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SOLUBILITY ENHANCEMENT AND PHYSICOCHEMICAL CHARACTERIZATION OF TADALAFIL BY INCLUSION COMPLEXATION METHOD

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ABSTRACT

In the present research work Tadalafil (TDF) used as a model drug. It is an antihypertensive drug belongs to BCS class II drug. It's poor water solubility i. e 3.48 µg/ml makes a suitable drug candidate for solubility enhancement. For the solubility enhancement combination of hydrophilic carriers and hydroxyl acids such as β-cyclodextrin, Hydroxy propyl-β-cyclodextrin, Citric acid and Tartaric acid were used respectively. In the preliminary study physical mixtures of TDF were prepared using hydrophilic carriers and hydroxyl acids. Based on the solubility results for further preparation of inclusion complexes combination of β-CD and Citric acid were used. Inclusion complexation (IC) were prepared by kneading and solvent evaporation method. Prepared complexes were then characterized physicochemically for saturation solubility study, XRD, DSC, SEM and CDR. The study results shown inclusion complex prepared by kneading method shown marked improvement in the solubility as compared to solvent evaporation method. Further inclusion complex prepared by kneading method were used to formulate conventional tablet. The prepared tablet were evaluated for pre compression and post compression study. IC containing conventional tablet then compared with marketed formulation for drug release study and shown significant improvement in the drug release from IC-conventional tablet as compared to marketed tablet. Inclusion complex prepared by kneading method and conventional tablet was found to be stable in stability study.

KEYWORDS: Tadalafil, Inclusion Complexation, β-cyclodextrin, Citric acid, Conventional tablet.

INTRODUCTION

About 40% of all new chemical entities (NCE) have poor bioavailability and fail to reach market on account of their poor aqueous solubility. The main cause of insufficient bioavailability is poor solubility and low dissolution rate in aqueous gastro-intestinal fluid.[1] Drugs having poor water solubility shows performance limitation such as erratic absorption. Effectiveness can vary from patients to patients and there can be strong effect of food. Poor availability leads to high dose. In Biopharmaceutical Classification System (BCS) for class II drugs the bioavailability is enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids.[2]

Various formulation strategies are included in inclusion complexation techniques which have been used effectively to enhance the solubility of poorly water soluble drug, because it is economically viable simple. Some recently used methods to prepare inclusion complexes are spray drying, hot melt extrusion, freeze drying, solvent evaporation and kneading method.[3]

In the present study Tadalafil (TDF) used as a model drug. Tadalafil, a phosphodiesterase-5 inhibitor, has been regarded as a first-line therapy in the treatment of erectile dysfunction (ED).[4] Numerous merits, such as long duration of action high selectivity and strong efficacy, enables the drug to be a primary choice for treating ED. However, tadalafil belongs to BCS class II.[5] This may cause highly variable drug plasma levels, and therapeutic failure. Hence it is important to bring desired formulation techniques for increasing the solubility and dissolution rate of the drug to improve the bioavailability, increases the predictability or reduction in dose. Numerous approaches for enhancing dissolution rate of TDF were reported including the use of solid dispersions, complexation with cyclodextrins, inclusion in microporous silicas, formulation of nanosuspension, use of nanostructured lipid carriers (NLCs) and self-nanoemulsifying drug delivery systems (SNEDDS).[6]

Cyclodextrin are cyclic oligosaccharides. It contains six, seven or eight glucopyranose units (α, β and y respectively) obtained by enzymatic degradation of starch. Cyclodextrins can form inclusion complexes with poorly water soluble drugs which improves pharmaceutical properties like bioavailability, solubility, stability, palatability and dissolution rate without affecting their pharmacological properties or intrinsic lipophilicity.[7] Hence to enhance the solubility of TDF inclusion complexation is prepared by using hydrophilic carriers such as citric acid and tartaric acid. Organic hydroxy acids, like citric acid and tartaric acid are often used as pH adjuster to improve the solubility or stability of drug complexed with CDs.[8]

Hydroxy acids shows synergistic enhancement in solubility of cyclodextrin where low solubility CDs such as β-CD is used.[9]

The objective of the present study is to enhance the solubility and physicochemical characterization of tadalafil by inclusion complexation method using carriers such as β-CD, Citric acid, Tartaric acid, HP-β-CD. The study includes characterization of tadalafil validation of analytical method, characterization of inclusion complexation, methods for solubility enhancement of tadalafil.

MATERIALS AND METHODS

Materials

Tadalafil (Emcure Pharmaceutical Ltd.Mumbai, India), β-CD, Citric acid, Tartaric acid (Research Lab fine chem, Mumbai, India), HP-βCD (Ajanta Pharmaceutical Ltd. Mumbai. India) provided as gift sample. Sodium starch glycolate, Microcrystalline cellulose, Magnesium stearate (Research Lab fine Chem, Mumbai India). All other reagents and solvents used were of analytical grade.

Methods

1. Preparation of physical mixture (PM)

The physical mixture of Tadalafil with various carriers was prepared by mixing the required amount of TDF and carriers for 5 min in a mortar until a homogenous mixture was obtained. This resulting mixture was sieved through an 80 mesh screen. The mixture was stored in a screw cap vial at room temperature.[10]

2. Preparation of Inclusion complexes

The selected hydrophilic carriers β-cyclodextrin and citric acid were used to prepare carriers at weight ratios of 1:1.5-1:0.25 using different preparation methods i.e kneading and solvent evaporation method.

3. Solvent evaporation method

In the solvent evaporation method, Tadalafil was dissolved in 20ml of methanol, while β-CD/ CA and HP- β-CD/CA was dissolved in distilled water respectively. The solutions were mixed together and stirred for 1h (Magnetic stirrer, Electrolab Mumbai). Methanol was evaporated by heating at 50ºC under constant stirring. The mixture was placed overnight for 24h in an oven at 50ºC to remove the residual solvent. The prepared complex was then

ground using mortar and pestle. After sieving through a 65 mesh sieve, the inclusion complex was kept in a closed container.[11]

4. Kneading method

β-CD and CA as well as HP- β-CD and CA in mortor is wetted with sufficient amount of water. TDF was slowly added into slurry. The mixture was dried in an oven. The dried complex was ground using mortor and pestle and sieved through mesh and kept in closed container.[12]

5. Phase solubility study

Phase solubility study was performed according to the method of Higuchi and Connors.[13] An excess amount of Tadalafil was added to distilled water containing various concentrations of β-CD, CA, HP- β-CD and TA (0.25-1M). The flask were shaken continuously at 30ºC for 24-48h on magnetic stirrer to reach equilibrium. Samples were withdrawn and filtered through 0.45µm membrane filter. Filtrate was diluted appropriately and assayed at 284.6 nm (V-630, Jasco, Japan).

The stability constant Kc was calculated from the phase solubility diagram using following equation

$$K_{1:1} = \text{Slope} / \text{Intercept}(1-\text{slope}) \qquad e.q\ 1$$

The slope was obtained from the plot of tadalafil concentration against hydrophilic carriers concentration. Intercept was the equilibrium solubility of tadalafil in water. [13]

Characterization of Tadalafil-Inclusion complexation

6. Saturation solubility

Solubility studies were performed by adding an excess amount of inclusion complexation of drug in fixed quantity of water and in sealed glass vials on orbital shaker (KYTOSE EOS-10M) (250 rpm) at constant temperature (25°C) until equilibrium for 24 h. An aliquot of solution was then withdrawn and filtered, the TDF concentration was determined spectrometrically at 284.6 nm (UV/Vis Jasco V 630).[14]

7. Drug Content

Drug content was conducted by dissolving a weighed quantity of drug into methanol, which selectively dissolved TDF. It was then filtered (Whatman paper 0.45um) to remove

undissolved cyclodextrin. The filtrate was analyzed spectrophotometrically at 284.6nm and quantity of TDF was determined against standard calibration curve in methanol.[15]

8. Compatibility study

Compatibility study was carried out by preparing mixture of drug and selected carriers. Mixtures were then stored at 37ºC for 30days and then samples were evaluated for FTIR and DSC.[16]

9. FTIR studies

The FTIR spectral measurements were taken at ambient temperature using JASCO Model 4100 series, Japan. The representative sample TDF was mixed with IR grade KBr in 1:100 ratios and triturated to obtain uniform blend. This blend was dried for 10min under IR lamp and then it was subjected to FTIR scan in the range of 400-4000cm^{-1}.[17]

10. X-ray Powder Diffraction (XRPD) studies

The XRPD patterns of TDF, physical mixture (TDF:βCD: CA) and Inclusion complex (TDF:βCD:CA) were recorded at room temperature using X-ray diffractometer BV (PV 17)D8 Advanced Germany Instrument, with Cu as anode material and graphite monochromator, operated at a voltage of 30 mA, 45 kV. The samples were analyzed in the 2θ angle scan range of 5θ- 60θ. The process parameters used were set as sampling pitch 0.0200° and scan speed 6°/min.[18]

11. Differential Scanning Calorimetry (DSC)

The DSC pattern of TDF, physical mixture (TDF:βCD:CA) and Inclusion complex (TDF:β-CD:CA) was recorded on a Mettler Toledo (DSC 823). Thermogram was obtained by heating 7–8 mg sample in crimped aluminum pans heating rate of 10°C /min, from 40°C to 300°C, in a nitrogen atmosphere (flow rate 40mL/min).[19]

12. Scanning Electron Microscopy (SEM)

Morphological analysis was performed using an S-4100 scanning electron microscope (Hitachi, Tokoyo, Japan). SEM photomicrograph were taken for comparison of the crystal morphology of Pure TDF powder, physical mixture and Inclusion complex. The sample were fixed on brass-stub using double sided adhesive tape and made electrically conductive by coating in a vaccum (6Pa) with platinum (6nm/min) using a Hitachi Ion Sputter (E-1030) for 120 s at 15mA. The SEM images were analyzed using an image analysis system.[19]

13. *In- vitro* dissolution studies

In vitro dissolution study was carried out in distilled water and phosphate buffer. *In vitro* dissolution studies of pure TDF, PM and TDF-complexation were carried out using USP Type II dissolution apparatus (Paddle type). TDF-IC equivalent to 59.4 mg of TDF were filled in musclin cloth was placed in 900 mL of dissolution media at 50 rpm and temperature 37 ± 0.5°C. Aliquot was withdrawn at specific time intervals (0,10,20,30,40,50 and 60 mins) and replaced by fresh dissolution media to maintain sink condition. The samples were filtered through whatmann filter paper (0.45µm) and analyzed by UV spectrophotometry at 284.6 nm. The cumulative percentage of TDF dissolved verses time was estimated graphically. The study was performed in triplicate for each formulation.[20]

14. Dissolution profile in Fasted State Simulated Intestinal Fluid (FaSSIF) and Fed State Simulated Intestinal Fluid (FeSSIF) Media

In order to determine the effect of food on the absorption of Tadalafil in the intestinal tract, the dissolution profile of inclusion complexation was performed in FaSSIF and FeSSIF media.[21]

15. Formulation and Development of conventional tablet

TDF-IC loaded conventional tablet were prepared by direct compression method according to formula given in table 1. The conventional tablets were compressed using 16 station rotary tableting press (Rotary Tablet Compressor Machine, CIPS Machinery) 8 mm round punch. Prepared tablets were evaluated for Hardness (Monsanto hardness tester), Friability (Roche Friabilator), weight variation and drug content.[22]

Table 1: Composition of TDF-IC tablet.

Sr.No	Ingredients	F1	F2	F3	Category
1	Solid dispersion (≈20mg TDF)	59.54mg	59.54mg	59.54mg	API
2	Microcrystalline cellulose	18	18	18	Diluent
3	Sodium starch glycolate	15	30	60	Disintegrant
4	Magnesium stearate	18	18	18	Lubricant
5	Talc	18	18	18	Glident

***all quantities are in mg**

16. *In-vitro* dissolution study

In vitro release studies were carried out in the USP dissolution test apparatus type II. 900ml of the dissolution medium of distilled water, pH 6.8 phosphate buffer and marketed tablet in 0.5% SLS (FDA guidelines) for TDF was taken in a covered vessel and the temperature was

maintained at 37ºC±0.5ºC. The speed of the paddle was set at 50rpm. Sampling was done at 0, 10, 20, 30, 40, 50 and 60 min. For each sample the dissolution medium was withdrawn and the same volume of dissolution medium was replenished at 37ºC. Withdrawn samples then passed through 0.45µm filter paper and it was determined by UV spectrophotometer at 284.6nm.[23]

17. Accelerated stability study

Stability study was carried out according to ICH guidelines Q1A (R2), (ICH) to determine the influence of formulation additives on the stability and also to determine the physical stability of the formulation under accelerated storage conditions. The tablets were stored in an aluminium foil and subjected to elevated temperature and humidity conditions of 25 ± 1°C/ 60 ± 5 % RH, 30 ± 1°C/ 65 ± 5% RH and 40 ± 2°C/ 75 ± 5 % RH.[24]

RESULTS AND DISCUSSION

1. Solubility determination of Tadalafil

The experimental saturation solubility of TDF in water was found to be 3.48 µg/mL and therefore, confirmed poor solubility of drug.

2. Phase solubility study

Phase solubility study was performed to investigate the solubility of Tadalafil in β-CD,CA, HP-β-CD and TA respectively. From "Fig.1,1.1,1.1.1,1.1.2" it can be seen that solubility of tadalafil increased proportionally with an increase in concentration of β-CD. Tadalafil in β-CD solution demonstrated a comparatively higher solubility than HP-β-CD, CA and TA at similar concentration, which could be explained by relatively higher solubilisation of Tadalafil in β-CD. The stability constant (Ks) value was found to be increased from 128.6 M^{-1} for β-CD to 166M^{-1}.These values indicated the formation of comparatively more stable inclusion complex of tadalafil/ β-CD than tadalafil /HP β-CD. It was reported that stability constant (Ks) value between 50 and 5000M^{-1} was considered as most suitable for the improvement of solubility and stability of poorly soluble drugs.[25]

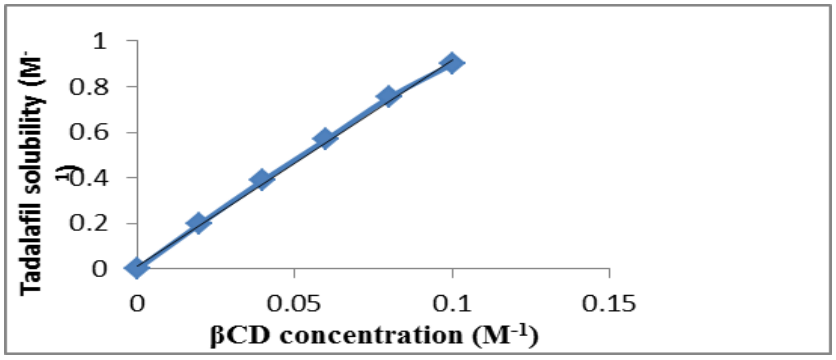


Fig. 1: Phase solubility of β-cyclodextrin.

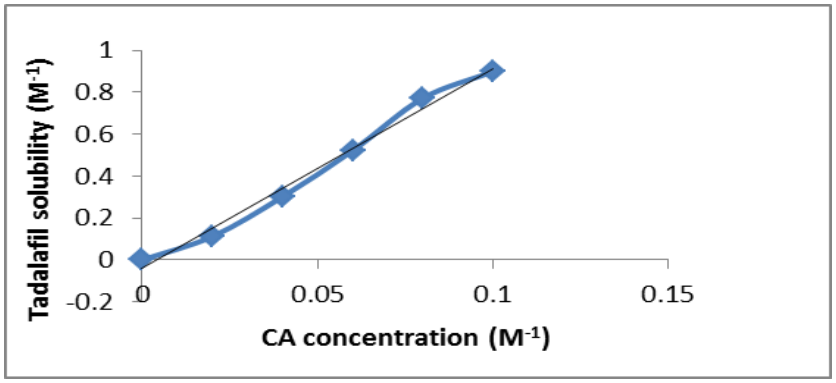


Fig. 1.1: Phase solubility of citric acid.

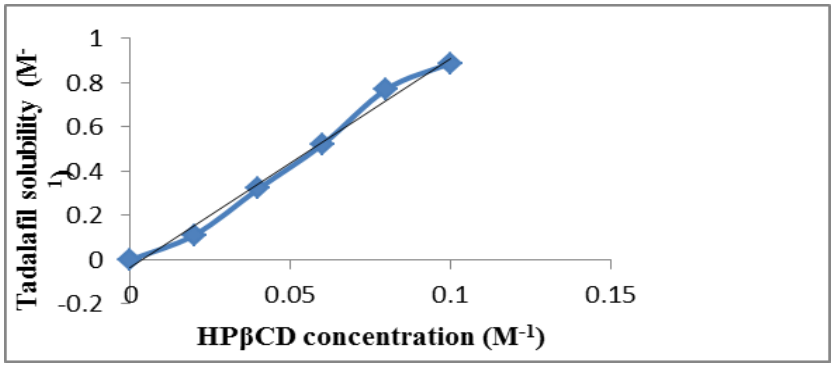


Fig. 1.1.1: Phase solubility of hydroxy propyl-β-cyclodextrin.

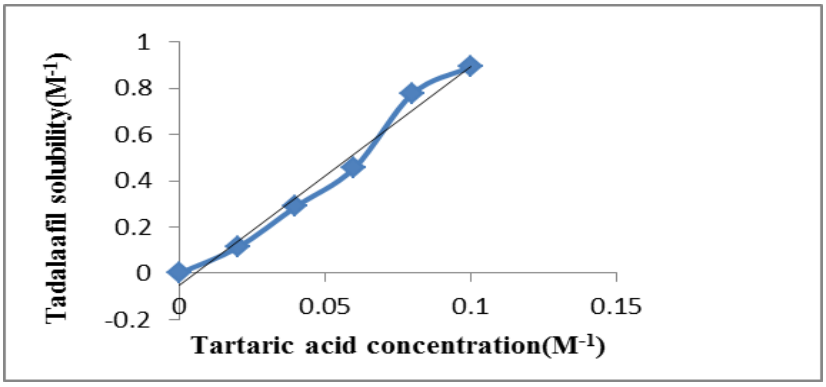


Fig: 1.1.2: Phase solubility of tartaric acid.

3. Tadalafil - Inclusion complexation

TDF-IC were prepared by kneading method and solvent evaporation method. Prepared complexes then studied for the solubility determination. It was observed that each of the preparation methods could increase the solubility of tadalafil but to a different extent. Kneading method produced the highest solubility of tadalafil in β- CD and CA compared to HP- β- CD and CA. For kneading method, the solubility of tadalafil/ β- CD and CA at ratio of (1:0.5:1M) was 4.78µg/ml and the solubility of tadalafil/ HP-β- CD and CA at ratio of (1:1.5:1M) was found 4.48 µg/ml whereas the solubility of tadalafil/ β- CD and TA at ratios (1:0.5:1M) was 3.42 µg/ml and the solubility of tadalafil/HP- β- CD and TA was 4.12 µg/ml. Hence the solubility of tadalafil was increased by complexation of β- CD and CA compared to HP- β- CD using kneading method. The same trend applied to solvent evaporation method in which the solubility of tadalafil/ β- CD and CA was found 3.63µg/ml and HP-β- CD 3.10µg/ml. Hence kneading method was more effective than solvent evaporation in solubility enhancement. This may be due to the acidic microenvironment created by the complex facilitates the dissolution of drug at higher pH values smaller particle size of the complexes is also responsible for the enhance solubility of drug.[26] Hydroxyl acids have remarkable solubilizing capacity due to the H-bond. Hydroxyl groups have capabilities to modify intra and intermolecular H-bond system of β- CD. CA is a semi crystalline polymeric carrier has been used to increase drug solubility because of its high hydrophilicity, ability to improve wettability and ability to induce water uptake helps to enhance solubility.[27]

4. FTIR Study

Objective of the present study was to check the solid state interaction between TDF and selected hydrophilic carriers. The study revealed that FTIR did not show any, significant shift in peaks or disappearance of characteristic peaks of TDF in Physical mixture. However TDF-IC shown broadening of peak shown in “Fig.2”. It indicates formation of TDF-IC with β-CD.

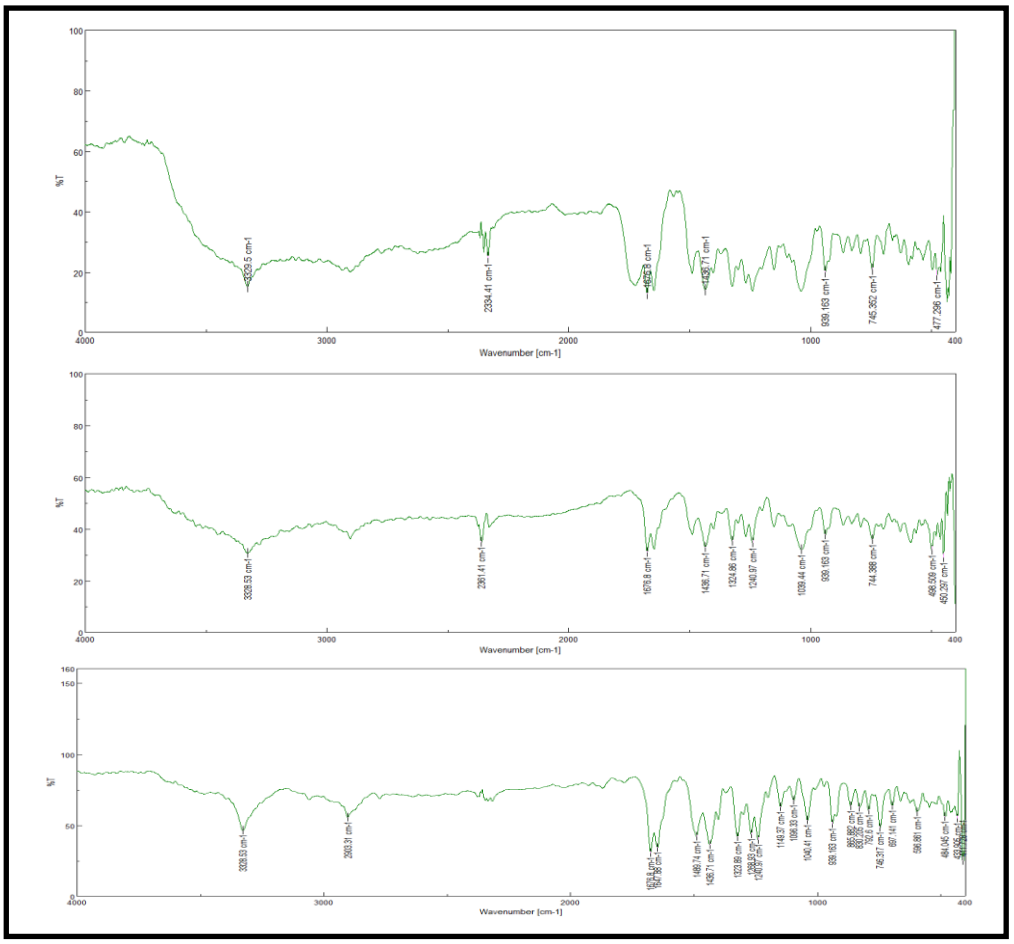


Fig. 2: FTIR spectra of (A) TDF (B) Physical mixture (PM); TDF:β-CD:CA (C) TDF-IC.

5. X-Ray Powder diffraction study (XRPD)

XRPD analysis can be determine the solid-form structure and crystal-packing relationship among individual molecules and excipients in the solid. X-ray diffractometer spectra of pure TDF shown sharp endothermic peak at diffraction angles (2Ɵ) 7.2º, 10.8º, 12.15º, 17.5º and 18.32º which indicates the crystalline nature of TDF. XRD of physical mixture revealed crystalline peaks of tadalafil. For kneading method showed a significant reduction in the number of crystalline peaks which reveals an amorphous appearance with negligible crystalline peaks. This indicated that complexation of β-CD and CA was able to change the crystalline form of tadalafil using kneading method. XRD results indicated the change of crystallinity of tadalafil to amorphous state. Amorphous solids have a higher molecular mobility and energy than the crystalline form.[28]

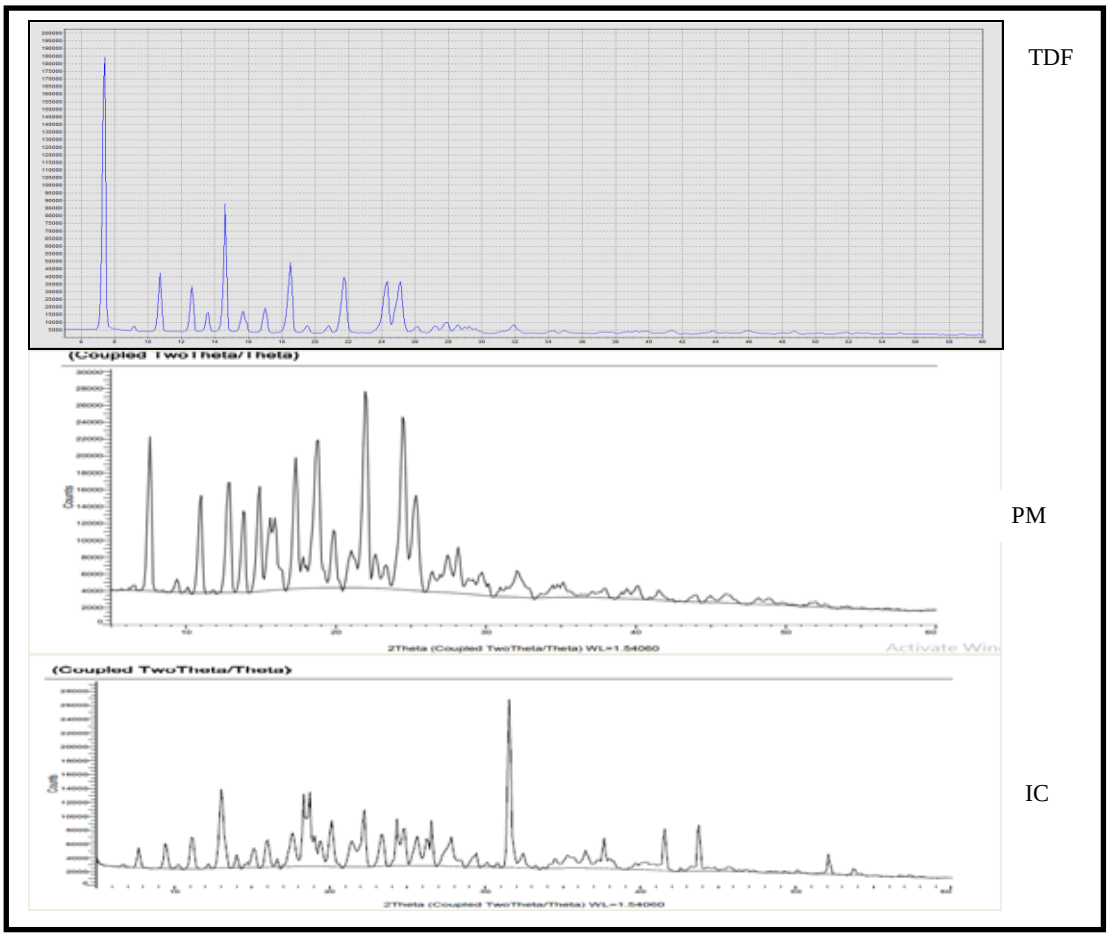


Fig. 2.1: XRPD Pattern of TDF, Physical mixture, Inclusion Complexation.

6. Differential Scanning Calorimetry (DSC)

DSC study was performed using pure TDF, physical mixture of TDF: β-CD:CA and TDF-IC. Pure TDF has shown well defined peak at 303.27ºC, corresponding to the melting point of crystalline TDF. The complexes prepared using physical mixture revealed an endothermic peak at 295.2ºC. This indicated that physical mixture was not able to incorporate Tadalafil inside the apolar cavity of β-CD.[29] Whereas TDF-IC by kneading method produced a negligible endothermic peak at characteristic melting point of crystalline Tadalafil at 154.01ºC.

Tadalafil has an enthalpy value of 114.52J/g. Formation of inclusion complex is associated with reduction of enthalpy value. Inclusion complexes prepared using physical mixture with β-CD: CA at ratio of 1:05:1M showed enthalpy values at 44.75J/g. IC prepared by kneading method shown enthalpy values at 12.86J/g. Preparation of inclusion complex using kneading method showed highest reduction value in enthalpy contributing to the highest solubility value observed in β-CD. Similar results obtained to Loh *et al*., 2016.

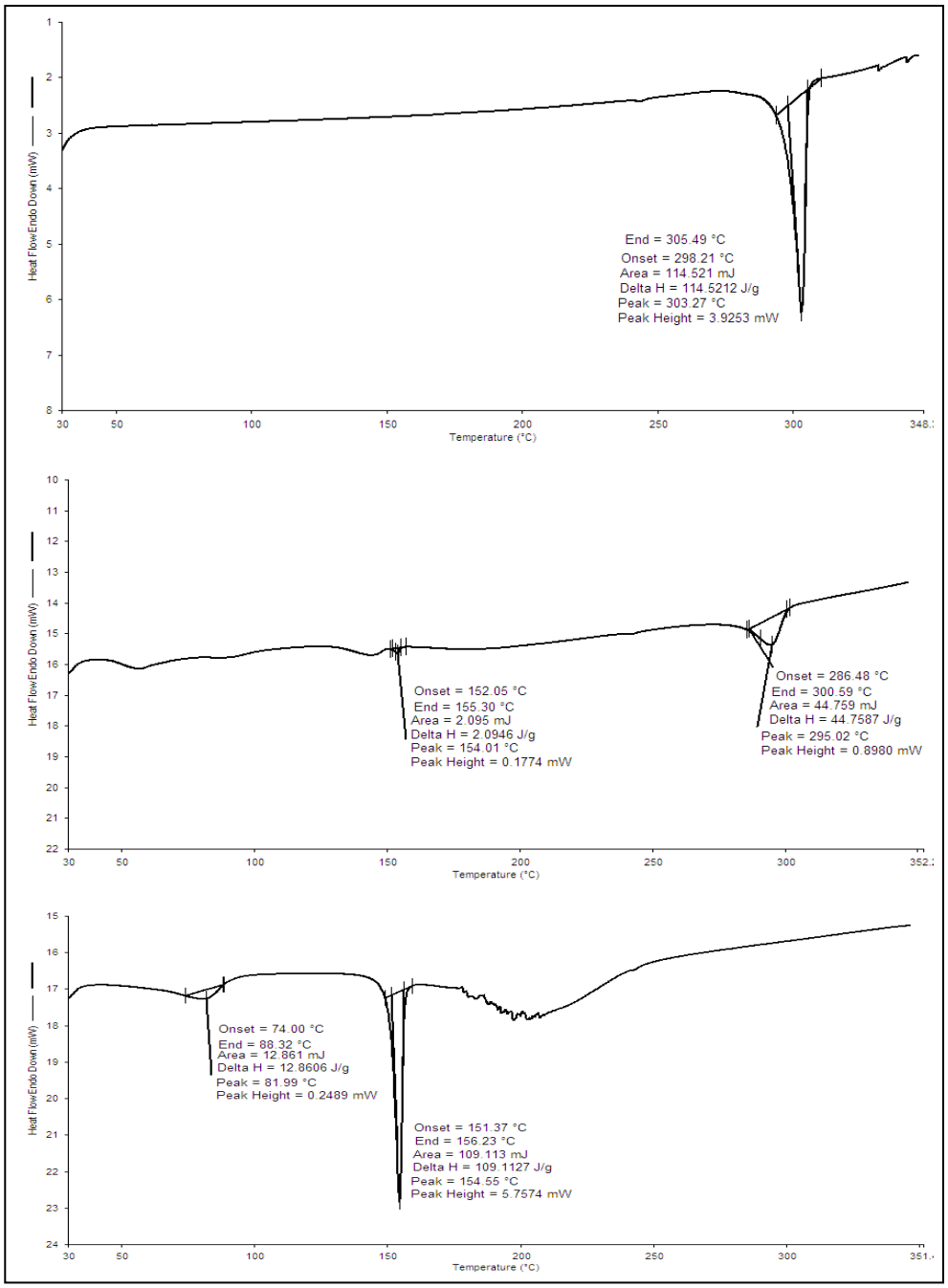
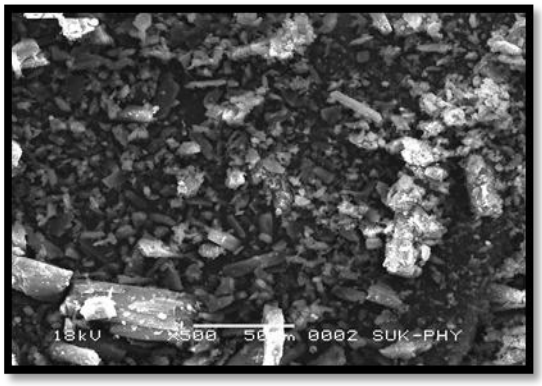


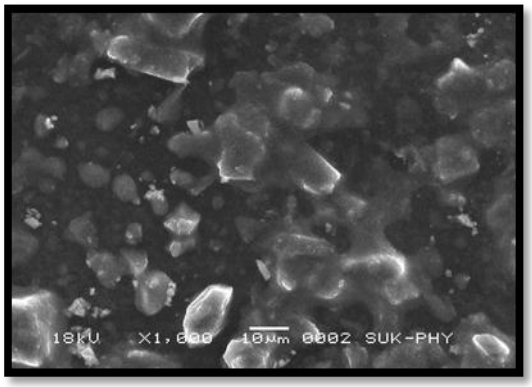
Fig. 2.2: DSC thermograms of TDF, PM, TDF-IC.

7. Scanning Electron Microscopy

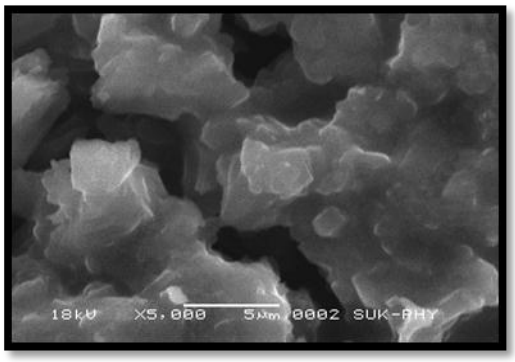
"Fig.2.3" displayed SEM photographs for TDF, Physical mixture and Inclusion complex. The drug crystals seemed to be smooth-surfaced, irregular in shape and size. Photograph of the physical mixture of drug and carrier depicted the presence of drug in crystalline form. Inclusion complexation appeared as uniform and homogeneously mixed mass with wrinkled surface. It might be due to homogeneous dispersion of drug within the carrier.[30]



A) TDF



B) PM



C) IC

Fig.2.3: SEM micrographs of A) TDF B) PM C) IC.

8. *In-vitro* dissolution study

In-vitro Dissolution study were done using an USP Type II dissolution rate test apparatus (Electro Lab). The mean dissolution profiles of Tadalafil Inclusion Complexes prepared using the three different methods are shown in "Fig.2.4". The dissolution of Tadalafil was 23.42%±1.01 while the dissolution of physical mixture was 63.86%±1.23 and the dissolution profile of TDF-IC by solvent method and kneading method was 81.6 % ± 1.57 and 95.87% ± 1.59 respectively. The results shows that formation of inclusion complex of TDF: β-CD: CA by kneading method improved tadalafil dissolution. The % drug release in physical mixture

was found lower because the drug was not completely amorphized and in inclusion complexation the % drug release was increased by kneading method compared to solvent evaporation method due to complete amorphization of TDF.[31]

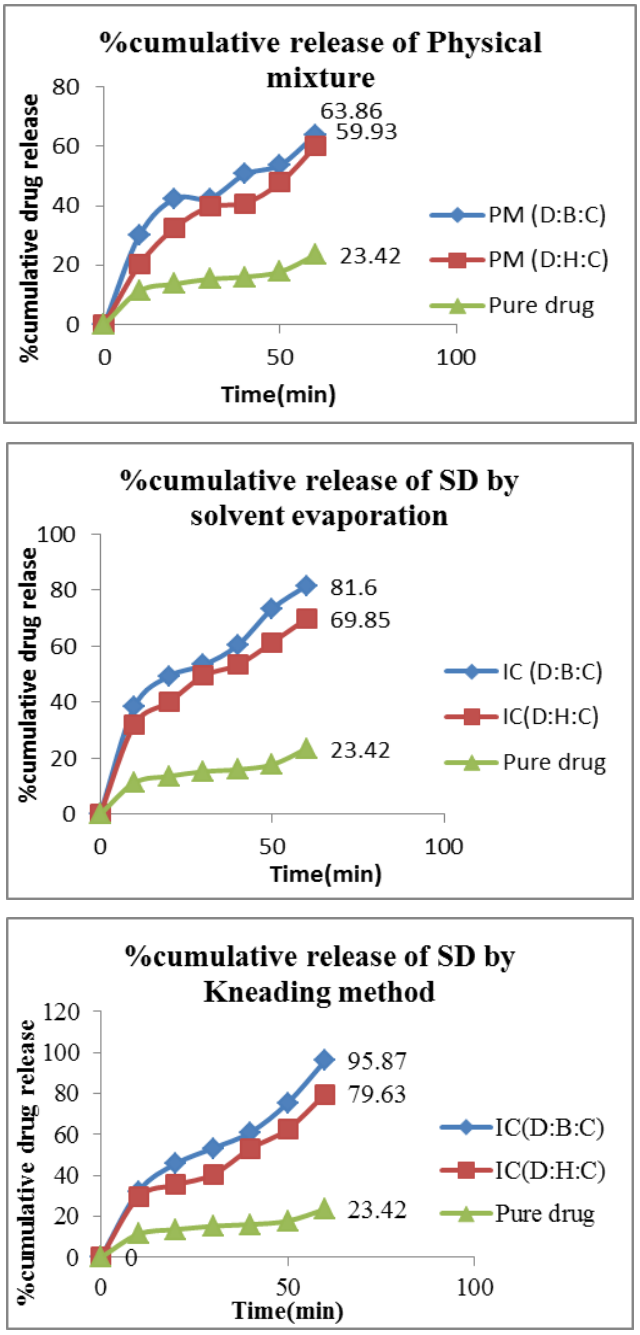


Fig. 2.4: % cumulative release of physical mixture, IC by solvent evaporation method, IC by kneading method.

9. Biorelevant dissolution media

In vitro dissolution in biorelevant media was performed in order to observe the effect of food on the absorption of Tadalafil. The two biorelevant media, Fasted state simulated intestinal

fluid and Fed state simulated intestinal fluid were studied to simulate the condition in the intestine in the fasted and fed states. The release of TDF-IC prepared by kneading method shown maximum dissolution rate. The FeSSIF media indicated better percent drug release as compared to FaSSIF media, indicating the effect of food on the absorption of TDF. So it was concluded that the formulation will be better absorbed when given with food. This study is concordant with the early study of the drug has food-related absorption.[32]

10. FORMULATION DEVELOPMENT OF TADALAFIL TABLET

For further development of formulation TDF-IC were formulated in the form of conventional tablet. For the preparation of tablet IC containing 20mg of TDF were taken. Tablet were prepared by direct compression method using 8mm flat punch. The prepared tablets were physicochemically evaluated.

11. Evaluation of blend powder

The blend of Tadalafil Inclusion complexation were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 28º, Carr's index values were less than 11 all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.[33]

12. Evaluation of Tablets (IP, 2007)

The data obtained from post-compression parameters such as weight variation, hardness and friability, disintegration time, assay and *in-vitro* dissolution study are given in table 2. The hardness test indicated good mechanical strength while at the same time allowing fast disintegration. The friability less than 1% indicated that the tablet had good resistance to external forces like shock and abrasion. Assay of the tablet was in acceptable limits. [34]

Table 2: Evaluation of TDF Tablet.

Sr.No	Parameters	F1	F2	F3	Reported limits
1	Thickness(mm)	1.05±0.21	1.53±0.23	1.27±0.3	-
2	Hardness Kg/cm2	4.08±3.2	4.26±0.38	4.23±1.32	4-6 Kg/cm2
3	Weight variation (mg)	Passes	Passes	Passes	Passes
4	%Friability	0.32±0.2	0.43±0.4	0.39±0.3	Less than 1%
5	Disintegration time	8minutes	12minutes	10minutes	0-15min
6	Drug content%	101.23±0.4	108.3±0.15	95.82±0.34	85-115%

**** Mean ± S.D (n=3)***

13. Dissolution Studies

The *In-Vitro* dissolution study was performed for three formulations (F1, F2, F3). These are prepared by varying concentration of disintegrant from 2.5 to 10% w/w. It was observed that formulation batch F3 shown maximum enhancement in the dissolution rate i. e 95.87% as compared to F1 and F2. This improvement in the drug release from the prepared tablet may be due to amorphization of TDF, increased wettability, dispersibility and reduction in particle size.[35]

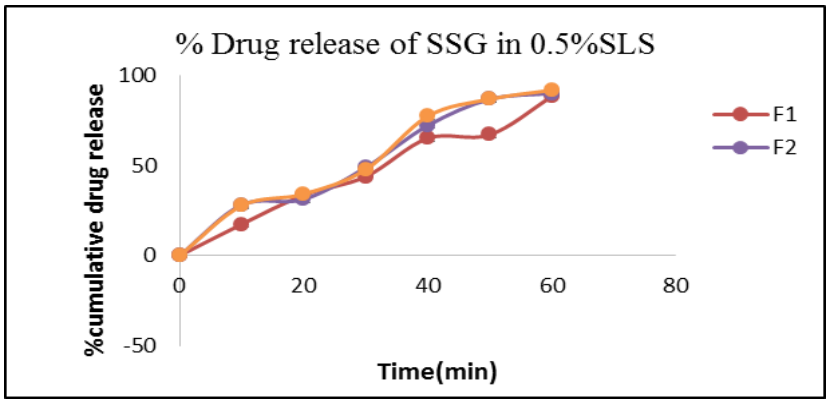


Fig. 2.5: Comparative effect of disintegrant (SSG) on drug release in 0.5%SLS.

Marketed Tablet Tadacip

Manufactured By: Cipla Pharmaceutical.

Dose: 20mg

TDF loaded IC were formulated in the form of conventional tablet. The prepared tablet then compared with marketed tablet and tablet containing pure TDF. The study result shown marked improvement in the drug release of conventional tablet (F3) as compared to marketed formulation i. e significant increase in the % CDR at the end of 1h with batch F3(4.7folds) with respect to marketed formulations (3.7 folds).[36]

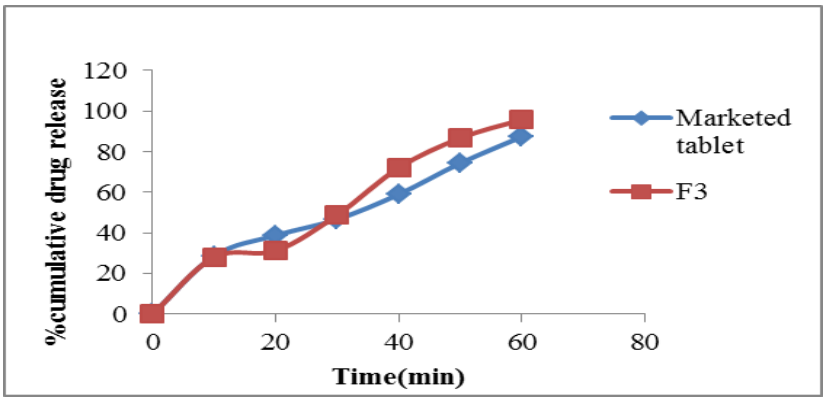


Fig. 2.6: Dissolution curve for Marketed tablet and Formulated batch F3.

14. ACCELERATED STABILITY STUDY

The stability study was performed in accordance to ICH guideline Q1A (R2). The samples were analysed for various evaluating parameters before and after stability study. The result showed good similarity with that of before evaluated parameters.

CONCLUSION

The three methods physical mixture, kneading and solvent evaporation were used to prepare inclusion complexation. Inclusion complex prepared by kneading method could increase the solubility and dissolution rate of tadalafil via formation of inclusion complex with β-CD and citric acid. Inclusion complex of β-CD/CA produced a comparatively higher solubility than that of HP-β-CD using the same preparation procedure. Tadalafil was converted from crystalline to amorphous form through inclusion complexation. Improvement in the solubility may depend on the capabilities of hydroxyl acid groups to modify the intra-molecular and inter-molecular H-bond system of β-CD. This indicates that other driving forces cooperate in the solubilizing enhancement effect.

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