DESIGN DEVELOPMEN OF LOVASTATIN MOUTH DISSOLVING TABLETS BY USING NOVEL SUPER DISINTEGRANTS

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ABSTRACT

The aim of this study is to formulate and significantly improve the bioavailability and reduce the side effects of Mouth dissolving tablets of Lovastatin. The precompression blends of Lovastatin were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. The precompression blends of all the batches indicate well to fair flowability and compressibility. Mouth dissolving tablets were prepared with various disintegrants like Lovastatin were developed successfully by the addition of three types of superdisintegrants namely Tulsion339 (F1 to F3), Explotab (F4 to F6), Croscarmellose sodium (F7 to F9) in different concentration ratios and were compressed into tablets. The formulated tablets were evaluated for various quality control parameters. The tablets were passed all tests. Among all the formulations F6 formulation containing drug and Explotab (15 mg concentration) showed maximum and good result that is 99.01% drug release in 30 min. Hence from dissolution data it was evident that F6 formulation is the better formulation.

Key Words: *Tulsion339, Explotab, Croscarmellose sodium, Lovastatin, superdisintegrants*

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 .

The US Food and Drug Administration responded to this challenge with the 2008 publication of Guidance for Industry: Mouth Disintegrating Tablets (Rosie et al., 2009).Three main points stand out in the final guidance:

- MDTs should have an *in vitro* disintegration time of approximately 30sec or less.
- Generally, the MDT tablet weight should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an MDT for both patients and regulators.
- The guidance serves to define the upper limits of the MDT category, but it does not supersede or replace the original regulatory definition mentioned. In other words, disintegration within a matter of seconds remains the target for an MDT.

NEED TO DEVELOP MDT:

The need for one of the non-invasive delivery system i.e., Mouth disintegrating tablets persists due to patients' poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

PATIENT FACTORS:

Mouth disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow tablets and capsules with an 8-oz glass of water. These include the following:

- Paediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms.
- Patients who are unwilling to take solid preparation due to fear of choking.
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2- blocker.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.
- A patient with persistent nausea, who may be journey, or has little or no access to water

EFFECTIVENESS FACTORS:

- Increased bioavailability and faster onset of action 0are a major claim of these formulations.
- Dispersion in saliva in oral cavity causes pregastric absorption from some formulations in those cases where drug dissolves quickly.
- Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs**.**
- Any pregastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism.
- Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric

metabolism, and for drugs that have a substantial fraction of absorption in the oral cavity and pregastric segments of GIT.

Materials: Tulsion 339, Explotab, Cross Carmellose Sodium, Aspartame, Talc, Mg Stearate, Lactose

METHODS:

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.

Formulation development:

Drug and different concentrations of super disintegrants (Tulsion339, Explotab and Croscarmellose sodium) and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass motor for 15 min.The obtained blend was lubricated with magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 min.The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

Pre compression parameters:

Measurement of Micromeritic properties of powders

Angle of repose: tan $\Theta = h/r$, Where , h and r are the height and radius of the powder cone.

Bulk density: The bulk density is calculated in g/cm^3 by the formula.

Bulk density = M/V_0 , V_0 = apparent unstirred volume, M= Powder mass

Tapped density: Tapped density = M/V_f , M = weight of sample powder taken, V_f = Tapped volume

Compressibility index: This formula for Carr's index is as below:

Carr's Index (%) = [(TD-BD)/TD] x100

Hausner's ratio: It is calculated by the following equation.

H = Pt / ρB , where ρT= tapped density, ρB = bulk density

Post compression parameters:

Thickness: The thickness of the tablets was determined by using Digital micrometer. 10 individual tablets from each batch were used and the results averaged.

Hardness: The hardness of the tablets is an indication of its strength measuring the force required to break the tablet across tests it. Hardness of ten tablets from each formulation was determined by using Monsanto hardness tester.

Weight variation: Twenty tablets are taken and their weight is determined individually and collectively on a digital weighing balance the average weight of one tablet is determined from the collective weight.

Friability: Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. The tablets are weighed and placed in roche friabilator. That is rotated at 25 rpm for 4 min. The tablets are dusted and weighed again .The percentage of weight loss is calculated again using the formula.

Friability = ([w_0-w]/w_0) x 100, Where w_0 = weight of tablet at time zero before revolution.

w = weight of the tablet after 100 revolutions

Drug content: The content of drug carried out by 5 randomly selected tablets of each formulation. The 5 tablets were grinded to get powder; this powder was dissolved in pH 6.8 phosphate buffer by sonication for 30 min and filtered through filter paper. The drug content was analysed spectrophotometrically at 238 nm using UV spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated.

Disintegration test : Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 min. and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

Wetting Time: A piece of tissue paper folded twice was placed in a small petridish containing 6ml of water. A water-soluble dye phenolphthalein was added to the petridish. The dye solution was used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of tissue paper in the petridish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in triplicates (n=3). The wetting time was recorded using a stopwatch.

Water Absorption Ratio (R): The weight of the tablet before keeping in the petridish was noted (W_b) using digital balance. The wetted tablet from the petridish was taken and reweighed ($W_{a`}$) using the same. The

Water absorption ratio, R, was determined according to the following equation:
$R = (W_a - W_b) / W_b * 100$,W_a= Weight of the tablet after absorption, W_b= Weight of the tablet before absorption

***In Vitro* Dispersion Time:** *In vitro* dispersion time was determined by placing one tablet in a beaker containing 10 ml of pH 6.8 phosphate buffers at 37±0.5°c and the time required for complete dispersion was determined. To check for reproducibility, the measurements were carried out in triplicates (n=3). The dispersion time was recorded using a stopwatch.

Dissolution test of Lovastatin: Drug release from Lovastatin tablets was determined by using dissolution test USP 24 type II (paddle). The parameters used for performing the dissolution were pH 6.8 medium as the dissolution medium of quantity 900 ml. The whole study is being carried out at room temperature of 37˚ C and at a speed of 50 rpm.

5 ml aliquots of dissolution media were withdrawn each time intervals (5, 10, 15, 20, 30 min) and appropriate dilution by UV Spectrophotometer. The Concentration was calculated using standard calibration curve.

Drug-Excipients compatibility studies: Drug excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions (in 1;1 ratio were to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly. Fourier Transform Infrared Spectroscopy (FTIR) studies were performed on drug, optimized formulation using Bruker FTIR. The samples were analyzed between wave numbers 4000 cm^{-1} and 550 cm^{-1}.

RESULTS:

Calibration 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.

Pre compression parameters: For each formulation blend of drug and excipients were prepared and evaluated for various pre compression parameters described earlier in methodology chapter.

The bulk density of all formulations was found in the range of 0.44- 0.59 and tapped density was in the range of 0.54- 0.66. The Carr's index and Hausner's ratio was calculated from tapped density and bulk density.

Weight variation and Thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown above. The average tablet weights of all the formulations were noted down.

Hardness and friability: All the Mouth Dissolving formulations were evaluated for their hardness using Monsanto hardness tester and the results are shown above. The average hardness for all formulations was found to be between (2.4±0.02– 2.9±0.04) kg/cm^2 which was found to be acceptable. Friability was determined to evaluate the ability of the tablets to with stand the abrasion during packing, handling and transporting. All the Mouth dissolving formulations were evaluated for their percentage friability using Roche friabilator and the results are shown above. The average percentage

friability for all the formulations was between 0.14±0.06 – 0.63±0.07 which was found to be within the limit.

Drug content: All formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown above. The assay values for all formulations were found to be in the range of (95.63±0.19–98.42±0.74). According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the Mouth dissolving formulation complies with the standards given in IP.

***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.

***In vitro* dispersion time:** Lovastatin Mouth Dissolving Tablets F6 formulation dispersed time was 28 secs. It was known that less dispersion time than other formulation. The *In vitro* dispersion time for all formulation was found to be in a range of **28 to 58** seconds

Water Absorption ratio: All the formulations were evaluated for water absorption ratio according to the procedure described in methodology section and the results are shown in table. The maximum water absorption ratio was shown by formulation F6 showed 99 **%.** Water absorption ratio is proportional to dissolution rate profile as higher the water absorption ratio Higher the dissolution. *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. The *in vitro* dissolution profile indicated faster and maximum drug release from formulation F6. Formulation F6 prepared by direct compression method by using Explotab superdisintegrants it showed release 99.01 % drug at the end of 30 min. When compared to other formulations F6 formulation showed maximum drug release. Based on *in vitro* release, disintegration time and wetting time formulation F6 was selected as the optimized formulation. Lovastatin was mixed with proportions of excipients showed no colour change providing no drug-excipient interactions.

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 (F7 to F9) 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. The formulation (F6) containing drug and Explotab showed good drug release at 15 mg concentration. Among all the formulations F6 formulation containing drug and Explotab (15 mg concentration) showed maximum and good result that is 99.01% drug release in 30 min. Hence from dissolution data it was evident that F6 formulation is the better formulation.

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