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Formulation Development and Characterization of Rosuvastatin Inclusion Complexation

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A B S T R A C T

The present investigation is to study the influence of β-Cyclodextrin and hydroxy propyl β-Cyclodextrin on 1:1, 1:2 molar ratios of Rosuvastatin inclusion complexations which are prepared by using various methods such as co-grinding, kneading method. Drug and excipient compatability studies like solubility, chemical interaction studies were performed for individual and combined forms. From the preformuation studies, it was found that individual and combined forms were compatible by the conduction of FTIR study. The prepared formulations were subjected for production yield, drug content, and *in-vitro* drug release. The cumulative percent drug release for the optimized formulation K2 showed 40.11% at the end of the 120 minutes. Hydroxy propyl β-Cyclodextrin had showed excellent dissolution profile of Rosuvastatin when compared to β-Cyclodextrin inclusion complications.

Keywords: Absorption, Amorphous, Crystalline, Solubility, Mass transfer.

A R T I C L E I N F O

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1. Introduction

Drug discovery and drug development often have different solubility screening requirements and methodologies have been developed to meet the needs of these different stages. The solubility behaviour of drugs remains one of the most

challenging aspects in formulation development1. The mechanism by which inclusion complexation enhances the solubility and dissolution involves particle size reduction to fine form or molecular level, conversion of crystalline form to amorphous form and by enhancing wettability [2]. This class of drugs (BCS-II) have a high absorption number but a low dissolution number. *In-vivo* drug dissolution is then a rate limiting step for absorption except at a very high dose number. Drugs belonging to this class have low solubility and high permeability, hence, the dissolution rate becomes the governing parameter for bioavailability. *In-vitro and in-vivo* correlation (IVIVC) is usually accepted for this class of drugs [3].

The bioavailability of these products is limited by their salvation rates. Hence, a correlation between the *in-vivo* bioavailability and the *in-vitro* salvation can be found. These drugs exhibit variable bioavailability and needs enhancement in the dissolution rate by different methods for improvement in bioavailability. These are also suitable for controlled release development. Bioavailability of poorly water-soluble hydrophobic drugs is limited by their solubility and dissolution rate. Several studies were carried out to increase the dissolution rate of drug4. One such study was inclusion complexation which has shown promising results in improving solubility, wettability, dissolution rate of drug and subsequently its bioavailability5. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins. The complexation with cyclodextrins was used for enhancement of solubility.

2. Materials and Methods

Materials

The following chemicals and solvents were used: Rosuvastatin (a gift sample from A-Z Pharmaceuticals, Chennai), β-Cyclodextrin and hydroxy propyl β-Cyclodextrin were purchased from Sigma Chemicals pvt Ltd, Mumbai. All the reagents used were of analytical grade satisfying Pharmacopoeial standards.

Prepartion of Inclusion Complexation

The inclusion complexation of Rosuvastatin and the carrier like β-Cyclodextrin was prepared in a 1:1, 1:2 molar ratios of Drug: β-Cyclodextrin respectively using physical mixture, co-grinding, kneeding and solvent evaporation technique [6].

Table 1: Preparation of Inclusion complexes of Rosuvastatin with β-Cyclodextrin

S.No	Method	Drug (mg)	β-Cyclodextrin (mg)	Drug: Polymer (Molar ratio)
1	Co-grinding	0.482	1135	1:1
		0.482	2270	1:2
2	Kneading	0.482	1135	1:1
		0.482	2270	1:2

Table 2: Preparation of Inclusion complexes of Rosuvastatin with HP β-Cyclodextrin

S.No	Method	Drug (mg)	HP B-Cyclodextrin (mg)	Drug: Polymer (Molar ratio)
1	Co-grinding	0.482	2250	1:1
		0.482	3100	1:2
2	Kneading	0.482	2250	1:1
		0.482	3100	1:2

Experimental Work

Preformulation Study

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as 'investigation of physical and chemical properties of the drug substance alone and when combined with excipients. These studies should focus on those physicochemical properties of the new compound that could affect drug performance and development of an efficacious dosage form[7-8]. The goals of the study therefore are,

- To establish necessary physicochemical parameters of new drug substance.
- To establish physical characteristics.
- To establish its compatibility with the various excipients.

Standard Curve of Rosuvastatin

Rosuvastatin is a white powder which is practically soluble in water. Though several methods are reported for its estimation, the UV spectrophotometric method is employed in the study. Rosuvastatin shows maximum absorbance at 274nm in methanol. Based on this information, a standard graph was constructed.

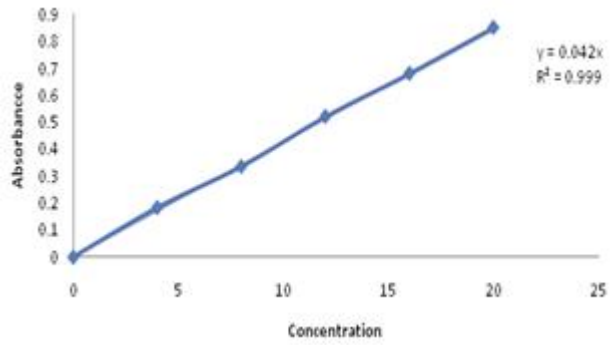

Figure 1: Calibration Curve of Rosuvastatin

FTIR Spectroscopy

Fourier Transform Infrared (FTIR) spectral measurements for Rosuvastatin and their Inclusion Complexation were recorded using FTIR spectrophotometer[9]. Potassium bromide pellet method was employed. The Inclusion Complexation was finely ground with KBr to prepare the pellets under a hydraulic pressure of 600 psi and background spectrum was collected under identical conditions. Each spectrum was recorded in range of 4000-400 cm^{-1} at the spectral resolution of 2 cm^{-1}.

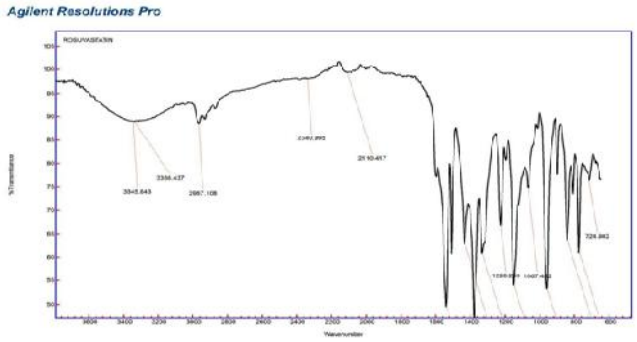

Figure 2: FT-IR spectra of Rosuvastatin

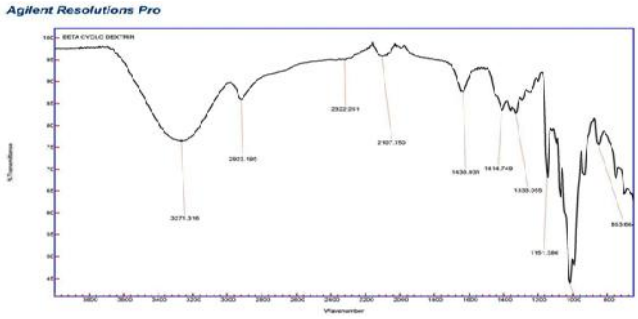

Figure 3: FT-IR spectra of β-Cyclodextrin

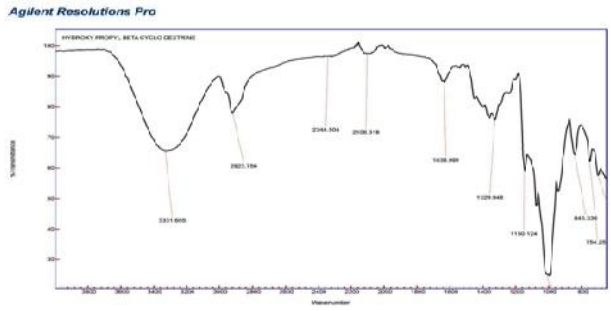

Figure 4: FT-IR spectra of hydroxy propyl β-Cyclodextrin

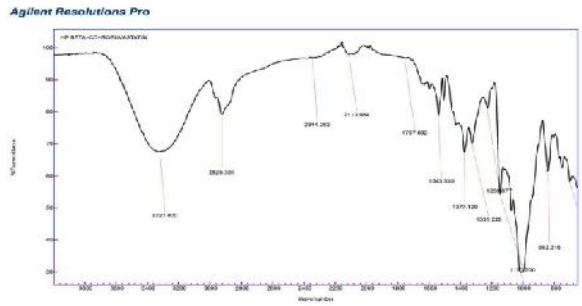

Figure 5: FT-IR spectra of Rosuvastatin, β-Cyclodextrin, Hydroxy propyl β-Cyclodextrin

3. Results and discussions

Evaluation Parameters

Determination of flow properties [10-14]

The flow properties of the powders can be predicted from the values of bulk density, tapped density, angle of repose, compressibility index and Hausner ratio. The flow properties were determined for Rosuvastatin inclusion complexation as per USP.

Bulk density

The bulk density was evaluated using bulk density apparatus. It was measured by pouring the weighed amount of pure drug and solid dispersions into a graduated measuring cylinder and the volume was noted. The procedure was repeated thrice and the mean was calculated. Bulk density is the ratio of weight of dry powder to its bulk volume.

$$Bulk\ density = \frac{Weight\ of\ dry\ powder\ (g)}{Bulk\ volume\ (cc)}$$

Tapped density

Tapped density is the ratio of weight of dry powder to its tapped volume. The weighed quantity of dry powder was taken in a graduated cylinder. The tapped volume was measured after tapping the measuring cylinders for 10 times from a one inch height from the base. The procedure was repeated thrice and the mean values were calculated.

$$Tapped\ density = \frac{Weight\ of\ dry\ powder\ (g)}{Tapped\ volume\ (cc)}$$

Compressibility index or Carr's index

Compressibility index was calculated using the following formula,

$$Compressibility\ Index\ (I) = \frac{Bulk\ volume - Tapped\ volume}{Tapped\ volume} \times 100$$

Compressibility index should be 10-15 % for good flow behavior. C.I > 38 % indicates very poor flow as per USP.

Hausner ratio

Hausner ratio was calculated using formula,

$$Hausner\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Hausner index above 1.60 indicates very poor flow. It should be in the range of 1.00 – 1.18 % to exhibit good flow characteristics.

Angle of repose

Angle of repose is considered as indirect measurement of powder flowability. The static angle of repose was measured as per the method described in USP. A funnel with the end of the stem cut perpendicular to its axis of symmetry was securely arranged above the graph paper placed on a flat horizontal surface. Sample was carefully poured through the funnel until the apex of the cone thus formed just reaches the tip of the funnel. The funnel height was maintained 2 cm from the top of the powder pile. The mean diameter of the base of the powder cone was determined and the tangent of the angle of repose was obtained by the following formula.

$$Angle\ of\ repose\ (\theta) = Tan^{-1}\frac{h}{r}$$

Where, 'h' is height of the heap and 'r' is radius of the heap. Angle of repose < 35°, indicates good flow behavior.

Percentage Practical Yield

Percentage crystal yield was calculated to know about percent yield or efficiency of any method and thus its help

in selection of appropriate method of production. The final weights of the prepared formulation were taken and percentage crystal yield was calculated by using the given formula.

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Drug Content

Good Practical yield of formulation was obtained and drug wastage is very low and percentae of drug content was estimated by single point drug analysis method. Equivalent weight of inclusion complexation containing 10 mg drug was weighed accurately and transferred in 10ml standard flasks and volume was made up to 10ml with 0.1N HCl buffer. Take 1ml from above the solution in 10ml standard flasks and volume made up to 10ml with 0.1N HCl buffer. The solution was filtered and analyzed for their drug content spectrophotometrically by measuring absorbance at 274nm.

Percentage of drug content was calculated by following formula:

$$\text{Drug Content} = \frac{\text{test absorbance} \times \text{standard dilution}}{\text{standard absorbance} \times \text{test dilution} \times \text{amount taken}}$$

***In-Vitro* Dissolution Studies**

The release of formulation from inclusion complexation was determined using USP paddle type dissolution apparatus. The dissolution test was performed using pH 7.4 buffer as dissolution media at 37 ± 0.5 ^{0}C with 50 rpm for 120 minutes. A sample of each preparation equivalent to 5 mg of drug was added to dissolution medium. A 5ml aliquot was withdrawn at different time intervals (5, 10, 15, 30, 45, 60, 90 and 120 minutes) and filtered and each sample was replaced with 5ml of fresh dissolution medium[15]. The filtered solutions were suitably diluted to 10ml with dissolution media. Samples were analyzed for its drug content spectrophotometrically by measuring the absorbance against blank at 274nm.

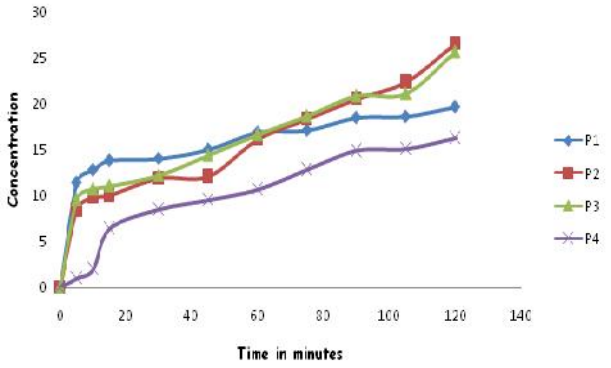

Figure 6: *In-vitro* drug release profile of P1-P4

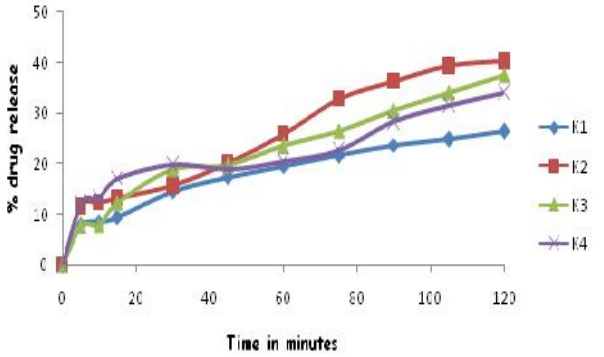

Figure 7: *In-vitro* drug release profile of K1-K4

Drug content of Rosuvastatin inclusion complexation was found between 33 mg – 67% in by kneading method which indicates incororation effeciency of excipient. Angle of repose of Rosuvastatin inclusion complexation was found at the range of 25.22’ to 41.4’ and indicates type of flows for the respective inclusion complexation. The bulk density of rosuvastatin inclusion complexation was found at the range of 2.67-9.48 and tapped density was found at the range of 1.62-8.82 and Carr’s index in between 5.5–13.25 and Hausner’s ratio of was found between 1.01–1.2. *In-vitro* drug release profile ranges from 16 to 40% in case of beta cyclodextrin and hydroxy propyl beta cyclodextrin. The percentage of drug release is more in case of Rosuvastatin Hydroxy propyl beta cyclodextrin inclusion complexation.

Figure 3: *In-Vitro* Dissolution Studies

Formulation Code	Drug Content (%)	Angle of Repose	Bulk Density	Tapped Density	Carr’s Index	Hausner’s Ratio
P1	33.54	25.22’	9.48	1.62	5.5	1.02
P2	57.09	27.30’	7.60	3.71	6.3	1.05
P3	38.09	30.54’	4.45	4.70	8.6	1.16
P4	67.05	35.22’	3.37	7.45	10.2	1.37
K1	0.65	27.86’	8.65	2.81	13.25	1.01
K2	2.50	29.90’	7.62	4.67	10.08	1.07
K3	0.95	35.95’	5.47	6.73	11.53	1.19
K4	1.90	41.40’	2.67	8.82	13.21	1.20

4. Conclusion

The present work was devoted to the improvement of the solubility and the dissolutions rate of Rosuvastatin. These improvements were achieved by forming inclusion complexes with β-Cyclodextrin & HPβ-Cyclodextrin. The method of preparation of the kneading technique had an effect on the type of complex formed. There is no

incompatibility between drug and excipient by the conduction of preformulation studies such as FTIR. The formulation K2 has showed more drug release when compared to the other formulations. Therefore we conclude that Rosuvastatin kneading complexes could be very useful to improve the solubility and stability profile with HP β-Cyclodextrin.

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