JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Liquisolid Compacts Based Orodispersible Tablets to Enhance Solubility of Atorvastatin using Experimental Design

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Article history:

Received 07 March 2017
Accepted 15 April 2017
Available online 15 Jun 2017

Citation:
Shah R., Banwait H., Rathi S. Patni P. Liquisolid Compacts Based Orodispersible Tablets to Enhance Solubility of Atorvastatin using Experimental Design **J Pharm Sci Bioscientific Res**. 2017. 7(3):245-250

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(www.jpsbr.org)

ABSTRACT: To obtain an enhanced in-vitro dissolution rate of Atorvastatin by using Liquisolid technique and Liquisolid tablets were optimized by QbD-DoE approach 32 full factorial design using Design Expert Software. The liquisolid tablets were formulated by using Polyethylene glycol (PEG- 400), as liquid vehicle, Avicel PH-102 as a carrier material, Aerosil as a coating material, and aspartame as sweetener and Kyron 314 as a superdisintegrant. The new mathematical model 32 full factorial design was utilized to formulate various liquisolid powder systems and to calculate amount of carrier material and coating material. All prepared liquisolid batches were subjected to weight variation, drug content uniformity, hardness, friability test, and disintegration test and dissolution tests. Liquisolid systems were also tested for DSC, FT-IR. From result of check point analysis of design data, ATLCODT1 shows higher Drug release (97.86%) at less wetting time (54.12 sec.) and disintegrating time (5.17 sec) which enhancing solubility of Atorvastatin by 4.16 mg/ml. Atorvastatin Liquisolid compacts enhance aqueous solubility and dissolution rate in compare to other solubility enhancement technique. Hence, this research work may be useful to formulate Orodispersible Tablets using Liquisolid Technique which may give rapid onset of action by rapid absorption, maximize efficacy, reduce dose and dose frequency & hence increase patient Compliance.

KEY WORDS: Liquisolid technology, Solubility enhancement, Orodispersible Tablet, Dissolution rate, DoE.

INTRODUCTION:

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological action. Poorly water soluble drugs will be inherently released at a slow rate owing to their limited solubility . The low solubility of many active pharmaceutical ingredients is one of the technical challenges in formulating as suitable dosage form for its best use. Recently more than 40% of new chemical entities developed in pharmaceutical industry are practically insoluble in water.

When combined with the *in vitro* dissolution characteristics of the drug product, the Biopharmaceutical Classification System (BCS) takes into account three major factors: solubility, intestinal permeability, and dissolution rate, all of which govern the rate and extent of oral drug absorption from immediate release solid oral-dosage forms. For BCS class II and IV drugs, the dissolution process is rate-controlling step, which determines the rate and degree of its absorption . The poor dissolution rate of water insoluble drug is a substantial problem confronting the pharmaceutical industry.

To enhance the dissolution various formulation techniques have been introduced with different degrees of success. The use of water soluble salts and polymorphic forms, formation of water soluble molecule complexes, drug micronization, solid dispersion, co-precipitation, Lyophilization, microencapsulation, and inclusion of drug solutions or liquid drugs into soft gelatin capsules are some techniques that have been reported to enhance the dissolution characteristics of water-insoluble drugs. But out of these a newer technique termed as liquisolid compact technique is found to be one of the most promising one.

Oral route is most common and popular route of administration of drug is oral route because of its systemic effect, patient compliance, less expensive to manufacture. Tablet provides high precision dosing [4]. Tablet form is the most widely used dosage form because of self-administration and ease in manufacturing. Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablet.

Tablet is the most popular among all dosage forms existing today because of its convenience of self-administration, compactness and easy manufacturing, however in many cases immediate onset of action is required than conventional therapy. To overcome these drawbacks, immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms. Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates.

The term “immediate release” pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. Immediate release dosage forms are those for which ≥85% of labelled amount dissolves within 30 min.

METHODOLOGY

Drug- Excipients Compatibility Studies by FT-IR

Potassium bromide IR disc will be prepared using Atorvastatin, Propylene glycol, poly ethylene glycol 200, Avicel PH 102, Arosile, sodium starch Glycolate, cross povidone, cross Carmalose sodium and mixture on Hydraulic Pellet press was be scanned 4000-400 cm-1 region in FTIR and obtained IR Spectrum was compared with a reference spectrum of Atorvastatin.

Drug-Excipients Compatibility Studies by DSC

Thermal analysis of Drug Atorvastatin and carrier-coating material will be studied employing differential scanning calorimetry which was done to check compatibility for Liquisolid compact formulations.

Thickness and Hardness test:

The thickness of tablets will be determined using a digital caliper; reading shown will noted. Hardness will be tested by using Monsanto tester

Friability test:

The friability of tablets will be determined using Roche friabilator. % friability will then have calculated using formula:

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

Weight variation test:

The test will be performed as per USB by weighing 20 tablets individually on electronic balance, calculating average weight, and comparing individual tablet weights to average.

In-vitro dispersion time:

In-vitro dispersion time will be measured by following procedure. Tablet will then carefully be positioned in center of petri dish containing 6 ml of water and time required for tablet to completely disintegrate into fine particles was noted. Three tablets from each formulation will randomly selected and *In-vitro* dispersion time was measured.

***In-vitro* disintegration test:**

The test will be carried out on 6 tablet using a tablet disintegration tester. Water at 37 ± 2 °C will be used as a disintegration medium and time taken for complete disintegration of tablet will noted with no palpable mass remaining in apparatus will be measured.

Wetting time:

A piece of tissue paper will be folded and placed twice and placed in a small petri dish containing sufficient water. A tablet will be kept on paper and time for complete wetting of tablet was measured.

Water absorption ratio (R):

The weight of tablet prior to placement in petri dish will be noted (Wb). Wetted tablet was removed and weighed (WA). Water absorption ratio, R, was then determined according to following equation.

$$R=100 \times (Wa-Wb)/Wb$$

Where, Wb and WA are tablet weights before and after water absorption, respectively

***In-vitro* release studies:**

The dissolution rate of formulations will be measured in dissolution test apparatus using USB type II. Dissolution studies was carried out using 900 ml of Phosphate buffer pH 7.4 at 37±0.5 °C at 100 RPM. 5 ml samples will be withdrawn at various time intervals and placed by 5 ml fresh phosphate buffer pH 7.4 to maintain sink condition. Solutions will be immediately filtered through filter paper, diluted and concentration of drug will be determined spectrophotometrically.

RESULT AND DISCUSSION

Potassium bromide IR disc was prepared using Atorvastatin, Propylene glycol, poly ethylene glycol 200, Avicel PH 102, Arosile, cross povidone and mixture on Hydraulic Pellet press was scanned 4000-400 cm-1 region in FTIR and obtained IR Spectrum was compared with a reference spectrum of Atorvastatin.

Figure:1 Identification of Drug- Atorvastatin by FT-IR Spectroscopy

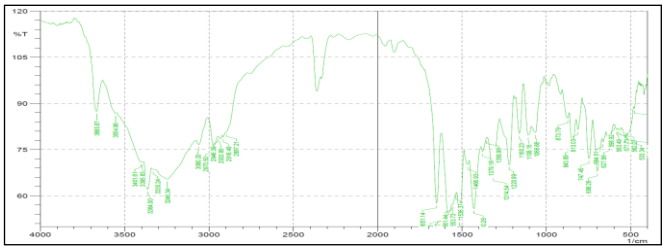
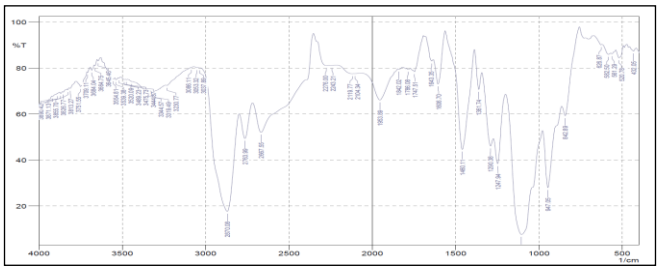


Figure:2 FT-IR graph of Atorvastatin+PEG-400+Avicel PH 102+Arosile+ Cross-Povidone+Aspartame



The obtained FT-IR spectrum compiles with standard data which further confirms Drug Excipient compatibility.

Drug-Excipients Compatibility Studies by DSC

Thermal analysis of Drug Atorvastatin and carrier-coating material was studied employing differential scanning calorimetry which was done to check compatibility for Liquisolid compact formulations.

Figure:3 DSC graph of Atorvastatin

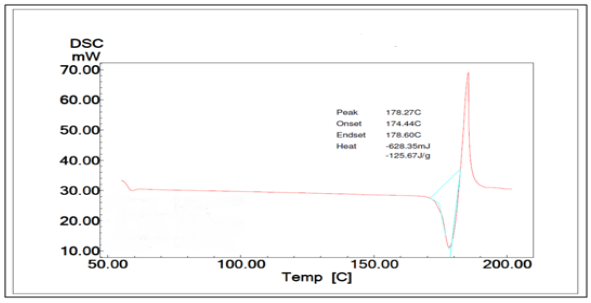
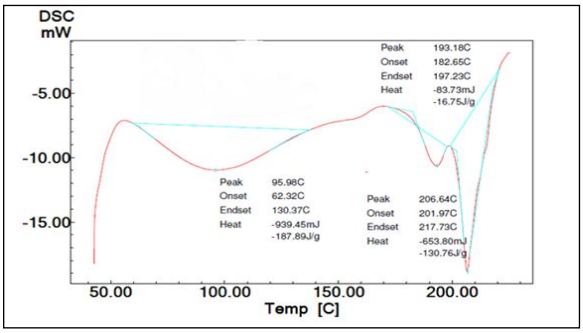


Figure: 4 DSC graph of Lamotrigine+Avicel PH 102+ Aerosil+ Crosspovidone+ PEG 400+ Aspartame



All DSC graph shows that drug Atorvastatin is compatible with all other excipients of formulation of Atorvastatin Liquisolid Orodispersible Tablets.

Thickness: Thickness of tablets measured by using digital Vernier caliper.

Table:1 Thickness of tablets

Formulation	Thickness(mm) (mean ± SD) (n=3)
ATLCODT1	4.06±0.15
ATLCODT2	4.14±0.13

Thickness of tablets of all batches was found to be in range of 4.06±0.15 to 4.14±0.15 mm.

Friability: Friability of tablets measured by using Roche friability apparatus.

Table:2 % friability of tablets

Formulation	%Friability (mean ± SD) (n=3)
ATLCODT1	0.109±0.015
ATLCODT2	0.147±0.017

Friability of all batches was come within official limit of not more than 1%.

Weight Variation: Weight variation study was performed using analytical weight balance.

Table:3 Evaluation data for Weight variation of tablets

Formulation	Weight variation (g) (mean ± SD) (n=20)
ATLCODT1	0.560 ± 0.005
ATLCODT2	0.562± 0.010

Both batches pass weight variation test as % deviations are within range of ± 5 %.

Drug Content

Table:4 Drug content (%) of tablets

Formulation	Drug Content (%) (mean ± SD) (n=3)
ATLCODT1	98.99±0.12
ATLCODT2	98.62±0.10

In-vitro Disintegration Time

Table:5 In-vitro Disintegration Time

Formulation	Disintegration Time (Sec) (mean ± SD) (n=3)
ATLCODT1	5.17±1.01
ATLCODT2	5.43±1.36

Wetting time

Table:6 Wetting time

Formulation	Wetting time (Sec) (mean ± SD) (n=3)
ATLCODT1	54.12 ± 1.23
ATLCODT2	55.23 ± 1.52

Water absorption ratio

Table:7 Water absorption Ratio

Formulation	Water absorption Ratio (mean ± SD) (n=3)
ATLCODT1	1.51±0.06
ATLCODT2	1.59±0.03

In-vitro Dispersion Time

Table:8 In-vitro Dispersion Time

Formulation	In-vitro Dispersion Time (Sec) (mean ± SD) (n=3)
ATLCODT1	16.14 ± 1.54
ATLCODT2	18.45 ± 1.45

In-Vitro Drug release study

Table:9 *In-vitro* Release Study of Atorvastatin Liquisolid Orodispersible Tablets

Time (min)	ATLCODT1 (Mean± S.D.) (n=3)	ATLCODT2 (Mean± S.D.) (n=3)
0	0.00	0.00
2	45.16±1.25	43.92±1.58
4	56.95±1.47	55.78±1.97
6	76.37±1.28	75.49±1.28
8	85.03±1.34	84.25±1.43
10	97.86.±1.92	96.87±1.62
15	-	-

CONCLUSION

The Liquisolid system is new technique for formulation of water insoluble drugs to enhance their aqueous solubility, absorption as well as dissolution rate which leading to enhancement of bioavailability of drugs as compared to conventional directly compressed tablets. Liquisolid technology can be used for purpose of formulating modified drug release system by selecting right excipient. It is effective technology in terms of production capability and low coast of formulation. Thus, this technology has potential for large scale manufacture. Excipients required in Liquisolid system are conventional and commonly available in market. On base of advantages of Liquisolid system, it is envisaged that Liquisolid system could play important role in modern solid dosage forms. Atorvastatin Liquisolid compacts enhance aqueous solubility and dissolution rate by maximizing surface area, aqueous solubility and wettability.

Further, Atorvastatin Orodispersible Liquisolid Tablets may give rapid onset of action by rapid absorption through pre-gastric absorption of Atorvastatin from mouth, pharynx and esophagus as saliva passed down and beneficial to reduce dose.

By combining Atorvastatin Liquisolid technique and Orodispersible DDS, may enhance solubility, dissolution rate by means of Liquisolid technique and can achieve rapid onset of action with lower dose of drug by using Orodispersible DDS and hence may increase patient compliance.

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