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An Overview on Immediate Drug Release of Pravastatin Drug

Dr. D. RamaBrahma Reddy*, Dr.Ch. N V S Mastan Rao*, K. John Abhi, M. Tirupathi Rao, K. Shankar, Mk. Lakshman, K. Neeleshbabu, K. Vamsi:

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ABSTRACT:
The objective of this research was to formulate fast dissolving tablets of Pravastatin sodium that disintegrate in the oral cavity upon contact with saliva and there by improve therapeutic efficacy. Pravastatin sodium is used for the treatment of myocardial infarction. Fast dissolving tablets of pravastatin sodium were prepared by direct compression method using three different superdisintegrants-Sodium starch glycollate, Croscarmellose sodium and Crosspovidone (2%, 4% and 6%) and three different diluents (mannitol and spray dried lactose) in different concentrations. Eighteen formulations were prepared by using different diluents and evaluated were evaluated for various pre and post compression parameters like angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio, tablet hardness, friability, weight variation, wetting time, water absorption ratio in vitro dispersion time, drug content and in vitro dissolution studies. FTIR and DSC studies revealed that there was no chemical interaction between the drug and the excipients. Formulation L6 was found to be the best on the basis of wetting time, in vitro disintegration time and in vitro drug release. The formulation L6 containing spray dried lactose as diluent and crosspovidone (6%) was found to be the optimized combination. Stability studies were carried out at 250°C±20°C/60%±5% RH and 400°C±20°C/75%±5% RH for formulation L6 for 60 days. The results of stability studies indicated no significant changes with respect to physicochemical properties, in vitro disintegration time, wetting time and in vitro drug release.

KEYWORDS: Fast dissolving tablets, Pravastatin sodium, Superdisintegrant, Direct compression, Sodium starch glycollate, Croscarmellose sodium, Crosspovidone.

I. INTRODUCTION:

Fast dissolving tablets become an emerging trend in the pharmaceutical industry. Fast dissolving tablets are ideal for all types of people, including for people who have swallowing difficulties, paediatric, geriatric, and bedridden patients. Fast dissolving tablets are also known as orodispersible tablets, mouth-dissolving tablets, orally disintegrating tablets, melt-in mouth tablets, Rapi melts, porous tablets, quick dissolving etc. Many drugs have the potentials to be made into orodispersible tablets.1 The speed of solubility of drug affects the rate of absorption of the drug. The faster the drug dissolve into solution, quicker the absorption and onset of clinical effect. They should readily dissolve or disintegrate in the saliva generally within<60seconds.

Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. The significance of oral disintegrating dosage forms is progressively being recognized in both, industry and academics. The small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes. Orally disintegrating tablets (ODT) are formulated by utilizing several processes, which differ in their methodologies and the ODTs formed vary in various properties such as, mechanical strength of tablet, taste and mouth feel, swallowability, drug dissolution in saliva, bioavailability and stability. Various processes employed in formulating ODTs includeFreeze-Drying or Lyophilization, cotton candy process, Molding, spray drying, mass extrusion and compaction (wet granulation, dry granulation, and direct compression). In the present study, the direct compression method was adopted to manufacture the ODT tablets, since it was very simple and do not require any sophisticated equipment's. The direct compression represents the simplest and most cost-effective tablet manufacturing technique.2 ODT by direct compression technique is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena

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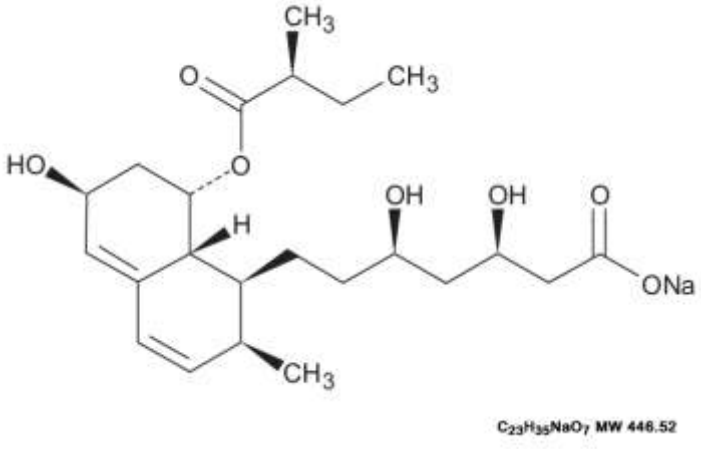
for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms.

STRUCTURE OFPRAVASTATIN:



Molecular formula- C23H35NaO7
Molecular weight-446.51
Boiling Point: 634.5ºCat 760 mmHg
Melting Point: 171.2-173 °C
Flash Point: 213.2ºC.

Adverse effects and contraindications:

Pravastatin has undergone over 112,000 patient-years of double-blind, randomized trials using the 40 mg, once-daily dose and placebos. These trials indicate pravastatin is well tolerated and displays few noncardiovascular abnormalities in patients.

Contraindications, conditions that warrant withholding treatment with pravastatin, include pregnancy and breastfeeding. Taking pravastatin while pregnant could lead to birth defects. While the amount of pravastatin ingested by an infant from breastfeeding is low, patients breastfeeding should not take pravastatin due to potential effects on the infant's lipid metabolism

Formulation Development of Pravastatin Fast Dissolving Tablets:

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses.9,10 A selected three level, two factor experimental design (32 factorial design) describe the proportion in which the independent variables Crospovidone and Croscarmellose sodium were used in formulation of Pravastatin Fast Dissolving Tablets. The time required for 50% (t50%), 90% (t90%) drug dissolution, Disintegration Time and Wetting Time were selected as dependent variables.

II. METHODS:

PVS-loaded PLGA nanoparticles (PVS–PLGA-NPs) were prepared by double emulsion method using a full 3^2 factorial design. The in vitro release and the physical stability studies of the optimized PVS–PLGA-NPs (F5) were performed. Finally, both hypolipidemic and hepatoprotective activities of the optimized F5 NPs were studied and compared to PVS solution.

III. RESULTS AND DISCUSSION:

Fast Dissolving tablets of Pravastatin were prepared and optimized by 32 factorial designs in order to select the best combination of different Superdisintegrants, Crospovidone, Croscarmellose sodium and also to achieve the desired rapid release of drug from the dosage form (by Disintegrating quickly). The two factorial parameters involved in the development of formulations are, quantity of Crospovidone & Croscarmellose sodium as independent variables (X1, X2), and in vitro dissolutionparameters such as t50%, t90%, Wetting time and Disintegrating Time as dependent variables. Totally nine formulations were prepared using 3 levels of 2 factors and all theformulations containing40 mg of Pravastatin were prepared as a Fast-Dissolving tablet dosage form by Direct Compression technique as per the formula. All the prepared tablets were evaluated for different post

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compression parameters, drug content, mean hardness, friability, mean thickness, Weight variation as per official methods and results. The hardness of tablets was in the range of 4.01±0.075-4.60±0.225 Kg/cm2. Weight loss in the friability test was not more than 0.70%. Drug content of prepared tablets was within acceptance range only. The Wetting Time of tablets was in the range of 31.05±0.75-62.95±0.85 sec. The Disintegration Time of tablets was in the range of 21.53±0.65-41.88±0.8 sec. Results for all Post-compression parameters. In-vitro Dissolution studies were performed for prepared tablets using Phosphate buffer pH 6.8 as a dissolution media at 50 rpm and temperature 37±0.5°C. The in-vitro dissolution profiles of tablets. (Kinetic Plots), Wetting Time Chart, Disintegration Time charts were shown in Figure 5,6. The dissolution parameters. Cumulative % Drug releaseof Factorial Design Formulations F1 -F9 at 30 mins were found to be in the range of 91.825-99.14 %. From the result, it reveals that the release rate was higher for formulations containing High level of Crospovidone/Croscarmellose sodium compared with other Formulations containing Lower level, due to High concentration of Superdisintegrant in combination, shows various disintegration mechanism such as wicking and swelling etc more compared with lower concentration and alone, drug may release rapidly and shows improved bioavailability. Excess of Superdisintegrant also prone to Friable. Therefore, required release of drug can be obtained bymanipulating the composition of Crospovidone and Croscarmellose sodium. Variation was observed in the Wetting time, Disintegrating time, t50% and t 90% due to formulation variables. Formulation F1 containing 16 mg of Crospovidone, 16 mg of Croscarmellose sodium showed promising dissolution parameter (Wetting time= 31.05±0.75 sec, Disintegrating time = 21.53±0.65 sec, t50% = 6.573 min, t90% = 21.843 min). The difference in burst effect of the initial time is a result of the difference in the Concentration of Superdisintegrants mixtures. This reveals that increased concentration of superdisintegrants resulted in a corresponding decrease in the Wetting Time, which might be due to the result of wicking and other possible disintegrating mechanisms. Disintegration time is directly proportional to wetting time. The in -vitro dissolution data of Pravastatin Fast Dissolving formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer-Peppas models to assess the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 4. It was observed from the above that dissolution of all the tablets followed First order kinetics with co-efficient of determination (R2) values in the range of 0.957 0.994. The values of r of factorial formulations for Higuchi's equation was found to be in the range of 0.868-0.993, which shows that the dissolution data fitted well to Higuchi's square root of time equation confirming the release followed diffusion mechanism. Kinetic data also treated for Peppas equation; the slope (n) values range from 1.243-1.875 that shows non-Fickian diffusion mechanism. Polynomial equations were derived for Wetting time, disintegrating time, t50% and t90% values by backwardstepwise linear regression analysis using PCP Disco software and Response surface plots were constructed using SIGMAPLOT V13 software. The Response surface plots for Wetting time, disintegrating time, t50% and t90% using X1 and X2 on both the axes respectively.

IV. CONCLUSION:

The present research work envisages the applicability of Superdisintegrants such as Crospovidone and Croscarmellosesodium in the design and development of FastDissolvingtablet formulations of Pravastatin utilizing the 32-factorial design. From the results, it was clearly understood that as the concentration of Superdisintegrant increases the release rate of drug was RAPID and both of these Superdisintegrants can be used in combination since do not interact with the drug which may be more helpful in achieving the desired fast Dissolving of the dosage form for rapid action and improved Bioavailability. The optimized formulation followed Higuchi's kinetics while the drug release mechanism was found to be Non-Fickian Diffusion, first order release type. Based on evaluation parameters, the optimized formulation F1 may be used for the effective management of hypercholesterolemia and to reduce the risk of cardiovascular disease. This may improve the patient compliance by showing rapid action via disintegration without difficult in swallowing and side effects which will ultimately improve the therapeutic outcome. We could be able to minimize the per oral cost of the Formulation.

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