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Designing of Sustained Release Formulations and Evaluation of Coating Thickness on Release Pattern.

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ABSTRACT

The development of sustained-release (SR) formulations has become a significant area of research in pharmaceutical sciences, aiming to improve drug efficacy, patient compliance, and therapeutic outcomes. Sustained-release systems are designed to release a drug at a predetermined rate, maintaining its therapeutic concentration in the bloodstream for an extended period. Coating of drug particles or dosage forms is a widely used technique to control drug release. The thickness of the coating plays a crucial role in modulating the release rate by acting as a diffusion barrier HPMC E15, a blend of hydrophobic and hydrophilic polymers, was employed as a coating material to regulate the release of Domperidone, a highly water-soluble medication. At pH 6.8, drug release patterns varied depending on the polymer mixes used. The study examined drug diffusion via plasticized Surelease®/Hydroxypropyl methylcellulose (HPMC E15) films made by coating non-pareil seeds with medication and polymers using solution layering method. Coating the pellets with more polymer reduced Domperidone release. The formulation was optimized using 32 complete factorial designs. The optimal formulation exhibits zero-order release kinetics, as evidenced by the release profile. Domperidone is often used to treat gastrointestinal problems, including GERD and peptic ulcers. Domperidone short half-life causes poor compliance and unpleasant responses. Therefore, a sustained release dosage form is necessary for greater therapeutic benefits and improved patient compliance. Domperidone sustained release pills were made from several polymers, including HPMC K100LV, HPC K100M, and EC22. Tablets were evaluated for physical parameters, including weight variation, hardness, thickness, friability, and drug content, using an electronic balance, Monsanto tester, Vernier caliper, Erweka friabilator, and UV/Visible spectrophotometer.

Keywords- Pellets, Nonpareil seeds, Surelease®HPMCE15, Coating,Solution layering technique.

INTRODUCTION

Developing oral sustained release systems for readily water soluble medicines with strong first pass metabolism has been a problem for pharmaceutical technologists. Improper formulation of highly water-soluble medicines can lead to rapid release and toxicity. Lian-Dong, Yang, Xing, & Qian(2006) found that oral administration may result in hazardous concentrations. Polymeric film coatings are commonly utilized in pharmaceutical formulations to achieve sustained and accurate drug release with high repeatability (Sousa, Sousa, Moura, Newton, 2002; Vaithiya lingam, Khan, 2002). Ethyl cellulose (Surelease®) is a popular hydrophobic polymer for pharmaceutical film coating due to its easy formability, excellent physiochemical characteristics, and low toxicity.

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Domperidone, a synthetic benzimidazole molecule similar to butyric phenones, is commonly used to treat gastrointestinal diseases such GERD and peptic ulcers. Domperidone does not pass the blood-brain barrier (BBB), lowering central nervous system and extra pyramidal adverse effects seen with other dopamine antagonists (Smit et al., 2002). Dopamine regulates gastric emptying by relaxing the stomach and reducing its motility (Weihrauch et al., 1979; Friedman et al., 1983). However, because to the short half— life. The recommended dose for Domperidone is 10mg, 3-4 times per day, which might lead to poor compliance and severe effects. To ensure patient compliance, Domperidone should be formulated in sustained-release dose forms. Sustained release technologies are necessary because to the high cost and limited patient compliance with traditional dosing forms. The oral route is the most often utilized method for medication delivery. Oral dose forms aim to achieve systemic effects via medication absorption in the gastrointestinal tract (Aulton, 1988). The oral route is the most effective way to administer drugs since it allows for precise dosage control.

To improve the pharmacokinetics of PPIs, drug formulations often include a combination of sustained- release (SR) and immediate-release (IR) components. This approachis designed to achieve both rapid onset for immediate relief of symptoms and extended therapeutic effects over time. Coating technologies are critical in controlling there lease profile of such dosage forms, and coating uniformity plays a pivotal role in ensuring predictable and consistent drug release.

Among the various formulation approaches, sustained and immediate release systems have gained significant attention for PPIs. Sustained release formulations provide a prolonged therapeutic effect by maintaining steady plasma concentrations, reducing dosing frequency, and improving patient compliance. Conversely, immediate release systems are designed to rapidly increase drug concentration in the bloodstream, offering fast relief from symptoms.

The uniformity of the coating applied to pellets or tablets plays a critical role in achieving the desired drug release profile. Coating uniformity ensures consistent drug release, prevents dose dumping, and protects the drug from environmental factors. Variations in coating thickness or quality can lead to suboptimal therapeutic outcomes or adverse effects, especially for drugs like PPIs, where precise release control is essential.

Optimizing coating parameters, including polymer selection, spray rate, drying conditions, and coating thickness, is critical to achieving the desired release kinetics. Advanced coating techniques, such as fluidized bed coating and pan coating, enable precise application of functional coatings to meet the dual objectives of sustained and immediate release. Evaluation methods, including dissolution testing, scanning electron microscopy (SEM), and content uniformity analysis, further aid in assessing coating quality and performance.

It is critical to increase the availability of more advanced formulations that are simple to prepare and administer, such as minitablets, Orodispersible tablets, and films, particularly those incorporating functional micro- or nanoparticles. Standard enteric-coated tablets or capsules are not appropriate for all people, resulting in typical issues such as dosage adjustments, crushing, or grinding of such forms. Additionally, it has a detrimental impact on patients' compliance and drug adherence. The majority of currently produced formulations are aimed at overcoming these challenges and improving the efficacy and safety of PPI treatment.

The physicochemical features of PPIs are briefly presented, with a focus on their pharmacokinetic and pharmacodynamic qualities, stability, and qualitative or quantitative analytical methods. We investigated the content and formulation of PPI-containing commercial medicines.

AIMANDOBJECTIVES

The primary goals of pellet coating in pharmaceutical formulations are to adjust drug release, protect the medication from external influences, and improve overall product properties. This is accomplished by adding a coating layer to tiny, spherical particles or pellets. Coating can manage medication release (for example, prolonged or enteric release), disguise the drug's flavor, and protect it from moisture, light, and air.

Delayed release dose forms are ideal for medications that are degraded in stomach juices, cause gastric discomfort, or are absorbed more efficiently in the intestine. These preparations include an alkaline core material

with the active ingredient, a separating layer, and an enteric coating layer.

Objectives-

Coating can be used to make sustained-release or enteric-coated pellets, which allow for a more predictable and regulated release of the medicine in the digestive system.

- Improve the stability of Proton inhibitor
- Low cost manufacturing
- Make the process is easy

MATERIALSANDMETHODS

The materials utilized in this study were gathered from several sources. Aurobindo Pharma Ltd in Hyderabad, India sent a complimentary sample of Domperidone Maleate. Loba Chemie Pvt. Ltd, Mumbai provided HPMCK4M, guar gum, Dicalcium phosphate, and sodium bicarbonate. S.D.Fine Chem. Ltd., Mumbai provided additional excipients including stearic acid, citric acid, Aerosol, and talc.

Formulation for Domperidone Sustained Release Tablets:

The factorial design approach identifies and prioritizes elements in a process. In addition, any interaction between the elements selected can be discovered. A factorial design includes selecting parameters and responses [19].

Domperidone tablets were designed and formulated by Bryon Pharmaceuticals Ltd. (Industrial Area Hayatabad), which has production facilities. Formulations of chosen drugs, sustaining agents, and excipients (excluding lubricants and glidents) were combined for 15 minutes in a mixer after passing through an appropriate mesh. The glidants and lubricants were added and blended for 5 minutes. The mass was crushed by a tablet compression machine (Yasmeen et al., 2005). Physical testing included electronic balance for weight variation, Monsanto tester for hardness, Vernier caliper for thickness, and Erweka friabilator for tablet friability. To ensure consistent drug content, the produced tablets underwent an assay technique and the absorbance of Domperidone solution was measured using a UV/Visible spectrophotometer. To conduct dissolving tests (in vitro release), manufactured tablets were tested in a pH 6.8 buffer media and analyzed using several kinetic models.

Methods:

Preparing medication pellets

Domperidone Continuous stirring was used to combine 20% w/v with a 1%w/vPVPK30 aqueous binder solution and 2% w/v talc (Rahman & Yuen, 2006). Using a coating pan (Insta coat R & D Coater, Ideal Cures Pvt. Ltd.,

Mumbai, India), the drug solution was sprayed onto 200 g of uncoated pellets as non-pariel seeds with a 14/16 mesh and a size of 850-1100 µm.

Preparation of Polymer Dispersion

Surelease® was diluted to 15% w/v in distilled water. To make a 5% solution of HPMC E15 in water, the powder was dispersed in 50 ml of warmed water (80-90oC) and then diluted with 50ml of cold water. The solution was stored overnight. Surelease® and HPMC E15 polymer blends were used to create a sustained release formulation. To prevent foaming, oleic acid was added to the dispersion.

Coating of drug pellets with polymer dispersion

A modest amount of talc (2% w/v) was added to a combination of different concentrations of Surelease® and HPMC E15 to prevent adhesion. The liquid was agitated using a magnetic stirrer before and during the coating process. The solution layering approach was used to cover 200 g of medication pellets with varying doses. Coating fluid was applied to pellets and dried in a pan for 5 minutes at intervals. Formulation codes were issued to batches based on Surelease®: HPMC E15 ratio and polymer coating load. Formulation code F1 combines Surelease® and HPMC E15 in a 70:30 ratio for a 15% coating load. Table III displays the formulation codes F2-9, which correspond to different polymer and coating mixtures. In the factorial design, the dependent variables are drug release (%), 50% (h), and 80% (h), whereas the independent variables are Surelease®:HPMC E15 ratio (X1) and coating load (X2).

Characterization of Pellets

Visual evaluation of non-pareil seeds confirmed their spherical form. The flow properties of these were investigated by the following tests:

- **Carr's index**
- **Angle of repose**
- **Drug content**

Invitro dissolution

Dissolution testing of formulations F1-F9 was done with USP XXVIII type I. The test was conducted with a 500 cc pH 6.8 phosphate buffer solution at 37 ± 0.5°C and 50 rpm stirring speed (United State Pharmacopoeia, 2005). A sample of five mL was taken at intervals of 0.5, 1, 1.5, 2,3, 4, 6, 8, 10, 12, 13, 14, 20, 21, 22, 23, and 24 hours and immediately. Replace with 5 ml of new pH 6.8 phosphate buffer solutions to maintain sink conditions in the dissolving jar. The drug content was measured at 274 nm with a UV spectrophotometer (Jasco, Japan).

RESULTS

Physical characteristics of pellets-

Non pareil seeds and sustained release pellets having Carr's index value in the range 14-16% and angle of repose of 22-240 showed good flow property (Aulton, 2002).

Drug Content-

Amount of drug in pellets was found to be 11% estimated spectrophoto metrically.

Invitro dissolution:

data analysis In 32 full factorial design, various factors were studied using all the possible combinations, as it was considered to be most efficient for estimating the influence of individual variables (main effects) and their interactions, using minimum experimentation (Figure 1).

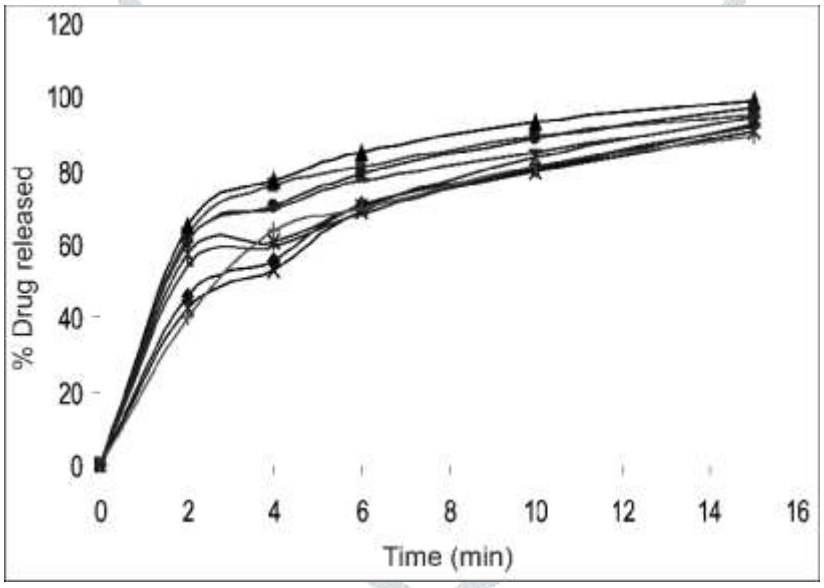

FIGURE1 –Dissolution profile of sustained release formulations of Doperidone pellets.

From the dissolution profile, it was concluded that batches F1-F3 of the ratio 70:30 released drug from97.21±1.91 % to103.26±1.13% for up to 6-7h, respectively. BatchesF4-F6 of the ratio 80:20 released drug from 98.57±0.49% to 104.9±2.25% up to 20-24 h, respectively, and F7-F9 of the ratio 90:10 released drug from 88.08±2.14% to 95.68±0.6 % up to 20-24 h, respectively.

Study of regression coefficient (r2) of different kinetic models

Different kinetic models were studied from dissolution profile of the different formulations of Domperidone sustained release pellets. The general poly nominal equation for percent release in terms of coded factors using multiple linear regression analysis is.

$Y=\beta0+\beta1X1+\beta2X2+\beta3X1X2+\beta4X12+\beta5X22+\beta6X1X22+\beta7X2X12+\beta8X12X2$

Where Y represents the measured response and X1 represents the value of the factors. β0, β1, β2…are the constants representing the intercept, coefficients of first-order terms, and coefficients of second- order quadratic terms, respectively. Further data was obtained by putting design experts results in to the above polynomial equation.

% Cumulative Release = +97.50-4.83*X1-1.47*X1 2 - 2.64*X2-0.68*X2 2 +0.41*X1 X2+0.59*X12 X2 -0.14*X1 X2 2 -0.66*X1 2 X2 2

t50%=+4.93+1.65*X1-0.77*X2+2.07*X12-0.47*X22+0.29*X1X2-0.36*X12 X2-0.36*X1X22+0.19*X12X22

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