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RESEARCH ARTICLE

Formulation and Evaluation of Atorvastatin Calcium Solid Dispersions

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ABSTRACT

Atorvastatin is useful in converting bad cholesterol to good cholesterol. As this bad cholesterol causes many diseases in human like increase in cholesterol levels in blood, Heart stroke, Heart failure, Anginal pains. These all problems can be controlled, when bad cholesterol converts into good cholesterol. So that Atorvastatin is used in process of converting bad cholesterol to good cholesterol. As it is also used in hyper cholesterolemia, hyper triglyceridemias, Myocardial infarctions, Strokes, Anginal pains, Cardiovascular disease. It is a class II drugs which is having high permeability but low solubility. Due to Atorvastatin having less solubility the drug may not show its action on time. Due to low solubility there is a need to enhance the solubility of atorvastatin. Solid dispersion is one of the most important solubility enhancement technique to enhance the solubility of drug. There are many other techniques under solid dispersion techniques. But here fusion method is used to enhance the solubility.

Keywords: Atorvastatin, cholesterol, solubility, solid dispersion

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CONTENTS

1. Introduction.	97
2. Materials and Method.	98
3. Results and Discussion.	99
4. Conclusion.	101
5. References.	101

1. Introduction

Solid dispersion is the method for improving the dissolution rate of sparingly soluble drugs where first proposed by Sekiguchi and Obi. Solid dispersion can be defined as a product formed by converting a fluid drug carrier combination to solid state. [1] This type of system can be

prepared by co-precipitation, melting or fusion, spray drying or freeze drying. The solubility of poorly soluble drugs may be improved by solid dispersion technique. Stabilization of unstable drugs is possible in solid dispersions. [2] It is also possible to formulate sustained

action preparation of certain drugs in insoluble carrier. The taste of the drug can also be masked by this technique.

Carriers used in solid dispersion:

Sugars: Dextrose, sorbitol, sucrose, maltose, galactose, xylitol, mannitol and lactose.

Acids: Citric acid, tartaric acid and succinic acid.

Polymeric materials: polyvinyl pyrrolidone, polyethylene glycol (PEG 4000,6000), hydroxyl propyl methyl cellulose, guar gum, xanthan gum, sodium alginate, methyl cellulose, pectin, hydroxyl ethyl cellulose, hydroxyl propyl cellulose and cyclodextrin. [3]

Preparation technique of solid dispersion

Kneading method:

In this method drug and suitable polymer different ratios is mixed in different ratios is mixed in a mortar and triturated with a small quantity of solvent to prepare slurry. The drug is then added slowly into a slurry with constant stirring the slurry which is prepared then air dried at 25°C for 24 HRS> The product is prepared and sieved through sieve #80 and stored in desiccator with fused NaCl. [4]. Atorvastatin calcium is a member of the drug class known as statin. Atorvastatin calcium is a synthetic lipid-lowering agent which is a competitive inhibitor of HMG-CoA reductase which inhibits 3 hydroxy-3-methylglutaryl-coenzyme reductase the rate determining enzyme located in hepatic tissue that produces mevalonate, an early and rate limiting step in cholesterol produced which in turn lowers the total amount of LDL cholesterol. Decreased hepatic cholesterol levels increase hepatic uptake of cholesterol and reduces plasma cholesterol levels. [5]. Atorvastatin calcium comes under BCS class II that shows low solubility and high permeability. [6] It is insoluble in water and very slightly soluble in distilled water. There are certain short coming of using atorvastatin as oral tablets which includes, (1) bioavailability of atorvastatin is highly variable due to its low aqueous solubility, (2) first pass metabolism, aqueous solubility lesser than 1 µg /ml will definitely creating a bioavailability problem affecting the efficacy of drug. [7] The primary use of atorvastatin is for the treatment of dyslipidemia and the prevention of cardiovascular disease. However the main limitation to therapeutic effectiveness of atorvastatin calcium is its poor absolute bioavailability (14%) but the systemic availability for HMG-CoA reductase activity is approximately 30%. Atorvastatin calcium has a half-life 14 hrs. Atorvastatin tablets contain the active ingredient atorvastatin, as atorvastatin calcium. [8]

2. Materials and Methods

Materials:

Atorvastatin calcium was obtained procured as a gift sample from Smilax laboratory limited, Hyderabad. All the other chemicals like Carbapol, Poly ethyleneglycol(PEG), Mannitol, Croscarmellose sodium(CCS) were obtained from SDFCL, S.D. fine-chemicals limited, Mumbai.

Apparatus:

U.V. Visible Spectrophotometer (Analytical Technologies Ltd), Electronic balance (WENSAR), FTIR (BRUKER), Friabilator (ELECTRO LAB FRIABILATOR), Hardness tester (ELECTRO LAB FRIABILATOR), Hot air oven.

Preformulation Studies:

Preformulation studies are one of the important prerequisite in development of any drug delivery system. These were performed on the drug, which included solubility and compatibility studies.

Description: Atorvastatin was physically examined for its colour and odour etc. [9]

Interaction Studies

Drug-polymer interaction study:

Drug-excipient interaction studies were determined by means of FTIR spectroscopy. Atorvastatin calcium powder was separately mixed with various excipients in the ratio of 20:80 for 3 weeks the resultant physical mixture was kept in sealed glass vials and placed at different temperatures. Two evaluation parameters were employed to study the interaction between the drug and excipients. The contents of each vial were observed for any change in their physical characteristics and for their characteristics peaks by FTIR spectrophotometer. Physical changes of drug excipient mixtures in solid state at different conditions are recorded. The FTIR data showed that Atorvastatin and excipient did not react with each other and retained their action at room temperature. [10]



Figure 1

FTIR related pictorial representation

Formulation of Atorvastatin solid Dispersion:

Atorvastatin solid dispersions are formulated using Poly Ethylene Glycol and Carbapol as polymers. CSS used as disintegrating agent. Magnesium Stearate used as lubricant and mannitol used as a diluent. A total of eight formulations are made, which first four formulations (F1, F2, F3, F4) composed of PEG as polymer where as formulations from F5-F8 (F5, F6, F7, F8) composed of carbopol as polymer. [11]

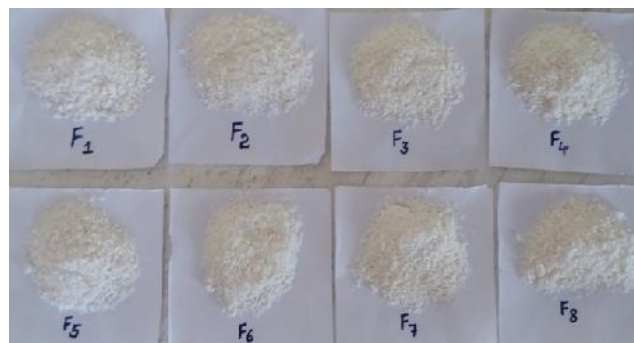


Fig 2: Formulations of Atorvastatin solid Dispersion

Characterization of Solid Dispersion Technique

Hardness: Hardness indicates the ability of the tablet to withstand mechanical shocks while handling. The hardness of the tablet was determined by Electro lab Hardness tester. The tablets were randomly picked and hardness of the tablets was determined [12].

Friability test:

The friability of the tablets was determined using Electro lab friabilator. It is expressed friabilator and operated at 25 rpm for 4 min or run up to 100 revolutions. Then the tablets were weighed again (Wf). The percentage friability was then calculated by,

% friability (F) = $\frac{\text{initial weight}(W1) - \text{Final Weight}(Wf)}{\text{initial weight}} \times 100$

Percentage friability of tablet less than 1% are considered acceptable. [13]

Weight variation:

20 tablets from each formulation weighed individually using digital balance and the test was performed according to the official method. Randomly selected pre- dusted tablets weighed again and the change in variation of weight is noted and tabulated.

%Deviation = $\frac{\text{individual weight} - \text{average weight}}{\text{average weight}} \times 100$

Estimation of Drug content:

The formulation equivalent to 10mg of Atorvastatin calcium was weighed and transfer to a 200ml flasks. Formulation were kept in 100ml distilled water and then sonicated for 72 hours, after 72 hours the contents of each flask were filtered through whatman filter paper. Filtrate was diluted properly and absorbance were determined using UV-Visible spectrophotometer.

In-Vitro Dissolution Studies:

The prepared solid dispersion was subjected to in vitro dissolution. Dissolution test was carried out using USP paddle apparatus. The stirring rate was 50 rpm, pH- 6.8 phosphate buffer was used as a dissolution medium and dissolution medium was maintained at 37 ± 1 o C. samples of 5ml was withdrawn at regular intervals of time, filtered and replaced with 5ml of fresh dissolution medium, dilutions were made and analysed for atorvastatin at 245nm.

Kinetics of drug analysis

Order of drug release: To determine the type order of drug release graphs were plotted between cumulative % of drug release vs. Time, log cumulative percentage of drug remaining vs. Time.

Korsmeyer-Peppas model:

Korsmeyer et al.(1983) derived a simple relationship which described drug release from a polymeric system.

$$M_t/M = Kt^n$$

Where,

M_t/M is a fraction of drug release or time t, k is the release rate constant and small n is the release exponent. In this model, the value of n characterizes the release mechanism of drug. $0.45 < n < 0.89$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II transport, and $n > 0.89$ to super case II transport.

Stability studies:

Stability testing should be performed to the finished product in order to provide evidence of how the active pharmaceutical ingredients quality varies with time under the various environmental factors like light, temperature and humidity, stability studies also include the study of formulation related factors such as interaction of active pharmaceutical ingredient with container, other drug, excipients and packaging materials.

3. Results and discussion

Pre- Formulation Studies

Drug-Polymer Interaction Studies:

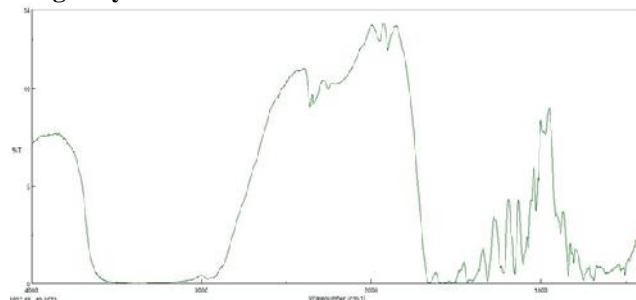


Fig 3: FT-IR spectrum of atorvastatin calcium

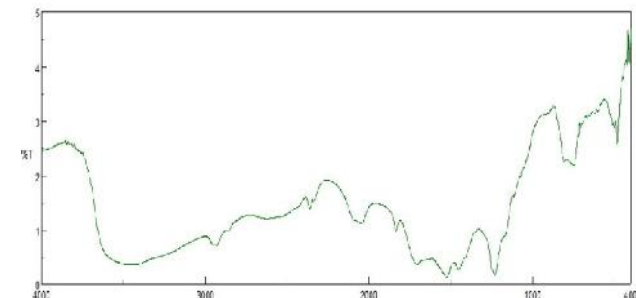


Fig 4: FT-IR spectrum of Carbopol

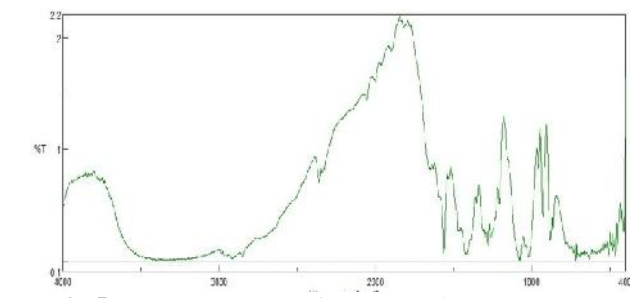


Fig 5: FT-IR spectrum of Atorvastatin and carbopol

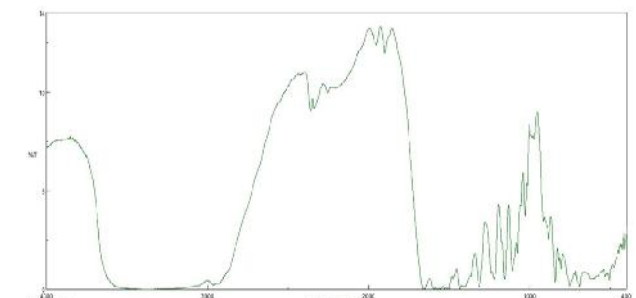


Fig 6: FT- IR spectrum of PEG

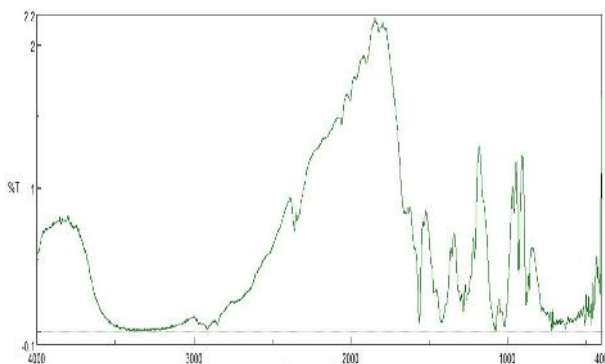


Fig 7: FT-IR spectrum of Atorvastatin and PEG

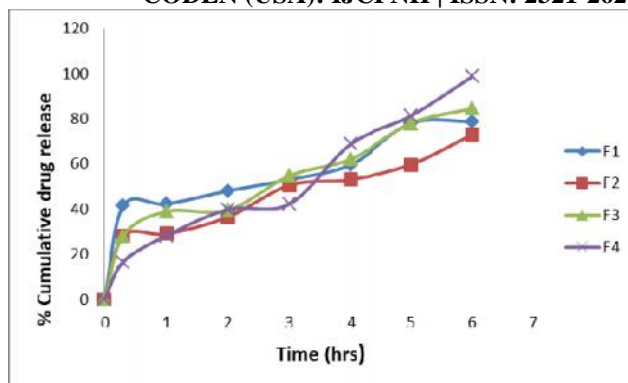


Fig 10: In-Vitro Drug release study of Atorvastatin (PEG)

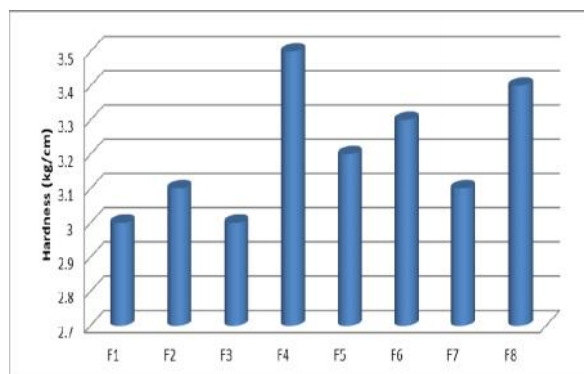


Fig 8: Hardness of Atorvastatin calcium tablets

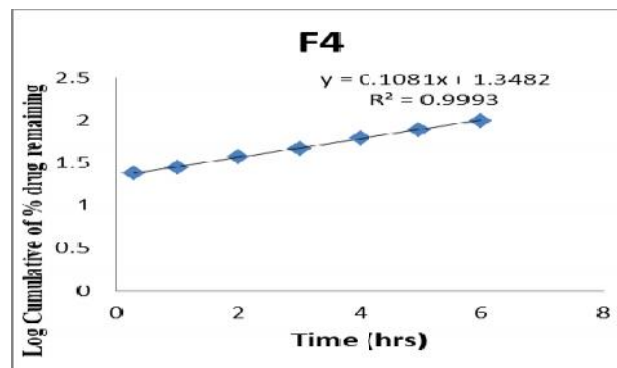


Fig 11: Graph of Cumulative % drug release Vs time of F4 formulation

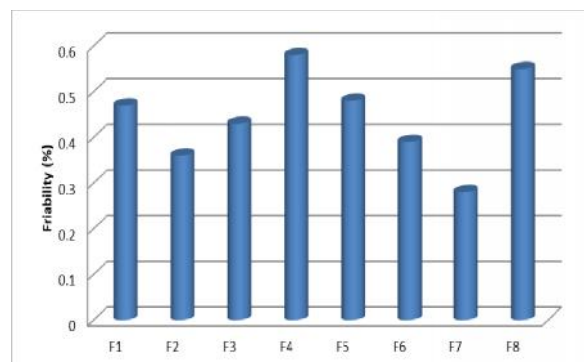


Fig 9: Friability test of Atorvastatin calcium tablets

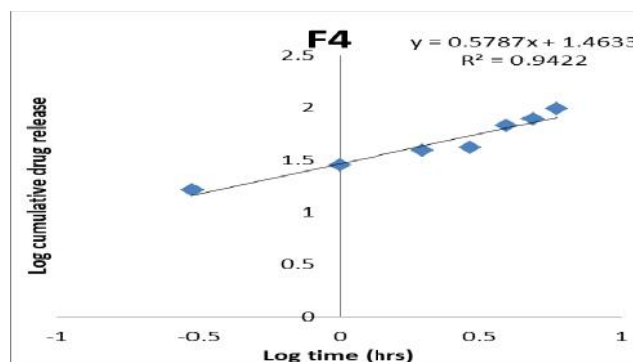


Fig 12: Korsmeyers-Peppas graph of F4 formulation

Table 1: Hardness test of Atorvastatin calcium tablets

Formulation	Hardness (kg/cm ³)
F1	3.0
F2	3.1
F3	3.0
F4	3.5
F5	3.2
F6	3.3
F7	3.1
F8	3.4

Table 2: Friability test of Atorvastatin calcium tablets

Formulation	Friability (%)
F1	0.47
F2	0.36
F3	0.43

F4	0.58
F5	0.48
F6	0.39
F7	0.28
F8	0.55

Table 3: % Drug content

S.NO	Formulation	% Drug content
1	F1	97.2
2	F2	96.5
3	F3	97.6
4	F4	98.8
5	F5	97.9
6	F6	96.1
7	F7	97.3
8	F8	97.9

Table 4: % Cumulative release of Atorvastatin with PEG (F4)

Time(hrs)	Absorbance	Concentration($\mu\text{g/ml}$)	Amount of drug release(mg)	%drug release	%Cumulative drug release
0.30	0.10	4.42	39.78	16.57	16.57
1	0.22	9.73	87.57	36.48	28.19
2	0.35	15.48	139.32	58.05	39.81
3	0.43	19.02	171.18	71.32	42.29
4	0.63	27.88	250.92	104.55	68.89
5	0.79	34.95	314.55	131.06	81.23
6	0.92	40.70	366.3	152.62	98.71

Weight variation:

All the tablets were falling within the range of (>130 mg and < 324 mg) <7.5% deviation.

Drug Content:

% drug content was determined and F4 formulation was found to be having more % of drug content when compared with other formulations.

In-vitro dissolution studies:

After in-vitro drug release studies it's clear that F4 formulation showing better release when compared to F1, F2, F3, F5, F6 and F7 formulations. In case of F1, F2, F3, F5, F6 and F7 formulations the % cumulative drug release were found to be 98.16%, 98.34%, 98.56%, 98.21%, 98.41% and 98.54% by the end of 6th hour, whereas F4 and F8 formulations has shown 98.71% and 98.68% of cumulative percentage of drug release. The results were tabulated in below table.

4. Conclusions

By this work the objective of enhancing the solubility of atorvastatin (Class II drug) has been achieved. A total of eight formulations are prepared in which first four formulations (F1, F2, F3, F4) composed of PEG as polymer where as formulations from F5-F8 (F5, F6, F7, F8) composed of carbopol as polymer. After going through a series of evaluation parameters, it is observed that F4 (Atorvastatin+PEG) formulation (1:2, drug: Polymer) is having better dissolution profile than the rest of remaining formulations. Hence it is evident the solubility of Atorvastatin is enhanced by means of Solid Dispersion techniques.

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