International Journal of
Innovative Drug Discovery

e ISSN 2249 - 7609
Print ISSN 2249 - 7617

www.ijidd.com

ENHANCEMENT OF SOLUBILITY & DISSOLUTION RATE OF PRAVASTATIN USING SOLID DISPERSION.

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ABSTRACT

The solubility and dissolution rate of pravastatin, a drug used for the treatment of hyperlipidaemia. Pravastatin 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 preliminary solubility analysis was carried out for the selection of the carrier and solid dispersion was prepared with Hydroxy Propyl Methyl Cellulose (HPMC) and Methyl Cellulose (MC). These 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. Solid dispersion prepared with polymer in 1:5 ratios shows the presence of amorphous form confirmed by the characterization study. The present investigations showed that solubility of Pravastatin sodium was markedly increased by its solid dispersion using PVP K30 as carrier. The formulation SDF8 containing (1:8) shows highest dissolution rate. Hence the solid dispersion a way is useful technique in providing fastest onset of action of Pravastatin sodium as well as enhanced dissolution rate. The study also shows that dissolution rate of pravastatin can be enhanced to considerable extent by solid dispersion technique with Polymer.

KEY WORDS: Solid Dispersion, Pravastatin Sodium, Solubility, Rate Constant, First Order Kinetics.

INTRODUCTION

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system and is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. Poorly water-soluble drugs after oral administration often require high doses in order to reach therapeutic plasma concentrations. The bioavailability of an orally administered drug depends on its solubility in aqueous media over different pH ranges. The insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water soluble compounds. Various techniques are used for the improvement of the aqueous solubility, dissolution rate, and bioavailability of poorly water soluble drugs include micronization, chemical modification, pH adjustment, solid dispersion, complexation, cosolvency, micellar solubilization, hydrotropy etc.

The oral route of drug administration is the most common and preferred method of delivery. However, several orally administered drugs have a reduced bioavailability due to poor water solubility. In biopharmaceutical classification system drugs with low aqueous solubility, slow dissolution rate, high dose, and high membrane permeability are categorized as Class II drug. To overcome low bioavailability, many of the modern oral drug delivery systems emphasize on formulation strategies such as alteration of solvent composition, carrier systems as well as chemical and physical modifications. Solid dispersion of drug in a water soluble polymer has been shown to be one of the most promising strategies to improve solubility. Increasing the Bioavailability of a poorly soluble drug is a challenging aspect of drug development. Because of the poor aqueous solubility the drug possess dissolution problems due to which the in vivo absorption of the drug is reduced and thus the bioavailability is reduced, making the drug inappropriate for oral consumption and therefore solubility enhancement become necessary for such drug candidate.

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Solid dispersion is a most simple and efficient technique for increasing the aqueous solubility of a drug. Pravastatin is a cholesterol-lowering agent that belongs to a class of medications known as statins. It was derived from microbial transformation of mevastatin, the first statin discovered. It is a ring- -hydroxyl group that does not require in vivo activation. Hence the objective of the present work was to obtained faster onset of action and successfully enhanced the bioavailability by developing solid dispersion.

MATERIALS & METHODS

Pravastatin Sodium

Pravastatin is a cholesterol-lowering agent that belongs to a class of medications known as statins. It was derived from microbial transformation of mevastatin, the first statin discovered. It is a ring- β -hydroxyl group that does not require in vivo activation. Pravastatin is one of the lower potency statins; however, its increased hydrophilicity is thought to confer advantages such as minimal penetration through lipophilic membranes of peripheral cells, increased selectivity for hepatic tissues, and a reduction in side effects compared with lovastatin and simvastatin (Mol. Weight: 446.5096

Materials and Instruments

The following materials that were procured from different sources some of which were analytical grade and best possible Laboratory Reagent were used as supplied by the manufacturer without further purification or investigation.

Preformulation Study

Physiochemical Properties of Pravastatin sodium

A) Physical evaluation

It refers to the evaluation by sensory characters-taste, appearance, odor, feel of the drug, etc.

B) Solubility:

Solubility of the drug was determined by taking some quantity of drug (about 1-2 mg) in the test tube separately and added the 5 ml of the solvent (water, ethanol, methanol, 0.1N HCl, 0.1 N NaOH and Chloroform) Shake vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature) (Indian pharmacopeia, 2007).

C) Melting point:

It is one of the parameters to judge the purity of drugs. In case of pure chemicals, melting points are very sharp and constant. Since the drugs contain the mixed chemicals, they are described with certain range of melting point (Reddy et al., 2016).

D) Identification Test FTIR Spectroscopy

Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound. The region from 0.8 μ to 2.5 μ is called Near Infra-red and that from 15 μ to 200 μ is called Far infra-red region.

Identification of Pravastatin sodium was done by FTIR Spectroscopy with respect to marker compound. Pravastatin sodium was obtained as White or off-white powder. It was identified from the result of IR spectrum as per specification (Dubey et al., 2017).

E) Loss on drying:

The moisture in a solid can be expressed on a wet weight or dry wet basis. On a wet weight basis, the water content of a material is calculated as a percentage of the weight of the weight solid. The term loss on drying is an expression of moisture content on a wet weight basis.

F) Bulk properties

Bulk density is defined as the mass of powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particles become more spherical in shape, bulk density is increase. In addition as granules size increase, bulk density decrease. Bulk properties such as particle size, bulk density etc. of a solid form, are likely to change during process development. Therefore, comprehensive characterization of all Preformulation lots is necessary to avoid misleading predictions.

G) Tapped density:

Tapped density is determined by measuring the volume of a known mass of powder sample before and after the tapping that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup (Newman, 1995).

Procedure:

Accurately weighed 10mg of powder was poured into the measuring cylinder carefully level the powder and read the tapped volume (after 50-60 times tapping), Vt to the nearest graduated unit. Calculate the tapped density in gm per ml, gm/ cm3 by the formula:

Tapped density = Bulk Mass/ Tapped Volume

H) Compressibility Index

Compressibility index (C.I.) is an important measure that can be obtained than 20% to 30% is defined as the free flowing material (Wells, 1998).

I) Hausner Ratio:

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner ratio = Tapped density / Bulk Density

J) Moisture content determination:

Principle: The titrimetric determination of water is based upon the quantitative reaction of water with an anhydrous solution of sulphur dioxide and iodine in the presence of a buffer that reacts with hydrogen ions.

K) λ_{max} Determination of λ_{max}:

The λ_{max} of Pravastatin sodium was determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer (Balaji and Katteboina, 2009).

RESULTS AND DISCUSSION

7.1 Physiochemical Properties of Pravastatin sodium:

A) Physical evaluation: Results of Physical evaluation are summarized in Table 3.

When the regression coefficient values were compared, it was observed that an "r" value of first order was maximum i.e. 0.917 hence indicating drug releases from formulation was found to follow first order kinetics.

Figure 1: Structure of Pravastatin sodium.

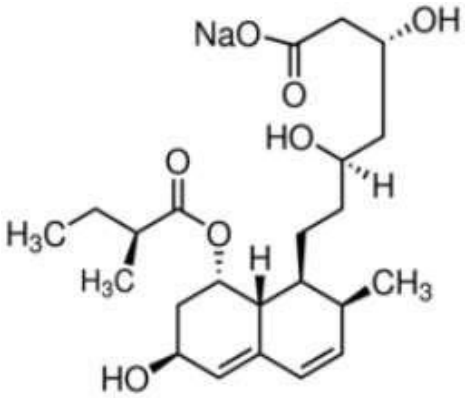


Table 1: List of drug and Excipients used.

S. No.	Name of chemical	Supplier
1.	Pravastatin sodium	Bioplus life science, Bangalore
2.	Methanol	Qualigens Fine Chemicals, Mumbai
3.	Ethanol	Qualigens Fine Chemicals, Mumbai
4.	Chloroform	Qualigens Fine Chemicals, Mumbai
5.	PVP	LobaChemie PVT. LTD. Mumbai
6.	Sodium lauryl sulfate	S. D. Fine Chem. Ltd., Mumbai
7.	Propylene Glycol	S. D. Fine Chem. Ltd., Mumbai

Table 2: List of Instruments Used

S. No.	Instrument	Manufacture
1.	Electronic Balance	Digital Balance Wensor
2.	FTIR	BrukerAlpha,Germany
3.	Dissolution Test Apparatus	Labindia DS 8000
4.	UV- Visible Spectrophotometer	Labindia Double BeamSpectrophotometer (3000 plus)
5.	Melting Point Apparatus	Contech Instruments Ltd., Mumbai

Table 3: List of Sensory Characters.

S. No.	Sensory characters	Result
1.	Colour	White or off-white powder
2.	Odor	Odorless

B) Solubility: Results of Solubility are summarized in Table 4.

Table 4: Solubility of Pravastatin sodium

Solvent used	Pravastatin sodium
Distilled Water	Slightly Soluble

0.1 N Hydrochloric acid	Soluble
Ethanol	Soluble
Methanol	Freely soluble
Chloroform	Soluble
Phosphate Buffer pH 7.2	Soluble

C) Melting Point: Results of Melting point are summarized in Table 5.

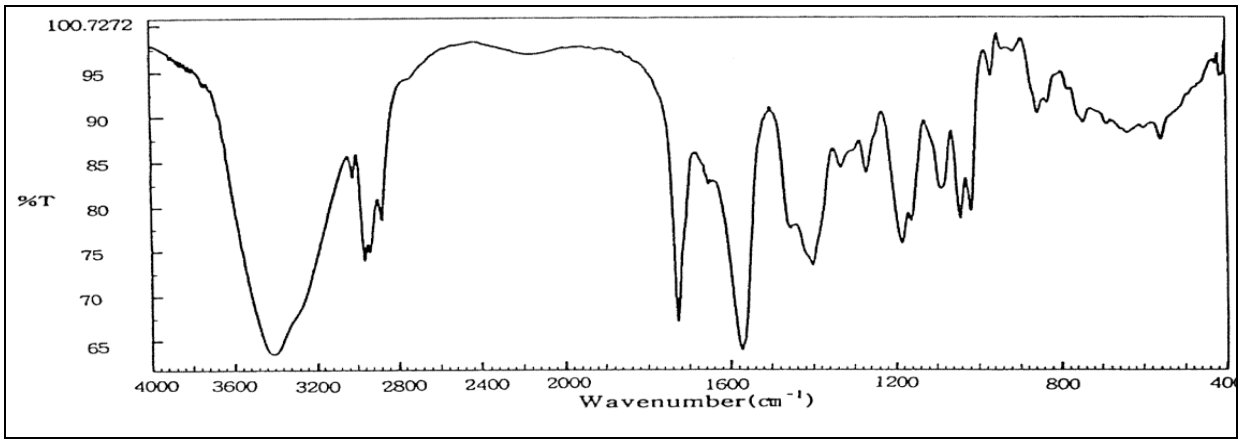
Table 5: Melting point of the Pravastatin Sodium.

S. No.	Melting Point of Pravastatin Sodium	Average Melting Point of Pravastatin sodium
1.	172 ºC-174 ºC	171 - 173°C
2.	171 ºC -173 ºC	
3.	171 ºC -173 ºC	

D) Identification Test FTIR Spectroscopy.

Sample of pure Pravastatin sodium

The IR spectrum of sample drug shows the peak values which are characteristics of the drug and the graph were shown in figure no. 2



E) Loss o drying: Results of Melting point are summarized in Table 6.

Table 6: Loss of drying of drug sample

S. No.	Initial weight	Final weight after 15 minutes	% loss of drying	Avg. % loss of drying
1.	5gm	4.97 gm	0.6 %	0.688
2.	5gm	4.91 gm	0.8 %	
3.	5gm	4.97 gm	0.6 %	

F) Bulk density: Results of Bulk densityare summarized in Table 7.

Table 7: Bulk density of Pravastatin sodium

S. No.	Bulk mass	Bulk volume	Bulk density	Avg. bulk density
1.	1 gm	3.2 ml	0.31 g/ml	0.31±0.0057
2.	1 gm	3.1 ml	0.32 g/ml	
3.	1 gm	3.2 ml	0.31 g/ml	

G) Tapped density: Results of Tapped densityare summarized in Table 8.

Table 8: Tapped density of Pravastatin Sodium

S. No.	Bulk mass	Tapped volume	Tapped density	Avg. tapped density
1.	1 gm	2.0 ml	0.50 g/ ml	0.50±0.015
2.	1 gm	1.9 ml	0.52 g/ ml	
3.	1 gm	2.0 ml	0.50g/ ml	

H) Compressibility Index: Results of Compressibility Index are summarized in Table 9.

Table 9: C.I. of Pravastatin sodium.

S. No.	Bulk density	Tapped density	C.I.
1.	0.31 g/ml	0.50 g/ml	38.0

I) Hausner'sRatio:Results Hausne'sr Ratioare summarized in Table 10.

Table 10: Hausner ratio of Pravastatin sodium

S. No.	Bulk density	Tapped density	Hausner ratio
1.	0.31 g/ml	0.50 g/ml	1.61

J) Moisture content determination: Results of Moisture content determination are summarized in Table 11.

Table 11: Moisture Content Determination.

S. No.	Drug	KF Factor	Amount of KF Reagent consumed	Moisture content
1	Pravastatin sodium	0.362	0.15ml	0.0543

K) λmax Determination: U.V. spectrophotometer (Labindia-3000+). The spectrum peak point graph of absorbance of Pravastatin sodium versus wave length was shown in figure 3:

Figure 3: Wavelength maxima of Pravastatin sodium in 0.1 N HCl

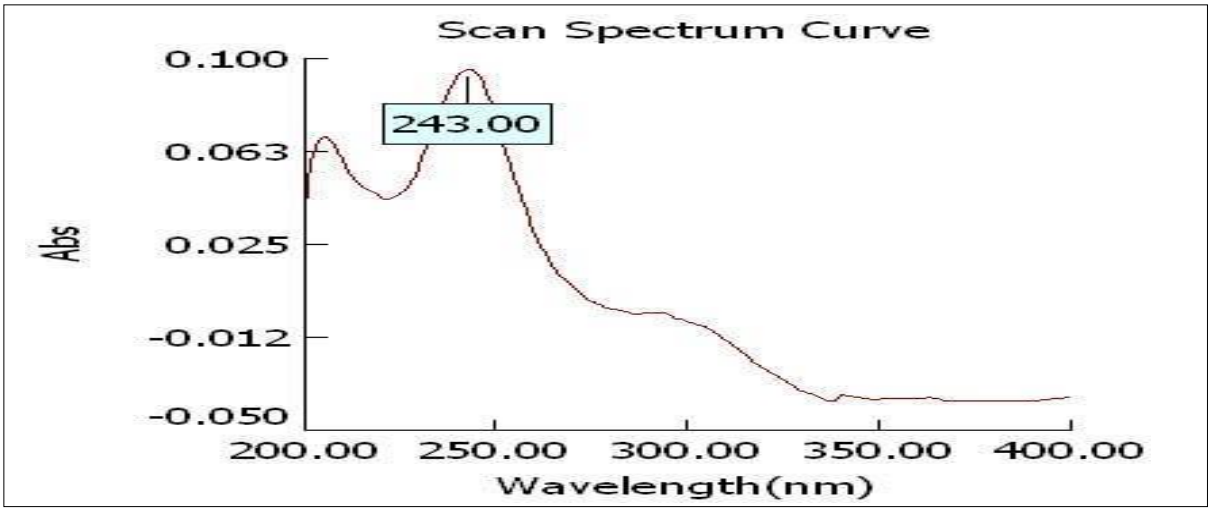


Table 12: Calibration curve of Pravastatin sodium.

S. No.	Conc. (µg/ml)	Absorbance
1	10	0.125±0.005
2	20	0.248±0.003
3	30	0.369±0.004
4	40	0.478±0.006
5	50	0.598±0.004

J) Release kinetics of Pravastatin sodium solid dispersion (optimized formulation SDF8):

Table 13: In-vitro drug release data for optimized formulation SDF8

Time (min)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
30	5.477	1.477	12.55	1.099	87.45	1.942
60	7.746	1.778	22.65	1.355	77.35	1.888
120	10.955	2.079	32.45	1.511	67.55	1.830
240	15.492	2.38	40.23	1.605	59.77	1.776

Table 14: Regression analysis data.

	Zero Order	First Order
Batch	**r^2**	**r^2**
SDF8	0.885	0.917

Figure 4: Graph of zero order release Kinetics of formulation SDF8.

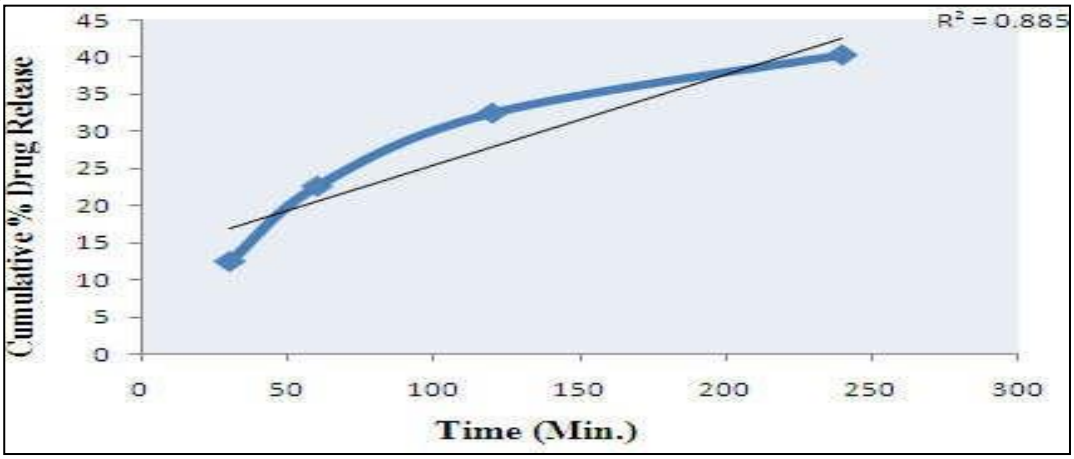
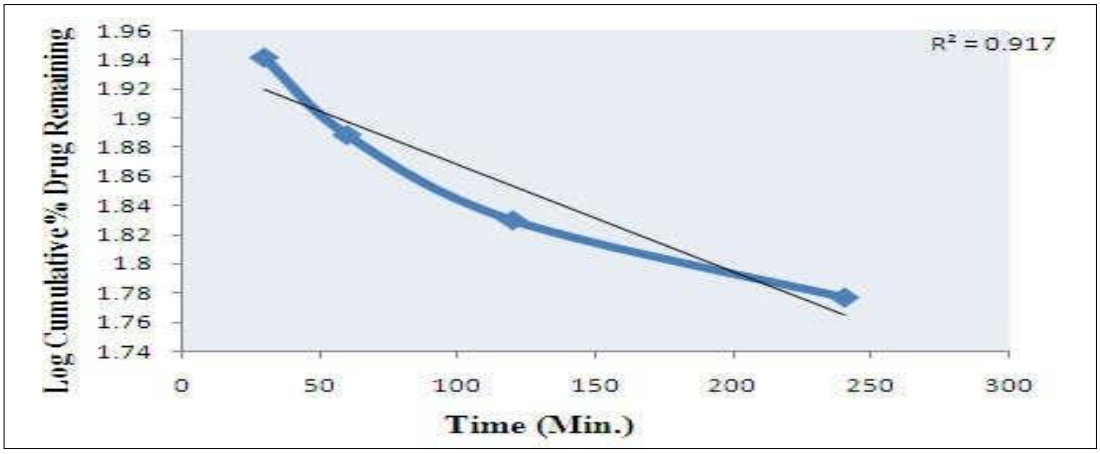


Figure 5: Graph of first order release kinetics of formulation SDF8 Table 7.8:



Conclusion

Increasing the Bioavailability of a poorly soluble drug is a challenging aspect of drug development. Because of the poor aqueous solubility the drug possess dissolution problems due to which the in vivo absorption of the drug is reduced and thus the bioavailability is reduced, making the drug inappropriate for oral consumption and therefore solubility enhancement become necessary for such drug candidate.

Preformulation of drug and excipient was performed in which physiochemical properties and other parameters of drug were studied. Physiochemical parameters such determination of solubility, melting point, partition coefficient, drug-excipient max scan using UV-spectrophotometry, FT-IR spectrophotometry wereperformed in this study. The obtained data from these studies were matched with the data given in standard monographs to confirm the authenticity of procured drug.

Procured Pravastatin sodium was odorless and White to off-white powder in nature. In solubility study it was found that drug was freely soluble in methanol and soluble in 0.1 N hydrochloric acid ethanol chloroform phosphate buffer pH 7.2. It was slightly soluble in distilled water. Melting point of drug was found 171 - 173°C while it was 170ºC reported in standard monograph.

The obtained FT-IR characteristic peaks of drug was matched with the peaks of drug given in standard monograph was revealed similar. Identification of Pravastatin sodium sample was done by infrared spectroscopy. Moisture content of Pravastatin sodium was found 0.0543mg.

The drug solution was scan on UV-spectrophotometer at 200-400 nm in Wavelength range to

determine the maximum absorbance (max) and it was found at 243nm. The calibration curve was prepared in 0.1 N HCl. The regression coefficient (R2) was 0.917 which was shows the linearity of curve.

Solid dispersion is a most simple and efficient technique for increasing the aqueous solubility of a drug. PEG 8000, PVP K 30 and SLS solid dispersion were used to prepare at weight ratios of 1:1, 1:2, 1:4 and 1:8, using three different preparation methods, physical trituration, kneading and solvent evaporation.

Values of First order was maximum i.e. 0.917 hence indicating drug release from formulations was found to follow first order kinetics. The present investigations showed that solubility of Pravastatin sodium was markedly increased by its solid dispersion using PVP K30 as carrier. The formulation SDF8 containing (1:8) shows highest dissolution rate. Hence the solid dispersion a way is useful technique in providing fastest onset of action of Pravastatin sodium as well as enhanced dissolution rate.

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