DESIGN AND DEVELOPMENT OF LOVASTATIN MOUTH DISSOLVING TABLETS BY USING NOVEL SUPER DISINTEGRANTS

Dr. Zakir Hussain
Associate Professor
Pharmaceutics
Vijaya College of Pharmacy
zakirhussains765@gmail.com

ABSTRACT

The present study is intended to develop the lovastatin fast dissolving tablets using superdisintegrants to improve the dissolution rate. Lovastatin fast dissolving tablets were prepared using direct compression method and were characterized for both pre-compression and post-compression parameters. One of the approaches is formulation of rapidly disintegrating tablets. These are useful for pediatric, geriatric and also dysphagic patients, leading to improved patient compliance. From the in vitro drug release studies the F9 tablets showed fast disintegration (38 sec) and almost complete drug release within the 10 min. The percent drug release in 10 min (Q10) and initial dissolution rate (IDR) of F9 tablets was 97.56±0.56%, 9.76%/min. These were very much higher compared to control tablets (38.41±0.23%, 3.841%/min). The relative dissolution rate (RDR) was found to be 2.93. The dissolution efficiency (DE) was found to be 43.26 and it is increased by 3.0 fold with F9 tablets when compared to control tablets. DSC and FTIR studies were carried out to understand the drug-polymer compatibility and revealed that there was no possible interaction between them. From the stability studies, F9 formulation showed the good stability and it was proved by calculating the similarity factor i.e., 82.56. Thus the developed fast dissolving tablets may be suitable to give rapid dissolution and rapid onset of action.

Keywords: *Lovastatin, Dissolution efficiency, Initial dissolution rate, Pre-compression parameters, Post-compression parameters, Similarity factor, Super-disintegrants.*

INTRODUCTION

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of paediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water.

For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Mouth disintegrating tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. An Mouth disintegrating tablet (MDT) is a solid dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed across the GIT. US FDA defined MDT tablets as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue". Recently European Pharmacopoeia used the term 'Orodispersible tablet' as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing. Mouth disintegrating tablets are also called as

mouth-dissolving tablets, fast disintegrating tablets, fast dissolving tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet.

Even though several novel drug delivery systems were developed, still the oral administration of tablets is the preferred method for the treatment of various disorders due to greater flexibility in design and high patient acceptance. But to overcome the common problems of tablets like slow onset of action and dissolution rate, preparation of the fast dissolving tablets (FDT) is one of the useful approaches. The following are the common methods to formulate the FDT: i.e., direct compression, wet granulation, molding, spray drying, freeze drying, and sublimation.

LITERATURE REVIEW

Neeraj Sharma (2023) The solubility and dissolution rate of Lovastatin, a drug used for the treatment of hyperlipidaemia. Lovastatin is a selective competitive inhibitor of HMG Co-A reductase. However, its absolute bioavailability is 5%. To increase the solubility of drug solid dispersion was prepared. Solid dispersion prepared with polymer in 1:5 ratios shows the presence of amorphous form confirmed by the characterization study. hese solid dispersions were analyzed for the solubility and in-vitro dissolution profile solid dispersion of drug with polymer has shown enhanced solubility with improved dissolution rate. Further FTIR, X-Ray studies were carried out. The present investigations showed that solubility of Lovastatin Sodium was markedly increased by its solid dispersion using PVP K30 as carrier. The formulation SDF8 containing (1:8) shows highest dissolution rate.

Bilal Yılmaz (2023) The oral availability of many drugs is problematic due to the pH of the stomach, enzymes, and first-pass effects through the liver. However, especially geriatric, pediatric, bedridden, or mentally handicapped patients and those with dysphagia have difficulty swallowing or chewing solid dosage forms. Oral Thin Films (OTFs) are one of the new drug delivery systems that can solve these problems. Pregabalin (PG) and Methylcobalamin (MC), which are frequently preferred for pain originating in the central nervous system, were brought together for the first time using OTF technology in this study. In this study, a quantification method for PG and MC was developed and validated simultaneously. Optimum formulations were selected with organoleptic and morphological controls, moisture absorption capacity, swelling capacity, percent elongation, foldability, pH, weight variability, thickness, disintegration time, and transparency tests on OTFs prepared by the solvent pouring method.

Dr V. Chandrakala (2022) Rapid dissolving oral film is the most advanced solid oral drug delivery systems, that dissolve or disintegrate within few seconds once placed in mouth without taking water or chewing. Drug directly reaches into systemic circulation therefore avoids first pass metabolism so bioavailability of medication may be improved. Now a day's most of the pediatric, geriatric and dysphagia patients who find difficulty in swallowing, the rapid dissolving oral film often helps to overcome such type of complications. In terms of stability, handling, administration, and distribution, rapid dissolving oral films have grater advantages than tablet, capsules, or syrups.

These compositions pharmacological activity is demonstrated by disintegration followed by dissolving. Hence disintegration has a major role for facilitating drug activity and thus gains popularity among other dosage forms. In this review, more importance is given on utilization of various super disintegrants comparing with other disintegrants.

Dr Priyanka Sinha (2022) Orally Fast Dissolving Strips (OFDS) is a novel drug delivery dosage form designed and developed as an alternative to orally conventional drug delivery system (tablets, capsules, syrups). Many drawbacks like gastrointestinal destruction of liable molecules, slow onset of action, low absorption of macromolecules and unavoidable fluctuation in the concentration of drug which may either leads to under-or-over medication. To overcome these difficulties, recent trends are shifting towards developing an innovative drug delivery system to improve safety, efficacy & patient compliance by fast dissolving technologies, which dissolves within a minute in oral cavity. OFDS are useful in patient such as pediatrics, bedridden or developmentally disabled, geriatric, who faces difficulty in swallowing solid dosage forms like tablets & capsules.

Tarek A. Ahmed (2021) Rosuvastatin is a hepato-selective statin of limited water solubility and poor oral bioavailability. The rationale behind this work was to develop pullulan based freeze-dried orodispersible tablets containing rosuvastatin flexible lipid-based nanoparticles (transfersomes) to enhance rosuvastatin bioavailability and hypolipidemic activity. Drug loaded transfersomes were prepared, characterized, and loaded into pullulan based freeze-dried orodispersible tablets. The prepared tablets were evaluated for their quality attributes and in vivo disintegration time. The pharmacokinetic behavior of the prepared tablets was studied on male Wistar rats and compared to commercial drug tablets. The hypolipidemic, hepatic enzyme and antioxidant activities were also assessed in poloxamer-induced hyperlipidemic rats.

Special Features of Mouth Dissolving Film

- Film should be thin and elegant.
- Available in various size and shapes.
- Unobstructive.
- Excellent mucoadhesion.
- Should processes fast disintegration without water
- Rapid release.

Advantages of Mdts:

- Ease of administration to geriatric, paediatric, mentally disabled, and bed-ridden patients, who have difficulty in swallowing the tablet.
- The MDTs do not need water for swallowing unlike conventional dosage forms. This is very convenient for patients who are travelling or do not have immediate access to water, and thus, provide improved patient compliance.
- Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for paediatric and geriatric patients.
- Bioavailability of drugs is enhanced due to absorption from mouth, pharynx, and oesophagus.

- Pregastric absorption can result in improved bioavailability and because of reduced dosage, improved clinical performance through a reduction of unwanted effects.

Selection of Super Disintegrants:

Super disintegrants not only affect the rate of disintegration, but when used at higher concentrations they also affect mouth feel, tablet hardness and friability. Super-disintegrants are selected according to critical concentration of disintegrant. Hence, various ideal characteristics of super disintegrants should be considered while selecting for a particular formulation.

- Produce rapid disintegration.
- Be compactable enough to produce less-friable tablets.
- Produce good mouth feel to the patient. Thus, small particle size is preferred to achieve patient's compliance
- Should have good flow properties to improve the flow ability of the total blend

Classification of Fast Dissolving Technology

The three types of fast-dissolving technology are as follows.

- Lyophilized systems
- Compressed tablet-based systems
- Oral thin film

Lyophilized systems

This approach includes forming tablet-shaped units from a medication suspension or solution with various structural excipients using a mould or blister pack. Following that, the units or tablets are frozen and lyophilized in a pack or mould. The resultant units have a high porosity, allowing water or saliva to penetrate quickly and disintegrate quickly.

Compressed tablet- based systems

This method is made using normal tablet technology, which involves direct compression of excipients. Depending on the technique of manufacturing, tablet technologies have varying degrees of hardness and friability. The speed of disintegration for fast-dissolving tablets compared with a standard tablet is achieved by formulating it using water soluble excipients, or super-disintegrate or effervescent components, to allow quick water penetration into the tablet's core.

Oral thin films

Oral films are a collection of flat films that are placed in the mouth. Dissolvable oral thin films (OTFs) or oral strips (OS) originated from the confection and oral care sectors in the form of breath strips during the last several years and have become a unique and highly recognized method of delivering vitamins and personal care items to consumers.

RESEARCH METHODOLOGY

Buffer preparation:

Preparation of pH 6.8 phosphate buffer:

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed.

Dissolved 6.805 g of potassium dihydrogen orthophosphate in to 800mL of Purified water and mixed. Added 112mL of 0.2M NaOH solution in to this solution, diluted to volume with purified water. Then adjusted the pH of this solution to 6.8 with 0.2M NaOH solution.

Analytical method development for Lovastatin:

a) Determination of absorption maxima

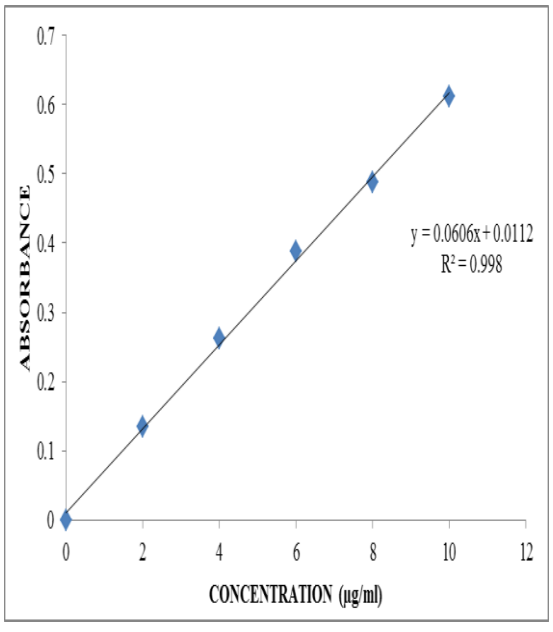
A spectrum of the working standards was obtained by scanning from 200-400 nm against the reagent blank to fix absorption maxima. The λ_{max} was found to be 238 nm. Hence all further investigations were carried out at the same wavelength.

b) Construction of standard graph

100 mg of Lovastatin was dissolved in 100 mL of pH 6.8 phosphate buffer to give a concentration in 1mg/mL (1000µg/mL) 1 ml was taken and diluted to 100 ml with pH 6.8 phosphate buffer to give a concentration of 0.01 mg/ml (10µg/ml). From this stock solution aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1 ml, were pipette out in 10 ml volumetric flask and volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 2, 4, 6, 8 and 10µg/ml respectively. The absorbance of each concentration was measured at respective (λ_{max}) i.e., 238 nm.

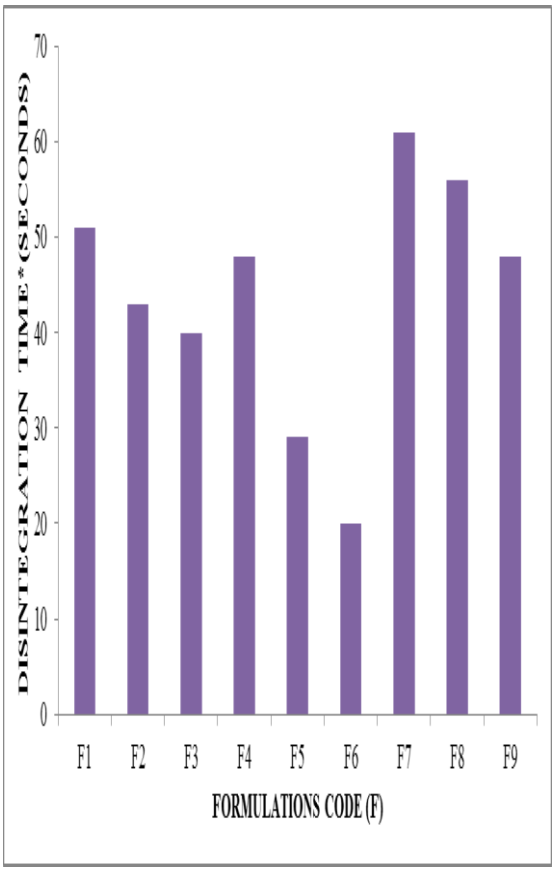
RESULTS

Preparation of Calibration Curve of Lovastatin:

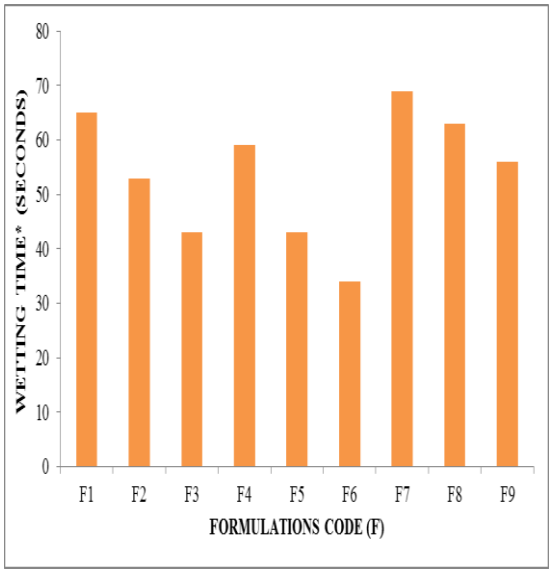


Graph 1: Standard curve of Lovastatin

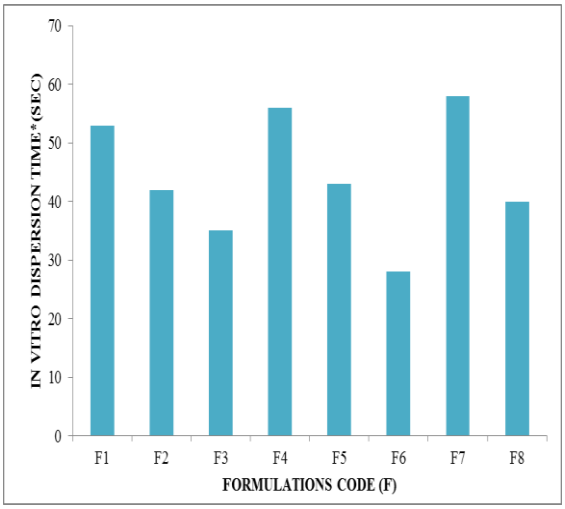
The regression coefficient was found to be 0.998 which indicates a linearity with an equation of Y= 0.060 X-0.011. Hence Beer-Lambert's law was obeyed.



Graph 2: In vitro Disintegration time graph



Graph 3: Wetting time graph

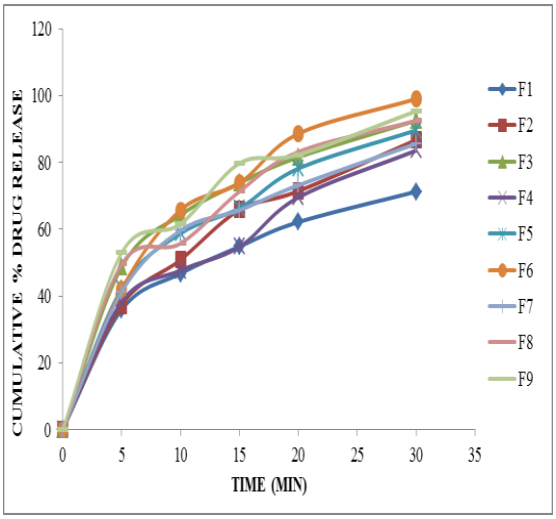


Graph 4: In vitro dispersion time

In vitro disintegration time: In vitro disintegration studies showed from 20 to 61 secs. These results indicate that the F6 formulation which shown less disintegration time than remaining formulations.

Wetting time: Wetting time to the time required to wet completely when kept motionless on the tissue paper in a petridish.

- All the FDT formulations were evaluated for their wetting time as per the procedure described in the methodology section, and the results are shown in table.
- The average wetting time for all the formulations was in the range of (34 to 69) seconds.
- It was also observed that formula F6 which had the least wetting time also had the minimum disintegration time showing a strong correlation between disintegration time and wetting time.



Graph 5: Dissolution profile of all formulations F1-F5

In vitro dissolution study was performed to evaluate the release profile of the drug from various formulated MDTs. The results of the study are used to relate the percentage of drug release from its dosage form as a function of time. The addition of super-disintegrants to the formulation aids in the quick disintegration of the formulation promoting the quick dissolution of the particles which in turn enhances the release of drug from the dosage form ultimately causing enhance bioavailability and quick onset of action of the drug.

CONCLUSION

Mouth dissolving tablets of Lovastatin were developed successfully by the addition of three types of superdisintegrants namely Tulsion339 (F1 to F3), Explotab (F4 to F6), Croscarmellose sodium in different concentration. The pre compression blend of Lovastatin Mouth dissolving tablets using super disintegrants were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The precompression blend or all batches indicating good to fair flowability and

compressibility. Mouth release tablets were prepared with various concentrations of superdisintegrants, and were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The tablets were passed all the tests. Hence from dissolution data it was evident that F6 formulation is the better formulation. OFDS's have emerged as a novel trend, and most pharmaceutical companies in this field continue their research &development activities to adapt their drugs from various categories to this technology. Oral strips have proved to be an innovative drug delivery system for all groups of patients with the problem of swallowing. It also offers many advantages over the other dosage forms, such as improved bio-availability and faster onset of action. Therefore, it can be concluded that OFDS's with excellent patient compliance and many advantages have innovative futuristic opportunities.

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