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Original Research Article

Enhancement of dissolution rate of Rosuvastatin calcium by complexation with β-cyclodextrins

Tanuja B*, Vasavi sowndarya A, Vijaya lakshmi.T, Sai mounika A, Venkata Ramana M, Ramarao N
Department of pharmaceutics, chalapathi institute of pharmaceutical sciences, Lam, Guntur, Andhra Pradesh

***Corresponding author**
Tanuja B
Email: tanubaby.812@gmail.com

Abstract: The objective of the study was to increase dissolution rate of Rosuvastatin calcium (RST), a poorly water soluble drug which is a 3-hydroxy3-methyl glutaryl CoA (HMG-CoA) reductase inhibitor, through inclusion complexation with β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD). The phase solubility studies indicated that the solubility of RST was significantly increased in the presence of β-CD and in the presence of HP-β-CD and A_L type curve was obtained. Apparent stability constant (Ks) was found to be 32.4 M^{-1} for β-CD and 39.4M^{-1} for HP-β-CD. The inclusion complexes in 1:1 molar ratio for RST and carriers were prepared by three different methods viz. kneading, solvent evaporation and microwave irradiation method. The prepared complexes were characterized using FTIR, differential scanning calorimetry (DSC) and Powder X-ray diffractometry. The FTIR spectra of the prepared complexes showed the characteristic peaks of RST indicates there is no compatibility problem of drug with carriers. The DSC and X-RD showed crystalline nature of the prepared complexes. The prepared complexes dissolution profile was compared with physical mixture and pure drug. All the prepared complexes showed improved dissolution rate. The inclusion complex prepared with HP-β-CD by Microwave irradiation method exhibited greatest enhancement of dissolution rate by three folds.
Keywords: Rosuvastatin calcium, β-cyclodextrin, Hydroxypropyl-β-cyclodextrin and microwave irradiation method.

INTRODUCTION:

The rate of absorption and bioavailability of poor water soluble drugs is often controlled by the rate of dissolution of the drug in the gastrointestinal tract [1]. The methods of enhancing the dissolution characteristics of slightly water-soluble drugs are solid dispersions, micronization, solvent deposition, prodrug approaches, use of surfactants and inclusion complexation etc. Among the various methods, cyclodextrin complexation is an industrially accepted technique. Rosuvastatin (RST), a poorly water soluble 3-hydroxy3-methyl glutaryl CoA (HMG-CoA) reductase inhibitor used as a hypolipidemic agent. It is used in the treatment of osteoporosis and Alzheimer Disease [2]. RST is amorphous nature, having less aqueous solubility, belongs to biopharmaceutical classification system (BCS-II) results in low bioavailability of 20% [3-6]. Cyclodextrins can form inclusion complexes with poorly water soluble drugs and have been shown to improve pharmaceutical properties like solubility, dissolution rate, bioavailability, stability and even palatability [7]. The objective of present study is to prepare inclusion complexes of rosuvastatin calcium with cyclodextrins by different methods such as kneading, solvent evaporation, and microwave irradiation method for improvement of dissolution rate and bioavailability of the drug.

MATERIALS AND METHODS:

Materials:

Rosuvastatin was gifted by Apotex laboratory. β- Cyclodextrin, hydroxy propyl-β-cyclodextrin were obtained as a gift sample from the Himedia Lab. Pvt. All the reagents and solvents used were of analytical grade obtained from local distributor.

Phase Solubility Studies: [8]

Phase solubility studies were carried out according to the method reported by Higuchi and Connors. An excess of RST was added to 10 ml portions of distilled water, each containing variable amount of β-CD. All the above solutions with variable amount of β-CD were shaken in rotary shaker for 24 hours. After shaking, the solutions were filtered and their absorbance was noted at 248nm. The apparent stability constants (Ks) were calculated from the phase solubility diagrams, by using the following equation:

$$Ks = \frac{\text{slope}}{So\ (1 - \text{slope})}$$

Where S_0 = solubility of rosuvastatin in water.

PREPARATION OF INCLUSION COMPLEXES:

The inclusion complexes of RST with β-cyclodextrins as per the table no.1 were prepared by following methods, i.e., kneading, microwave irradiation and solvent evaporation techniques. The physical mixtures were also prepared for comparison.

Preparation of inclusion complexes by kneading method: [9, 10]

RST and β-cyclodextrins with 1:1 molar ratio was accurately weighed. A homogenous paste was prepared by mixing β-cyclodextrins and RST with a small amount of water in a mortar. The paste was further ground for 90 min. The obtained mass was dried at 40°C in an oven for 24h. The dried complexes were ground to fine powder and screened through 60 mesh sieve.

Preparation of inclusion complexes by Solvent Evaporation method (SE): [11-13]

To prepare binary system by SE method, accurately weighed quantities of RST and β-cyclodextrins were added to minimal volume of methanol and sonicated on a bath sonicator for 5 min to get a clear solution. This solution was then stirred on a magnetic stirrer at 60°C. The pasty mass thus obtained was dried by storing overnight in a vacuum dessicator, sifted through 60 mesh sieve and collected.

Preparation of inclusion complexes by Microwave-irradiation method: [14-16]

RST and β-cyclodextrins with 1:1 molar ratio was accurately weighed. A homogenous paste was prepared by mixing cyclodextrin and RST with a small amount of methanol in a mortar. The paste formed was irradiated in a microwave at 60°C for 90seconds at 120 Hz. The obtained mass was sifted through 60 mesh sieve and collected.

EVALUATION OF INCLUSION COMPLEXES:

Drug content estimation:

Binary systems equivalent to 50 mg of RST were weighed and dissolved in 100mL phosphate bufferpH6.8. The solutions were filtered through membrane filter (0.45µm). The solutions were then diluted suitably, drug content was analysed by spectrophotometrically at 248nm. Each sample was analysed in triplicate.

***In-vitro* dissolution studies:**

The dissolution studies were performed using USP 28 type II apparatus. Phosphate buffer pH 6.8 (900mL) was employed as dissolution medium at temperature 37±0.5 ^{0}C. The rotation speed was 50rpm. A sample (5mL), of the solution was withdrawn from the dissolution apparatus up to 30 mins at various time intervals, samples were filtered through 0.45µm membrane filter and diluted to suitable concentration with phosphate buffer pH 6.8 and analysed UV spectrophotometrically at 248 nm.

Physical characterization of inclusion complexes:

Fourier transforms infrared spectroscopy (FTIR):

Pure RST, physical mixtures of RST with β-cyclodextrin and hydroxypropyl-β-cyclodextrin and complexes prepared by kneading, microwave and solvent-evaporation were mixed with potassium bromide(KBr), an infrared transparent matrix at 1:10(sample: KBr) ratio. The KBR discs were prepared by compressing in hydraulic press. Scans were obtained from 400 to 4000cm^{-1}.

Differential scanning calorimetry (DSC):

Pure RST, physical mixtures of RST with β-cyclodextrin and hydroxypropyl-β-cyclodextrin and complexes prepared by kneading, microwave, and solvent evaporation method were subjected to DSC studies using TA instruments Q20 model. Empty aluminium sample pan was used as reference material. Samples were scanned at the rate of 10°C/ min from room temperature to 300°C where in nitrogen gas was used as purge gas at a flow rate of 50mL/min.

Powder X-ray diffraction (XRD) studies:

Pure RST, physical mixtures of RST with β-cyclodextrin and hydroxypropyl-β-cyclodextrin and complexes prepared by kneading, microwave, and solvent evaporation methods were subjected to XRD studies. The scanning rate employed was 2°C min, and samples were analysed between 2θ angles 10-80° at a voltage of 40kV and a current of 30mA.

RESULTS AND DISSCUSION:

Phase Solubility Studies:

The solubility of RST in water is found to be 0.0886mg/ml. The phase solubility diagrams of RST: β-CD and HP-β-CD was obtained by plotting solubility of RST against the concentration of carriers. The solubility curves were classified as the A_L type, which indicates that inclusion complex in the molar ratio of 1:1 between the guest and the host molecule were improves the solubility. The phase solubility profile indicates that the solubility of RST was significantly increased in the presence of β-CD, HP-β-CD and apparent stability constant (Ks) was found to be 32 M^{-1} for β-CD and 39.4 M^{-1} for HP-β-CD (figure 1).

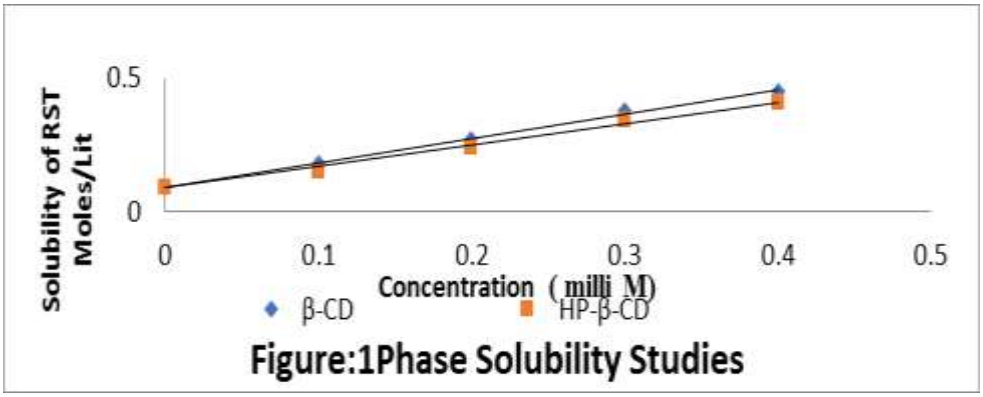

Figure:1Phase Solubility Studies

Drug Content Estimation:

UV spectrophotometry was used to determine the drug content of all inclusion complexes. From the results of drug content in all the prepared complexes ranged from 98.77 % to 99.88%.

IR Spectroscopy

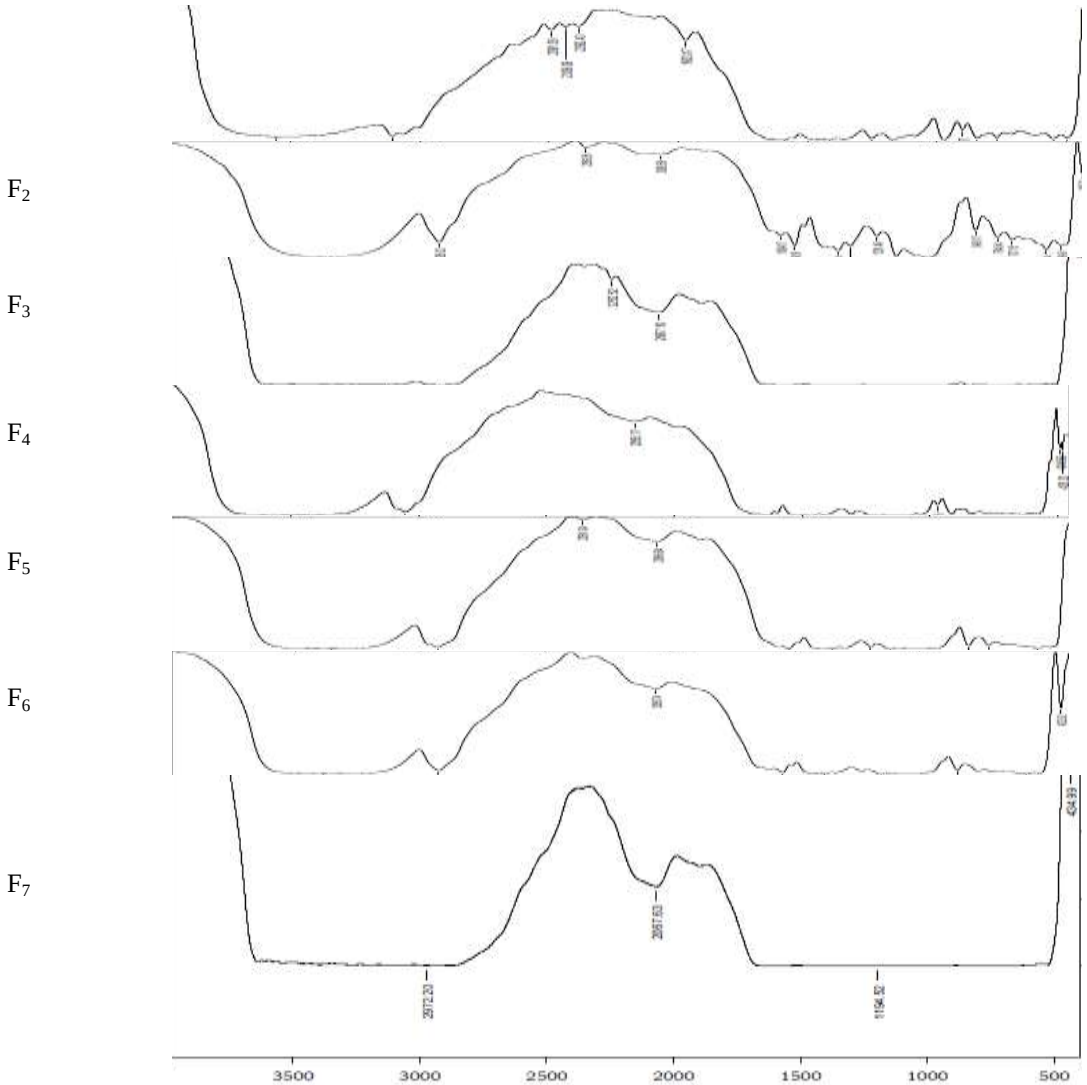

Figure 2. FTIR spectra (F_1) RST, (F_2) RST-β-CD (Kneading method), (F_3) RST-HP-β-CD (kneading method), (F_4) RST-β-CD (microwave irradiation method), (F_5) RST-HP-β-CD (microwave irradiation method), (F_6) RST-β-CD (solvent evaporation method), (F_7) RST-HP-β-CD (solvent evaporation method).

RST Compatibility with carriers was confirmed by FTIR studies. FTIR Spectra of pure drug and inclusion complexes of Rosuvastatin with β-CD, HP-β-CD prepared by different methods are given in figure:2. As clearly seen from the spectra, the characteristic peaks of Rosuvastatin at 2239, 2252.52, 2358.95, 2361.04 were modified slightly shifted because of complex formation (Figure 2).

Differential scanning Calorimetry:

The thermal behaviour RST-β-CD complex was studied using DSC to confirm the formation of complex. DSC thermogram of RST, β-CD, HP-β-CD and all inclusion complexes are shown in above figures. The DSC thermogram of RST showed an exothermic peak at 127°C corresponding to its melting point. The DSC thermogram of RST-β-CD, HP-β-CD complex showed endothermic peak at different temperature by different method of preparation, which is different from the pure drug, which gives clear evidence that there is formation of the complex. (figure:3)

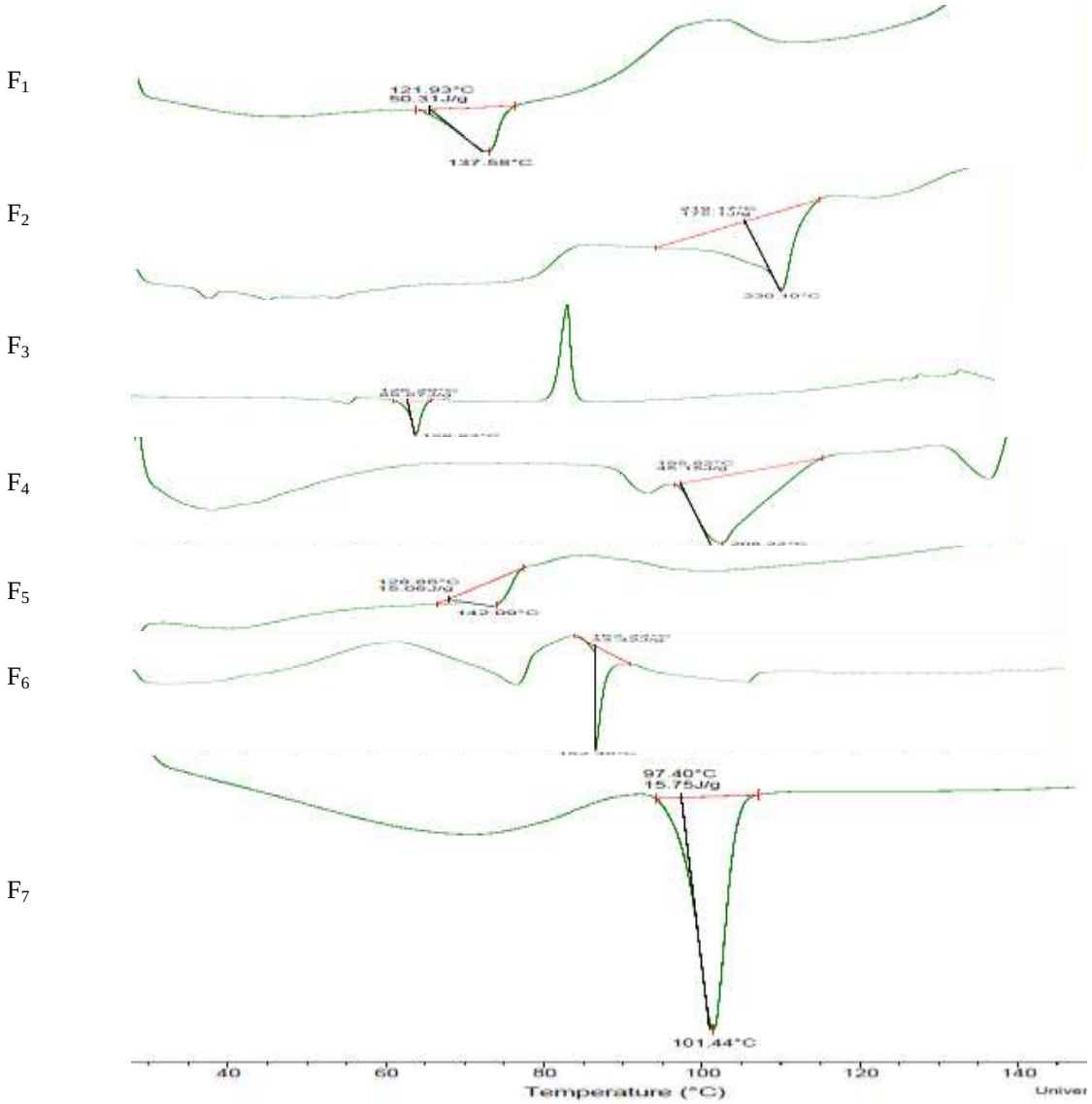

Fig 3: DSC thermogram. (F_1) RST, (F_2) RST-β-CD (Kneading method), (F_3) RST-HP-β-CD (kneading method), (F_4) RST-β-CD (microwave irradiation method), (F_5) RST-HP-β-CD (microwave irradiation method), (F_6) RST-β-CD (solvent evaporation method), (F_7) RST- HP-β-CD (solvent evaporation method).

X-ray diffraction:

Powder X-ray diffraction analysis was employed in the characterisation crystalline nature. The analysis of characteristic regions reflects the crystallinity of the sample. The diffraction pattern of RST indicates amorphous nature of the drug. The variation in diffraction pattern of prepared complexes conforms complex formation. The X-ray diffractograms of complexes showed new peaks indicating crystalline nature of prepared complexes in (figure: 4)

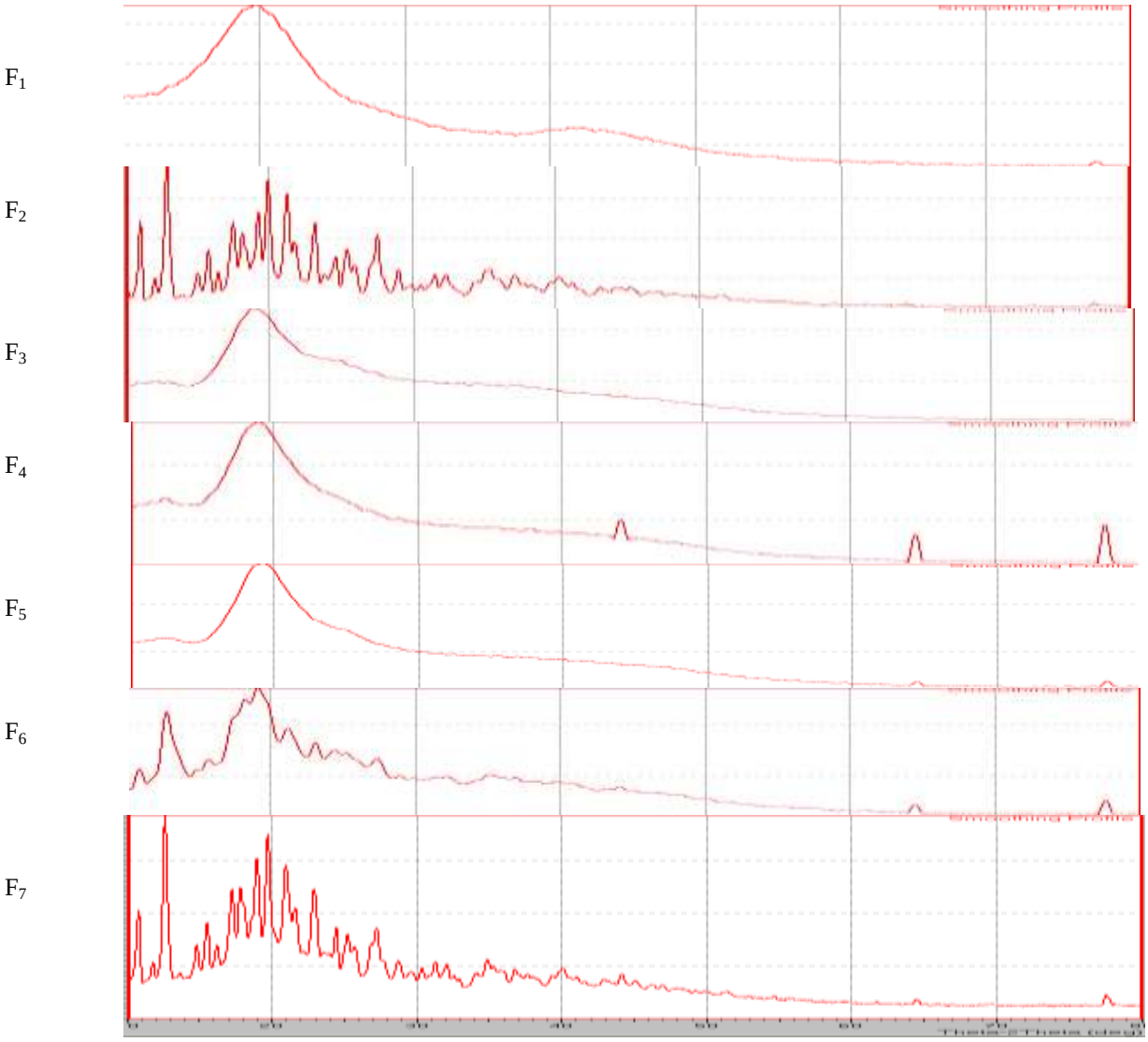

Fig 4 X-ray diffractograms, (F_1) RST, (F_2) RST-β-CD (Kneading method), (F_3) RST-HP-β-CD (kneading method), (F_4) RST-β-CD (microwave irradiation method), (F_5) RST-HP-β-CD (microwave irradiation method), (F_6) RST-β-CD (solvent evaporation method), (F_7) RST- HP-β-CD (solvent evaporation method).

***In-vitro* dissolution studies:**

Cyclodextrins are highly water soluble it was expected to instantly dissolve in the medium under the condition of dissolution test. The release rate profile was drawn as the cumulative percent release on y-axis and time on x-axis which showed in fig 5.

Table 1: Preparation of complexes by various methods

S. No	Formulation	Drug: carrier in 1:1 molar ratio
1	F_1	RST
2	F_2	RST: β-CD (Physical Mixture)
3	F_3	RST: β-CD (Kneading Method)
4	F_4	RST: β-CD (Solvent Evaporation method)
5	F_5	RST: β-CD (Microwave irradiation method)
6	F_6	RST: HP-β-CD (Physical Mixture)
7	F_7	RST: HP- β-CD (Kneading Method)
8	F_8	RST: HP-β-CD (Solvent Evaporation method)
9	F_9	RST: HP-β-CD (Microwave irradiation)

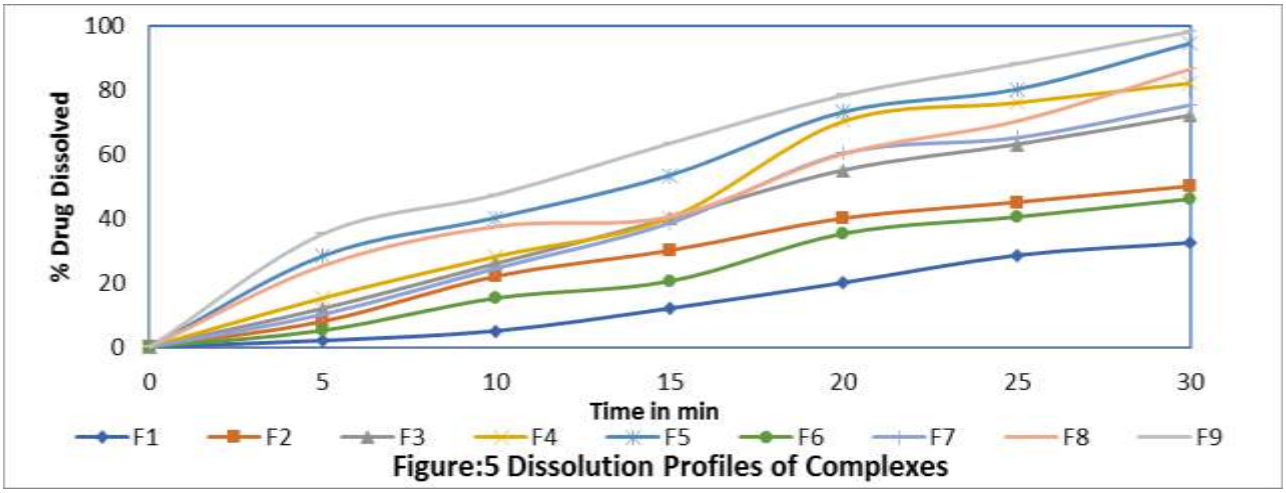

Figure:5 Dissolution Profiles of Complexes

CONCLUSION:

Phase solubility studies of RST with β-cyclodextrins improved solubility and the curves obtained were classified as A_L type. From the phase solubility studies, it is evident that complexation of RST with β- cyclodextrin in 1:1 molar ratio will improve the solubility, hence dissolution rate. The FTIR spectra of prepared complexes showed characteristic peaks of RST with slight shift in the values indicate complex formation and compatibility problems. The X-ray diffraction pattern of pure RST shows only two broad peaks indicates amorphous nature of the drug. The complexes diffraction pattern showed increased number of sharp peaks indicates improved crystalline nature of prepared complexes which aids in formulation development. The DSC thermogram of RST showed, sharp endothermic peak, the melting point of RST was found to be 127°C. The prepared complexes showed increase in melting point and broad peaks indicates slightly improved crystallinity of the drug in complexes. The dissolution profiles of the complexes indicate improved dissolution rate of the drug from the complexes compared to the pure drug.

Rosuvastatin is a BCS Class –II drug which is poorly water soluble and highly permeable the absolute bioavailability was found to be 20%. The phase solubility study gives A_L type of curve. The various inclusion complexes were prepared by using different methods like kneading, solvent evaporation, microwave irradiation methods in 1:1 molar ratio by using carriers like β-CD, HP-β-CD. The complexes, were subjected to various compatibilities studies like FTIR, DSC, XRD were performed. The prepared complexes showed improved dissolution rate compare to pure drug; hence the complexation will improve the bioavailability of the drug. The inclusion complex prepared by microwave irradiation technique with β-CD shows 2.5 folds increase in dissolution rate and HP-β-CD shows 3 folds increase in dissolution rate.

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