ejpmr, 2023,10(4), 76-80

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW OF ORALLY FAST DISSOLVING FILM OF D2 RECEPTOR ANTAGONIST

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Article Received on 08/02/2023 **Article Revised on 28/02/2023** **Article Accepted on 20/03/2023**

ABSTRACT

The objective of the resent work was to formulate fast dissolving film of D_2 receptor antagonist so as to achieve higher oral bioavailability by minimizing the first pass metabolism and to enhance the compliance by elderly and pediatric patients. D_2 receptor antagonist being water insoluble drug pose a challenge in formulating fast dissolving film. So, in order to enhance the solubility solid dispersion were prepared using β-Cyclodextrin as carrier. The physical mixture and solid dispersion by kneading in the molar ratio 1:1, 1:2 and 1:3 of D_2 receptor antagonist and β-Cyclodextrin were prepare and evaluated for drug content, %yield and in vitro drug release.For preparing film, initially trial batches were prepared utilizing HPMC E3, E5 and E15 LV and pulllulan as film forming polymers and PEG 400 as plasticizer. Based on the trial batchesthe best film forming agent was selected. Optimization of films were done by factorial design taking concentration of polymer and PEG 400 as dependent variable and tensile strength, %elongation, elastic modulus, disintegration time and drug release at 2 min were taken as dependent variables. Polynominal equation were derived and validity of equation was checked by preparing and evaluating chek point batches. Surface plots were constructed and desdirability of the film was calculated and based on it optimized batch for both plain drug and solid dispersion film was determined. Mechanical properties and drug release was compared between the two films and based on it the best film was finally selected.

KEYWORDS: Fast dissolving film, β-Cyclodextrin, Solid dispersion, Factorial design.

INTRODUCTION

A route of administration in pharmacology and toxicology is the path by which a drug, fluid, poison, or other substance is taken into the body.[1] Routes of administration are generally classified by the location at which the substance is applied. Common examples include oral and intravenous administration. Routes can also be classified based on where the target of action is. Action may be topical (local), enteral (system-wide effect, but delivered through the gastrointestinal tract), or parenteral (systemic action, but delivered by routes other than the GI tract). Routes of administration are usually classified by application location (or exposition). The route or course the active substance takes from application location to the location where it has its target effect is usually rather a matter of pharmacokinetics (concerning the processes of uptake, distribution, and elimination of drugs). Nevertheless, some routes, especially the transdermal or transmucosal routes, are commonly referred to routes of administration. The location of the target effect of active substances are usually rather a matter of pharmacodynamics (concerning e.g. the physiological effects of drugs[2]). Furthermore, there is also a classification of routes of administration that basically distinguishes whether the effect is local (in "topical" administration) or systemic (in "enteral" or "parenteral" administration).

Oral administration (*per os*) is a route of administration where a substance is taken through the mouth. Many medications are taken orally because they are intended to have a systemic effect, reaching different parts of the body via the bloodstream, for example.[1]

Oral administration is a part of enteral administration, which also includes

- Buccal (dissolved inside the cheek)
- Sublabial (dissolved under the lip) and
- Sublingual Administration (dissolved under the tongue). Note that due to rapid absorption many consider SL a parenteral route.

Enteral medications come in various forms, including[1]

- Tablets to swallow, chew or dissolve in water or under the tongue
- Capsules and chewable capsules (with a coating that dissolves in the stomach or bowel to release the medication there)
- Time-release or sustained-release tablets and capsules (which release the medication gradually)
- Powders or granules
- Teas

- Drops
- Liquid medications or syrups.

Recent trends in Pharmaceutical formulation development technology have presented viable dosage alternatives for patients who may have difficulty swallowing tablets or liquids. Traditional tablets and capsules administered with an 8-oz. (One glass) of water may be inconvenient or impractical for some patients. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking. For example, a very elderly patient may not be able to swallow a daily dose of antidepressant in the form of a Caplet shaped Tablet. An eight-year-old with allergies could use a more convenient dosage form than antihistamine syrup. A schizophrenic patient in the institutional setting can hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic. A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker. Fast-dissolving tablets (FDTs) / Orally disintegrating tablets (ODTs) are a perfect fit for all of these patients. Fast-dissolving drug delivery systems have rapidly gained acceptance as an important new way of administering drugs. There are multiple fast-dissolving OTC and Rx products on the market worldwide, most of which have been launched in the past 3 to 4 years. There have also been significant increases in the number of new chemical entities under development using a fast-dissolving drug delivery technology.

The Center for Drug Evaluation and Research (CDER), US FDA defined Oral Disintegrating Tablets (ODT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue."

FDTs disintegrate and/or dissolve rapidly in the saliva without the need for water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity, and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. When put on tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. Their growing importance was underlined recently when European Pharmacopoeia adopted the term **"Orodispersible Tablet"** as a tablet that to be placed in oral cavity where it disperses rapidly before swallowing.

Salient Features of Fast Dissolving Drug Delivery System

- Ease of administration for patients who are mentally ill, disabled and uncooperative.
- Quick disintegration and dissolution of the dosage form.
- Overcomes unacceptable taste of the drugs.
- Can be designed to leave minimal or no residue in the mouth after administration and also to provide a pleasant mouth feel.
- Ability to provide advantages of liquid medication in the form of solid preparation. Adaptable and amenable to existing processing and packaging machinery.

Significance of Oral Disintegrating Tablets

Oral Disintegrating Tablets offer dual advantages of solid dosage forms and liquid dosage forms along with special features which include

1. Accurate dosing

Being unit solid dosage forms, provide luxury of accurate dosing, easy Portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.

2. Enhanced bioavailability

Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and esophagus.

3. Rapid action

Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in oral cavity.

4. Patient compliance

No need of water to swallow the dosage form. Hence, it is convenient for patients who are traveling and do not have immediate access to water.

5. Ease of administration

Convenient to administer specially for geriatric, pediatric, mentally disabled and bed ridden patients who have difficulty in swallowing.

6. Obstruction free

No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.

7. Enhanced palatability

Good mouths feel, especially for pediatric patients as taste masking technique is used to avoid the bitter taste of drug.

8. Simplepackaging

No specific packaging required. It can be packaged in push through blisters.

9. Business avenue

Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.

10. Cost effective

Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.

Characteristics of Fast Dissolving Delivery Systems

1. Ease of administration

Fast Dissolving Delivery Systems are easy to administer and handle hence, leads to better patient compliance. Usually, elderly people experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphasia.

2. Taste of the medicament

As most drugs are unpalatable, mouth dissolving delivery systems usually contain the medicament in taste masked form. Delivery systems dissolve or disintegrate in patient's mouth, thus releasing the active ingredients which come in contact with the taste buds and hence, taste masking of the drugs becomes critical to patient compliance.

3. Hygroscopicity

Several fast dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal condition from humidity which calls for specialized product packaging.

4. Friability

In order to allow fast dissolving tablets to dissolve in the mouth, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle which are difficult to handle, often requiring specialized peel-off blister packaging.

5. Mouth feel

Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a product.

METHODS

Preparation of film

The major problem in the preparation of fast dissolving film is its water solubility. Domperidone has water solubility

- Solvent casting
- Semisolid casting
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling

1. Solvent casting method

In solvent casting method water solublepolymers are dissolved in water and the drug along with other Excipients is dissolved in suitable solvent then both the solutions are mixed and stirred and finally casted in to the Petri plate and dried.

2. Semisolid casting

In semisolid casting method firstly a solution of watersoluble film forming polymer is prepared. The resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. Then appropriate amount of plasticizer is added so that a gel mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be be 1:4.

3. Hot melt extrusion

- In hot melt extrusion method firstly the drug is mixed with carriers in solid form. Then the extruder having heaters melts the mixture. Finally the melt is shaped in to films by the dies. There are certain benefits of hot melt extrusion.
- Fewer operation units
- Better content uniformity
- An anhydrous process

4. Solid dispersion extrusion

In this method immiscible components are extrude with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

5. Rolling Method

In rolling method a solution or suspension containing drug is rolled on a carrier. The solvent is mainly water and mixture of water and alcohol. The film is dried on the rollers and cutted in to desired shapes and sizes. Other ingredients including active agents dissolved in small portion of aqueous solvent using high shear processor Water soluble hydrocolloids dissolved in water to form homogenous viscous solution.

The solvent casting method was used for the preparation of the films. The required amount of filmforming polymer was allowed to hydrate in 7 ml of distilled water for about 1-2 hrs and then uniformly dispersed to get clear solution of film forming polymer. After that the required amount of plasticizer was added to the film forming solution.

Other ingredient including drug or solid dispersion of Domperidone and Beta-cyclodextrine were dispersed in

3 ml of distilled water. Both the solution were kept in bath sonicator for 1 hr so as to remove the entrapped ir and also to micronized the drug solid dispersion particles.

Both the solution were then mixed and casted in a glass peridish (50.28 cm^2) and was dried at room temperature. The glass petridishes were put on the leveled surface during drying to avoid variationin the thickness. The film took approximetly 24 hrs to dry at room temperature. The dried film was carefully removed from the petridish and was cut into size required for testing. The films were stored in airtight plastic bags till further use.

Evaluatiom Parameters

(1) Identification of drug

- **FTIR**

Drug may Domperidone

KBr discs were prepared by grindingdifferent sample (2mg) each with KBr (200mg) and then compressing the whole into discsusing hydraulic press.Finally, the disk wasinserted into the IR sample holder. Then run the spectrum.

(2) Spectorophotometric Analysis of Domperidone

Drug may Domperidone

The absorbance at both 458 and 495 nm was approximately identical but 458 nm was selected, because of low blank absorbance. In method yellow colour complex peaking at multi wavelengths but 394 nm was chosen as it gives highest absorbance and more intensive colour

(3) Drug- Excipient compatibility study

FTIR Drug may Domperidone

FTIR spectrum of pure drug domperidone. FTIR studies showed no evidence of interaction between the drug and expients. Enhancement of dissolution characteristics of poorly soluble drug Domperidone is being explored in current study.

DSC Drug may Domperidone

The drug-excipients compatibility study was carried out by Differential Scanning Calorimetry (DSC) which reveals no interaction between drug and excipients.

(4) Solubility enhancement of Domperidone by solid dispersion technique

- **Preliminary study for selection of carriers**

The studies indicated that the dissolution of drug and stability of solid dispersion was improved. Solubility studies of DMP with various hydrophilic carriers including sorbitol, mannitol, PEG In the present work, DMP was solubilized using solid excipients.

- **Selection of suitable carrier based on phase solubility study**

Based on the considerable good solubility as compared to the other and the carrier. Based on obtaining data from the solubility study of domperidone with excipients.

(5) Evaluation of solid dispersion of Domperidone

- **Estimation of drug content in prepared Solid dispersions**

Solid dispersion is molecular dispersion of drug in a polymer matrix which leads to Solvent evaporation technique and other was employed to prepare films of different. The solid solution/dispersion was evaluated for drug content, purity, solid state and water-soluble drugs by solubility parameter calculation and thermal analysis

- **Percentage Yield**

Percent yield is the percent ratio of actual yield to the theoretical yield. It is calculated to be the experimental yield divided by theoretical yield multiplied by 100%. It's possible for percent yield to be over 100%, which means more sample was recovered from a reaction than predicted.

- **In- Vitro dissolution study**

Dissolution testing is an in vitro method that characterizes how an API is extracted out of a solid dosage form. The dissolution test is an empirical in-vitro test used to quantify the dissolution rate of an active pharmaceutical ingredient (API) from a dosage form into solution.

(6) Characterization of optimized solid dispersion of Domperidone

- **FTIR**

Fourier-transform infrared spectroscopy (FTIR) is a technique used to obtain an infrared spectrum of absorption or emission of a solid, liquid or gas. An FTIR spectrometer simultaneously collects high-spectral-resolution data over a wide spectral range.

- **DSC**

Differential scanning calorimetry (DSC) is a thermoanalytical technique in which the difference in the amount of heat required to increase the temperature of a sample and reference is measured as a function of temperature.

- **X-ray Diffraction Study**

X-ray diffraction (XRD) is a technique used in materials science for determining the atomic and molecular structure of a material. This is done by irradiating a sample of the material with incident X-rays and then measuring the intensities and scattering angles of the X-rays that are scattered by the material.

CONCLUSION

The aim of present work was to formulate and evaluate fast dissolving film of D_2 receptor antagonist. Advances in technology have led to the utilization of various newer

routes of drug delivery which includes transdermal, nasal, injectable and various other routes of administration. Despite of all this oral route of drug delivery especially tablet remains still the most preferred delivery route. Oral dosage forms included tablets, capsules and liquid preparation which are meant to be taken orally and that transit throught the GIT for postbuccal absorption. However, some patient, particularly pediatric and gediatric patients are unwilling to take these solid preparation due to fear of chocking.

Desirability function was employed to select an optimized batch. The batch that had desirability value near to one was considered to be optimized. The polynominal equation showing relationship between formulation variables and each response were derived. Two check point batches namely for the film with D_2 receptor antagonist and the film with solid dispersion were prepared in order to check validity of the derived polynominal equation. The value of each response predicted by this equation was found to be good agreement with obtained experimental values of each response. Surface plots showing relationship between independent variables and responses were prepared. The surface plot and polynominal equation indicate that increase amount of pullulan result in increase in tensile strength, % elongation, elastic moduls and disintegration time but decrease in the drug release. In the same way, the surface plot and polynominal equation also showed that drug release increase while tensile strength and elastic modulus decrease.

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