to 2 cm in sigmoid colon. Unlike the small intestine, the colon does not have any villi but due the presence of plicaesemilunares, which are cresentic folds, the intestinal surface of the colon is increased to 1300 $c.m^2$. The wall of colon is made of 4 layers, serosa, muscularisexterna, sub mucosa, mucosa. The serosa is the exterior coat of the large intestine and consists of arioler tissue i.e. covered by single layer of squamous mesothelial cells. Muscularisexterna is the major coat of the large intestine and is composed of an inner cerculer layer of fiber that surrounds the bowel and of the outer longitudinal layer. The submucosa is the layer of connective tissue that lies immediately beneath the mucosa. The mucosa is divided in to epithelium, lamina propria and muscularis mucosae. The muscularis mucosae consist of a layer of smooth muscle and separate the mucosa from the lamina propria.

Functions of colon

The colon serves four main functions, such as:

1. Creation of a suitable environment for the growth of colonic microorganism such as Bacteriods, Eubacterium, Enterobacteriaceae.
2. Storage reservoir of fecal contents.
3. Expulsion of the contents of the colon at a suitable time.
4. Absorption of water and electrolytes from the lumen, concentrating the fecal contents and secretion of K^+ and HCO_3^-.

Extended Release Dosage Forms

Extended release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing drug over an extended period of time after administration of a single dose. Extended release dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate release dosage forms. The release can be a zero-order, first-order or

biphasic release. The term controlled release, prolonged action, and sustained releases are used synonymously with extended release. USP uses the term to describe a formulation that does not release active substance immediately after oral dosing and that also allow a reduction in dosing frequency. Since the release from a controlled release dosage form is dependent on release of drug from dosage form therefore the drug release pattern is more uniform and approaches the desired zero order release rate, in contrast to the conventional immediate release formulations where drug release is more fluctuating and is need for frequent dosing to maintain the desired drug level in the body. Some drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. When conventional immediate release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys associated with the taking of each dose. However, when doses are not administered on schedule, the resulting peaks and valley reflect less than optimum drug therapy.

It is desirable to maintain a therapeutic blood concentration in order to achieve the desirable pharmacological effects. To maintain a narrow range of therapeutic blood concentration it is desirable to have a dosage form that can deliver the drug in a more sustainable or controlled way to achieve the desired results. Extended release tablets and capsules are commonly taken once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended release products provide an immediate release of drugs that promptly produces the desired therapeutic effect, followed by gradual release of additional amount of drugs to maintain this effect over a predetermined period. The sustained plasma drug levels provided by extended release products often eliminate the need for night dosing, which benefits not only the patient but the patient but the caregiver as well.

Characteristics that make a drug suitable for Extended Release formulation:

- **Drug is administered in relatively small doses:**

The need for large single doses would lead to dosage units too large for the patient to swallow.

- **The drug doesn't exhibit a very slow rate of elimination:**

A drug with a slow rate of elimination has a long elimination half-life and hence is naturally long acting. Therefore, extended release forms are not necessary. A drug with elimination half-life of 2-4 hrs is ideal.

- **The drug possesses a good margin of safety:**

Dose dumping such as with patient misuse (e.g. chewing of tablet) can result in high drug levels that make toxic.

- **Drug is used in treatment of chronic conditions:**

To ensure patient adherence prescribed regimens, an extended release form is taken once/twice daily. This is convenient for patients who require long term treatment for chronic conditions.

- **The drug has appropriate molecular size, good solubility and lipophilicity**:

The drug should be absorbed by passive diffusion and the absorption should not be dependent on drug solubility.

Factors Influencing the Design and Performance of extended Release dosage forms

Drug Properties

The physicochemical properties of a drug include stability, solubility, partitioning characteristics, charge and protein binding; play a dominant role in the design and performance of controlled release systems. The design of controlled release delivery system is subject to several variables of considerable importance. Among these are the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy, and the properties of the drug. Each of these variables is interrelated, and this imposes certain constraints upon choices of route of delivery, the design of delivery system, and the length of therapy.

Partition coefficient:

Ideally, the release of an ionisable drug from a controlled release system should be programmed in accordance with the variation in pH of the different segments of gastrointestinal tract so that the amount of preferentially absorbed species and thus the plasma level of drug will be approximately constant throughout the, time course of drug action. Between the time that a drug is administered and the time it is eliminated from the body it must diffuse through a variety of biological membranes that act primarily as a lipid like barrier. A major criterion in evaluation of a drug to penetrate these lipid membranes is its apparent oil/water partition coefficient (K), defined as:

$$K = Co/Cw \quad - (1)$$

Where, Co is the equilibrium concentration of all forms of the drug, e.g., ionized and unionized, in an organic phase at equilibrium, and Cw is the equilibrium concentration of all forms in aqueous phase. In general, drugs with extremely large values of K are very oil soluble and will partition into membranes quite readily. The more effectively a drug crosses membrane the greater its activity.

Drug stability:

Drug stability of importance for oral dosage forms is the loss of drug through acid hydrolysis and/or metabolism in the GI tract. Since a drug undergoes degradation at a much slower rate than a drug in suspension or solution, it would seem to improve significantly the relative bioavailability of a drug that is unstable in the GI tract by placing it in a slowly available controlled release form. For those drugs that are unstable in stomach, the most appropriate controlling unit

would be the one that releases its contents only in the intestine.

Protein binding:

Distribution of a drug into the extra vascular space is governed by equilibrium process of dissociation of drug from the protein. The drug-protein complex can serve therefore as a reservoir in the vascular space for controlled drug release to extravascular tissues, but only for those drugs that exhibit a high degree of binding. Thus the protein binding characteristics of a drug can play a significant role in its therapeutic effect, regardless of the type of dosage form. Extensive binding to plasma proteins will be evidenced by a long half-life of elimination for the drug and such drugs generally do not require a controlled release dosage form.

Molecular size and diffusivity:

A drug must diffuse through a variety of biological membranes, drugs in many controlled release systems must diffuse through a rate controlling membrane or matrix. The ability of a drug to diffuse through membranes, it's so called diffusivity (diffusion coefficient) is a function of its molecular size.

Approaches to achieve extended release dosage forms

1. Reservoir System
2. Osmotic System
3. Matrix System

1. Reservoir Polymeric Systems

A typical reservoir system consist of a core containing solid drug or highly concentrated drug solution surrounded by a film or membrane of a rate controlling material. In this design, the only structure effectively limiting the release of the drug is the polymer layer surrounding the reservoir. Based on Fick's first law of diffusion, one dimensional release rate of a drug from a reservoir system at steady state is given by:

$$dQ/dt = D\ A\ K\ /L \times C$$

Where

- Q is the total amount of drug released at time t
- D is the diffusion coefficient of the drug
- A is effective membrane surface area for drug diffusion
- K is partition coefficient of drug between the barrier membrane and external aqueous phases.
- L is diffusional path length
- C is the drug concentration gradient between the solubility, Cs, in the reservoir and the drug concentration, Ce, in the external aqueous medium.

The membrane coating is essentially uniform in composition and thickness, for a given molecule and system composition, D, A, K, L and ΔC are constant in equation under sink conditions (Cs>>Ce). Thus the amount of drug released as a function of time can be obtained by integration:

$$Qt = D\ A\ K\ \Delta C/L \times t = kt$$

k is the release rate constant. The driving force of such systems is the concentration gradient of active molecules between reservoir and sink. Thus, the drug releases from this type of system follows apparent zero order kinetics until ΔC is no longer constant, due to complete dissolution of solid drug in the core. It is applicable to soluble drugs because the reservoir system relies on ΔC as the driving force for drug diffusion. For insoluble drugs, the values of Cs may be too low to render adequate driving force, resulting in over-attenuated and incomplete drug release.

Drug release from a reservoir system usually varies with pH, unless the solubility of the active is pH-independent. To achieve pH-independent release for drugs with pH-dependent solubility, Cs in the core needs to remain unchanged. Success with Incorporating of buffering agents to maintain constant pH in the core has been reported. In developing oral products based on ER reservoir technology, polymer film coated beads or tablets and microencapsulates (microparticles, microspheres or nanoparticles) are common dosage form presentations. Aqueous dispersions are applied mostly as drug release barrier include Ammoniomethacrylate copolymers (Eudragit RL, 30D, RS30D), Methacrylic ester copolymers (Eudragit, NE30D, polyvinyl acetate aqueous dispersion (kollicoat SR 30D).

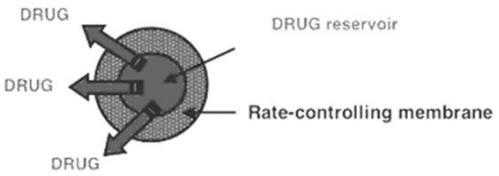

Figure 1: Reservoir drug delivery system

Table 1 – Commercial products based on Reservoir Drug Delivery System

Products	Active ingredient	Manufacturer
Nico-400	Nicotinic acid	Jones
Nitrospan capsules	Nitroglycerin	Rorer
Cerespan capsules	PapaverinHCl	Rorer
Histapan capsules	Chlorpheniramine maleate	Rhone-Poulenc Rorer
Measurin tablets	Acetylsalicylic acid	Sanofi-Winthrop
Bronkodyl capsule	Theophylline	Winthrop

Advantages

- Zero order delivery is possible.
- Release rate variable with polymer type.

Disadvantages

- System must be physically removed from implant sites.

- Difficult to deliver high molecular weight compounds.
- Potential toxicity if system fails.

Osmotic Pump System:

It is similar to a reservoir device, but contains an osmotic agent that acts to imbibe water from surrounding medium via a semipermeable membrane. Such a device called elementary osmotic pump was first described by Higuchi in 1975. The delivery of active agent from the device is controlled by water influx across the semipermeable membrane. The drug is forced out of an orifice in the device by the osmotic pressure generated within the device. The size of the orifice is designed to minimize solute diffusion, while preventing the build-up of hydrostatic pressure head that has the effect of decreasing the osmotic pressure and changing the volume of the device. Drug release from this system is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the property of drug and system. In developing oral products, two types of osmotic pump systems have frequently used, a one-chamber EOP system, e.g., Push-Pull and Push-Stick.

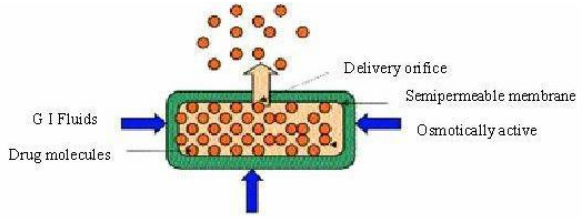

Fig. 2: Representation of Elementary Osmotic Pump

Table 2: List of Commercially Marketed Oral Osmotic Drug Delivery Products

Product name	Drug
Acutrim	Phenylpropranolamine
Alpress	LP Prazosin
Calan SR	Verapamil
Cardura XL	Doxazocinmesylate
Concenta	Methylphenidate
Efidac 24	Pseudoephidrine
Glucotrol XL	Glipizide

Materials used osmotic pump systems: Cellulose acetate is the most commonly used polymer that constitutes the semipermeable membrane of an osmotic pump device. Other polymers used are cellulose butyrate, polyurethane, ethyl cellulose, PEG, PVC, and PVA. Osmotic agents such as sodium chloride are another key ingredient of an osmotic system.

Advantages:

Zero order release rates are obtainable. Reformulation is not required for different drugs. Release of drug is independent on the environment of the system.

Disadvantages:

System can be much more expensive than conventional counterparts. Quality control is more extensive than most conventional tablets.

Matrix Systems:

Historically, the most popular drug delivery systems have been the matrix because of its low cost and ease of fabrication. Methods of altering the kinetics of drug release from the inherent first order behaviour especially to achieve a constant rate of drug release from matrix devices have involved several factors.

Requirements of matrix materials:

- They must be completely inert and non-reactive with the drug and additives in the tablet.
- They must be able to form stable and strong matrices when compressed either directly or more often as granules prepared by the addition of a binding agent.
- They must be non-toxic.

In a matrix system, the drug substance is homogeneously mixed into a rate controlling material and other active ingredients as a crystalline, amorphous or molecular dispersion. Technical advancements in area of matrix formulation made controlled release products development much easier than before and improved upon the flexibility of delivering a wide variety of drugs with different physicochemical and biopharmaceutical properties. Matrix technologies have often proven popular among the oral controlled drug delivery technologies because simplicity, ease of manufacturing, high level of reproducibility, stability of raw materials and dosage form and ease of scale up and process validation. This is reflected by the large number of patents filed each year and by the commercial success of a number of novel drug delivery systems based on matrix technologies. Matrix-based delivery technologies have steadily matured from delivering drugs by first-order or square-root-of-time release kinetics to much more complex and customized release patterns. In order to achieve linear or zero-order release, various strategies that seek to manipulate tablet geometry, polymer variables, and formulation aspects have been applied. Various drug, polymer, and formulation-related factors, which influence the *in situ* formation of a polymeric gel layer/drug depletion zone and its characteristics as a function of time, determine the drug release from matrix systems.

Various mathematical models, ranging from simple empirical or semi-empirical (Higuchi equation, Power law) to more complex mechanistic theories that consider diffusion, swelling, and dissolution processes simultaneously, have been developed to describe the mass transport processes involved in matrix-based drug release.

Non-Steroidal Anti-Inflammatory Drugs

Many people use medications to control pain associated with inflammation. Although steroids are effective for reducing inflammation, they can cause many adverse side effects. As an alternative, patients may choose to use drugs in a class known as non-steroidal anti-inflammatory drugs, or NSAIDs, to treat minor pain and inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed categories of drugs worldwide in the treatment of pain and inflammation in many conditions.NSAIDs are used primarily to treat inflammation, mild to moderate pain,

and fever. Specific uses include the treatment of headaches, arthritis, sports injuries, and menstrual cramps.

Mechanism of action

Prostaglandins are a family of chemicals that are produced by the cells of the body and have several important functions. They promote inflammation, pain, and fever; support the blood clotting function of platelets; and protect the lining of the stomach from the damaging effects of acid. Prostaglandins are produced within the body's cells by the enzyme cyclooxygenase (COX). There are two COX enzymes, COX-1 and COX-2. Both enzymes produce prostaglandins that promote inflammation, pain, and fever. However, only COX-1 produces prostaglandins that support platelets and protect the stomach. Nonsteroidal anti-inflammatory drugs (NSAIDs) block the COX enzymes and reduce prostaglandins throughout the body. As a consequence, ongoing inflammation, pain, and fever are reduced. Since the prostaglandins that protect the stomach and support platelets and blood clotting also are reduced, NSAIDs can cause ulcers in the stomach and promote bleeding.

All non-steroidal anti-inflammatory drugs including diclofenac sodium work by inhibiting cyclooxygenase, the enzymes responsible for synthesizing prostaglandins and compounds that cause inflammation, pain and fever. Although available without a prescription, the use of NSAIDs can cause unwanted adverse effects. However, when used appropriately, NSAIDs are an appropriate treatment option for minor inflammation and pain, especially in musculoskeletal injuries, the Cleveland Clinic says.

NSAIDs are used in following conditions:

NSAIDs are used primarily to treat inflammation, mild to moderate pain, and fever. Specific uses include the treatment of headaches, arthritis, sports injuries, and menstrual cramps. Ketorolac (Toradol) is only used for short-term treatment of moderately severe acute pain that otherwise would be treated with opioids. Aspirin (also an NSAID) is used to inhibit the clotting of blood and prevent strokes and heart attacks in individuals at high risk. NSAIDs also are included in many cold and allergy preparations.

Methods of preparation

Extended Release Tablets were prepared by two methods, Direct compression and Wet granulation.

Direct compression:

- Required amount of all ingredients were weighed accurately according to formula.
- Ingredients were sifted through BSS #30 further lubricated with lubricants and glidants which were sifted through BSS #44 and then thoroughly mixed for 10 min.
- Finally powder mixture was directly compressed into tablets using a 16 station compression machine equipped with round

and standard concave tooling of 8.6mm diameter.

Wet granulation:

In this method following steps were followed:

- Intragranular and Extragranular ingredients were dispensed according to formula.
- Intragranular ingredients were moistened with ethanol (30ml) and kneaded continuously until the subjective end point of suitable consistency was attained.
- The wet granulations were placed in aluminium foil trays and these were dried in a hot air oven at 60 °C until a moisture content of 0.5-2% was achieved.
- The dry granules were milled using BSS #30 and lubricated with magnesium stearate and talc sifted from BSS #44.

The granulations were compressed into tablets using a compression machine equipped with round and standard concave tooling.

Evaluation of Tablets:

The tablets were evaluated for following parameters.

Weight variation test:

Weight variation of the formulation will perform as per USP 32. 20 tablets will weighed using a electronic balance individually and compared with the average weight of the twenty tablets.

Hardness: The hardness of five tablets will determine using any type hardness tester and the average values were calculated.

Thickness:

The Thickness of the tablets will determine by using Digital verniercalliper. Five tablets will use, and average values will be calculated.

Friability:

The friability of the tablets will measure in a Roche friabilator. Tablets of a known weight (W_0) or a sample of tablets will dedust in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability is calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1% w/w.

% Friability = (W0-W)/W0 × 100

Drug content (Assay):

Drug content is determined by taking an accurately weight amount of powdered drug with suitable medium of proper pH and solution is filtered through 0.45µm nylon filter. The absorbance is measured, using double beam UV visible spectrophotometer.

Assay = Test Absorbance/ Standard Absorbance×100

***In-Vitro* Drug Release Study:**

Dissolution studies are conducted to determine the release pattern of the product. Dissolution test for the drug is carried out as per USP method for dissolution test for tablets using apparatus-II.

The volume of the dissolution medium is 900 ml with rotating the paddle at 50 rpm with temperature 37°C ± 0.5°C. An aliquot of 5ml of samples are withdrawn at different time periods (1, 2, 4, 6, 8, 12, 16, 20, 24 hrs.). The samples are filtered through nylon filters, suitably diluted and analysed at suitable

λmaxusing double beam UV/Visible spectrophotometer. The content of drug was calculated using equation generated from standard calibration curve. The dissolution study is continued for 24hours to get a stimulated picture if drug released *in vivo* condition. The drug release profiles obtained are fitted into several mathematical models and drug release mechanism is determined from the matrix tablet.

Dissolution testing has emerged as a highly valuable in-vitro test to characterize the performance of a dosage form .The popularity of dissolution testing is based on the fact that solubilisation of a drug in gastrointestinal fluid is a prerequisite for the drug to be absorbed and available to the systemic circulation .The dissolution testing is performed as a relatively fast and inexpensive technique to evaluate pharmaceutical dosage forms before they are tested in clinical trials. It is prudent to have extensive dissolution data to maximize the chances for success in bioavailability testing in humans.

Application of Dissolution

Dissolution testing can be used to:

- to detect the influence of critical formulation and manufacturing variables in formulation and development and research and development
- to assist in selection of a best formulation
- to check the changes during stability studies;
- to establish final dissolution specifications for the pharmaceutical dosage form ;
- to develop IVIVC
- as a quality control tool
- To establish the similarity of pharmaceutical dosage forms.

Modelling of dissolution profile

In vitro dissolution has been recognized as an important release element in drug development. Under certain conditions it can be used as a surrogate for the assessment of bioequivalence. The quantitative interpretation of the values obtained in the dissolution assay is facilitated the usage of a generic equation that mathematically translates the dissolution curve in function of some parameters related with the pharmaceutical dosage forms. In some cases, that equation can be deduced by a theoretical analysis of the process, as for example in zero order kinetics.

In most cases, with tablets, capsules, coated forms or prolonged release forms that theoretical fundamental does not exist and sometimes a more adequate empirical equation is used. To compare dissolution profiles between two drug products model dependent (curve fitting), statistic analysis and model independent methods can be used.

Conclusion

The colonic region of the GIT has become an increasingly important site for drug delivery and absorption. CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. Colon

specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. Considering the sophistication of colon-specific drug delivery systems, and the uncertainty of current dissolution methods in establishing possible in-vitro/in-vivo correlation, challenges remain for pharmaceutical scientists to develop and validate a dissolution method that incorporates the physiological features of the colon, and yet can be used routinely in an industry setting for the evaluation of CDDS.

From the above discussion, it concludes that the extended release dosage form are drug delivery system which by virtue of formulation and product design, provide drug release in a modified form distinct from that of the conventional dosage forms. Drug release can either be delayed or extended in nature. It is effective tool for drugs that are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic effects; when compared to conventional dosage form it provides improved patient compliance. This concept, however, requires accurate adjustment of the physicochemical parameters of core material, coating formulation and tableting excipients. Many drugs are formulated as sustained release dosage form to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug. Hence, extended release drug delivery system is the preferred dosage form for the drugs having short half-life, so as to maintain the drug plasma level in therapeutic index for prolonged period of time.

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