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Original Article

Formulation and evaluation of Tadalafil oral disintegrating tablets with enhanced dissolution rate by complexation

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Keywords: Tadalafil (TDF), Orally disintegrating tablet (ODT), β-cyclodextrin (βCD), sodium starch glycolate (SSG), croscarmellose sodium (CCS), crospovidone (CPV), direct compression, *in vitro* dissolution studies

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ABSTRACT:

Aim: In the present study was to enhance the solubility of Tadalafil (TDF) by forming inclusion complexes with β-cyclodextrin (βCD) and further to enhance its dissolution rate by formulating orally disintegrating tablet (ODT) by direct compression technique. **Objectives:** To perform the phase solubility studies, for to determine the ratio of drug: carrier ratio in the formation of complexes. Physico-chemical characterization of complexes by DSC and X-ray diffraction studies. To check the superiority of selected superdisintegrants [sodium starch glycolate (SSG), croscarmellose sodium (CCS), crospovidone (CPV)] in enhancing the dissolution rate of TDF. To fasten the onset of action and thereby increasing TDF's bioavailability in comparison to its conventional tablets. **Methods:** Standard calibration curve of TDF in pH 6.8 phosphate buffer was constructed by spectrophotometric method, drug-excipient compatibility was checked by FT-IR studies. All the Formulations were evaluated for pre- & post-compression studies. Accelerated stability studies up to 3 months were conducted for the optimized formulation, as per ICH guidelines. **Results and Discussions:** polymers used in the study are compatible with TDF. Pre- & post- compression parameters were within the acceptable limits for all formulations. *In vitro* dissolution kinetic studies indicate the release of TDF from ODT increases with the increased concentration of superdisintegrants. The order of superdisintegrants in enhancing the dissolution rate of TDF is CPV>SSG>CCS. Formulation F6, had the highest dissolution efficiency at 5 min (DE_5=39.55 %); first order dissolution rate constant (K_1 =0.1052 min^{-1}) with a regression coefficient (r^2=0. 9844) and lesser time for 50% of drug release (t_{50}=4 min), was considered as the optimal ODT. It passed the test for stability as per ICH guidelines. **Conclusion:** The optimized TDF ODT with its 1:4 βCD complex was formulated by the direct compression technique, with 6% w/w CPV as superdisintegrant, which will fasten the onset of action and enhances the bioavailability of TDF in comparison to its conventional tablets.

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INTRODUCTION

The oral route is the most preferred route of administration of dosage forms, due to its potential advantages like ease of administration, convenient dosing, self-medication, no pain and patient compliance. Hence tablets and capsules are the most popular dosage forms [1], but the important drawback of these dosage forms is dysplasia [2] which can be solved by developing orally disintegrating / dissolving tablet (ODT), which disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing [3]. In pharmaceutical sciences, disintegration usually means the process by which a solid dosage form breaks up, when it comes in contact with aqueous medium and thus promotes the rapid release of drug for faster absorption and good bioavailability [4, 5].

ODT provides ease of administration, immediate action, self-medication and increases patient compliance [6]. TDF is a potent and selective phosphodiesterase-5 (PDE5) inhibitor used for the treatment of erectile dysfunction which was approved by the FDA in November 2003 [7].

Compared to sildenafil and vardenafil, TDF has the advantages of longer duration of action of approximately 36 h, and minimized potential for vision abnormalities due to its high selectivity for PDE5 vs PDE6 [8, 9]. However, it has the disadvantage of poor aqueous solubility (BCS Class-II drug). This may cause highly variable drug plasma levels, and therapeutic failure. Therefore, it is important to introduce effective formulation techniques to enhance the solubility and dissolution rate of the drug aiming to improve its bioavailability, increase the predictability of the response and/or to reduce the dose. Complexation with cyclodextrins (CD) has been widely used to enhance the bioavailability of poorly soluble drugs by increasing the drug solubility, and dissolution rate.

The aim of the present work is to study the interaction of TDF with βCD in solid state, and to enhance the dissolution rate of the TDF as a primary step in the development of TDF ODT. TDF-βCD inclusion complex is prepared by the kneading method. DSC and XRD were used to evaluate the physicochemical properties of the complexes. TDF ODT were prepared by direct compression technique. The present study was also aimed to optimize the type and concentration of superdisintegrant among, SSG, CPV and CCS.

MATERIALS AND METHODS

Materials: Tadalafil was obtained from Hetero Drugs Pvt Ltd, Hyderabad, India as a gift sample, powder vanilla flavor was a gift sample from Firmenich, Chennai, β-cyclodextrin, sodium starch glycolate, croscarmellose sodium (Ac-DI-Sol), crospovidone (Polyplasdone XL-10), mannitol (PERLITOL-S D-200) and remaining excipients were procured from S.D. Fine Chem. Pvt. Ltd., Mumbai. All the excipients used in the study were of analytical grade.

Methods:

The Standard calibration curve of TDF in pH 6.8 phosphate buffer [10]**:**

Preparation of stock solution-I: Stock solution-I (1mg/mL) was prepared by dissolving 50 mg of TDF in 10 mL of methanol in a 50mL volumetric flask and the volume was made up to mark with pH 6.8 phosphate buffer.

Preparation of stock solution-II: Stock solution-II (100 µg/mL) was prepared by taking 10 mL of stock solution-I into a 100mL volumetric flask and the volume was made up to mark with pH 6.8 phosphate buffer.

Procedure: Aliquots of (0.5 to 3 mL) of Stock solution-II was transferred into a series of 10 mL volumetric flasks and the volume was made up to mark with pH 6.8 phosphate buffer to obtain concentrations of (5 to 30 µg/mL).

The obtained concentrations were analysed at the λmax 284 nm using a UV-Visible spectrophotometer (UV-1700, Shimadzu, Mumbai, India) and their absorbance were noted. The Standard calibration curve was plotted by taking concentration of drug solution (µg/mL) on X-axis and absorbance on Y-axis (Fig. 1).

Phase solubility studies: were performed according to the method reported by Higuchi and Connors [11]. Excess of tadalafil (equivalent to 20mg) was added to 10 ml of distilled water containing various concentrations of βCD (0.02-0.1 mM), taken in a series of test tubes covered with black paper and the dispersions was shaken for 48 h on orbital shaker.

The dispersions after equilibrium were filtered using Whatman filter paper (No. 40). The filtered samples were suitably diluted and assayed for TDF content by UV analysis against blank prepared with the same concentration of βCD. The phase solubility diagram was constructed by plotting the dissolved TDF concentration against the respective concentration of βCD. The binding constant (K_a) was calculated from phase solubility diagram using its slope and intercept value.

The apparent stability constant (K_c) was calculated from the initial linear portion of the phase solubility diagram, according to the equation:

$$K_c = slope/[intercept\ (1 - slope)] \quad \text{Eq. No. (1)}$$

Preparation of TDF-βCD inclusion complexes [12]: Were prepared by kneading method. Calculated amount of TDF and βCD was triturated in a mortar with a small volume of water – ethanol (1:2 v/v) solution. The thick slurry that formed was kneaded for 45 min and then dried at 45 °C. The dried mass was pulverized and sieved through sieve no. 60. Store in cool place, and in air tight container.

Physicochemical characterization of TDF-βCD inclusion complex [12]**:** DSC thermograms and X-ray diffractograms were recorded for pure TDF, pure βCD, and TDF-βCD inclusion complexes.

Differential Scanning Calorimetry (DSC): DSC thermographs were recorded using a differential scanning calorimeter (DSC-1, Star System, Metllar Toledo). The apparatus was calibrated with purified indium (99.9%). Samples (2 mg) were placed in flat-bottomed aluminium pan and heated at a constant rate of 10 °C/min, in an atmosphere of nitrogen in a temperature range of 40–400°C.

X- Ray Diffractometry (XRD): The X-ray diffractiograms were recorded using Philips diffractometer (PW 1140) and CuKa radiation; voltage, 40 kV; current, 20 mA. Diffractogram were run at a scanning speed of 2°/min over the diffraction angle of 2θ and range of 3°–70°.

Drug-excipient compatibility studies by FT-IR [12]**:** FT-IR studies were performed on TDF and TDF: Polymers (1:4 ratio respectively) by an IR spectrophotometer (Shimadzu, FTIR 8700), in the region between 400 and 4000 cm^{-1} by the direct sampling method. The comparative FT-IR spectra were represented in Fig. 4.

Preparation of TDF ODT [12]**:** All the formulations were prepared by direct compression method, by keeping the amount of TDF constant at 5 mg. The composition of other excipients is varied as mentioned in formulation table (Table 1). In these formulations SSG, CCS & CPV are used as superdisintegrants, mannitol as a directly compressible diluent, aspartame is an artificial sweetener, powder vanilla flavor as a flavoring agent, magnesium stearate as a lubricant, colloidal SiO_2 as glidant. TDF and all the other excipients excluding magnesium stearate and colloidal SiO_2 were co-sifted through Sieve No. # 40 (ASTM), blended uniformly in a poly bag for 10 min and lubricated with Sieve No. # 60 (ASTM) passed magnesium stearate and colloidal SiO_2 and mixed in a poly bag for an additional 2-3 min. Tablets were compressed on a tablet compression machine (10 station, Yogesh Pharma Machinery Pvt. Ltd., India) fitted with 8 mm standard round punches with an Avg. Wt. of 120 mg and hardness of 2-3 kg/cm^2.

Table 1: Formulation table of TDF ODT

INGREDIENTS	2% SSG	4% SSG	6% SSG	2% CPV	4% CPV	6% CPV	2% CCS	4% CCS	6% CCS
	F1	F2	F3	F4	F5	F6	F7	F8	F9
TDF-βCD (1:4)	5+20	5+20	5+20	5+20	5+20	5+20	5+20	5+20	5+20
SSG	2.4	4.8	7.2	-	-	-	-	-	-
CPV	-	-	-	2.4	4.8	7.2	-	-	-
CCS	-	-	-	-	-	-	2.4	4.8	7.2
HPC $_{EXF}$	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
Aspartame	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Powder vanilla flavor	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Colloidal SiO_2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Mg. stearate	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Mannitol	81.8	79.4	77	81.8	79.4	77	81.8	79.4	77
Total	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**

*Quantity of ingredients per each tablet was expressed in mg; Total Wt. of a tablet is 120 mg

Precompression Studies [13]**:** The directly compressible ODT blends were evaluated for their flow properties.

Angle of Repose (θ): Was determined by funnelling method, the blend was poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2 cm above hard surface. The blend was poured till the time when the upper tip of the pile surface touched the lower tip of the funnel. The θ is calculated by the equation.

$$\theta = \tan^{-1} h / r \quad \text{Eq. No. (2)}$$

Where, θ = angle of repose, h = height of heap and r = radius of base of heap circle.

Density:

Bulk density (BD): A quantity of 2 gm of ODT blend from each formulation, previously lightly shaken to break any agglomerates formed, was introduced into a 10mL measuring cylinder and the volume is noted as bulk volume. The BD was calculated by the equation.

Bulk density (BD) = weight of powder/ Bulk volume …… *Eq. No. (3)*

Tapped density (TD): After the determination of BD, the measuring cylinder was fitted with a tapped density apparatus. The tapped volume was measured by tapping the powder for 500 times.

Later the tapping was done for another 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for another 1250 times and the constant tapped volume was noted. The TD was calculated by the equation.

Tapped density (TD) = Wt. of powder / Tapped volume …… *Eq. No. (4)*

Carr's Index (CI): The percentage of CI is calculated by the equation.

Carr's index (CI) = (TD-BD) ×100 / TD …… *Eq. No. (5)*

Hausner's Ratio (HR): is a number that correlates to the flow ability of a powder. It is calculated by the equation.

Hausner's Ratio (HR) = TD /BD …… *Eq. No. (6)*

Precompression studies of all the formulations were carried out in triplicate; the consolidated results (mean±SD) were tabulated in (Table 3).

Post compression studies [13]**:**

Tablet Weight variation test: An electronic balance (Mettler Toledo, 3-MS-S / MS-L, Japan) was used to accurately weigh the individual Wt. of twenty tablets which were randomly selected from each formulation. The (mean±SD) values were calculated.

Friability test: The friability of the 20 tablets from each batch (n=1) was tested by a friabilator (SINGLA, TAR 120, Germany) At a speed of 25 rpm for 4 min. The tablets were then dedusted, reweighed, and percentage weight loss was calculated by the equation,

% Friability = (initial Wt.- Wt. after friability) × 100 / initial Wt. …… *Eq. No. (7)*

Hardness test: To evaluate the diametrical crushing strength, 3 tablets from each formulation were tested using a hardness tester (Monsanto type hardness tester, MHT-20, Campbell Electronics, India). The mean±SD values were calculated.

Thickness: Thickness of 3 tablets from each formulation was determined using a Vernier caliper (Mitutoyo Corporation, Japan). The mean±SD values were calculated.

***In vitro* disintegration time & fineness of dispersion** [14]**:** It is specified in the European Pharmacopeia (EP 6.0), the disintegration time determination procedure for ODT is same as that of conventional uncoated tablets and the tablets should be dispersed within less than 3 min. The obtained tablet's dispersion was passed through a sieve screen with a nominal mesh aperture of 710 mm to confirm the fineness of dispersion. It was carried out in replicates of 3 tablets from each formulation and mean±SD values were calculated.

Wetting time and water absorption ratio [15]**:** A piece of tissue paper folded twice was placed in petri dish having an internal diameter of 5.5 cm, containing 6 mL of water. A tablet was placed on the paper and the time required for complete wetting was measured as wetting time, using a stopwatch. The wetted tablet was then reweighed and water absorption ratio (R) was determined using following equation.

$$\textit{Water absorption ratio (R)} = [(W_a - W_b) / W_b] \times 100 \quad \textit{Eq. No. (8)}$$

Where, W_b and W_a were the weights of the tablet before and after water absorption.

Assay [12]**:** To evaluate the drug assay, 3 tablets from each formulation were powdered in motor and pestle. Blend equivalent to 1 mg of TDF was accurately weighed and transferred into a 100mL volumetric flask, then, the volume was made up to 100mL with pH 6.8 phosphate buffer and ultra-sonicated for 2 min to extract the TDF from the tablet blend and filtered through 0.45 µm Poly Tetra Fluoro Ethylene (PTFE) filter disc. The filtrate was suitably diluted if necessary and its absorbance was measured by UV-Visible spectrophotometer at 284 nm.

Post compression studies of all the formulations, except friability test were carried out in triplicate (n=3); the consolidated results as, mean±SD were tabulated in (Table 4).

***In vitro* dissolution studies** [12]**:** Were performed for 3 tablets form each formulation using the dissolution apparatus (Lab India Disso 2000, Lab India Analytical Instruments Pvt Ltd, India) with USP-II / Paddle**.**

Each dissolution flask contains 900 mL of pH 6.8 Phosphate buffer; the speed of the paddle was maintained at 50 rpm; the temperature was kept stable at 37°C ± 0.5°C. At required time intervals, 5 mL of dissolution media was withdrawn with a pipette containing 0.45 µ (PTFE) filter disc, suitably diluted if necessary and its absorbance was measured by UV-Visible spectrophotometer at 284 nm.

Furthermore, 5 mL of fresh pH 6.8 phosphate buffer was replaced to the dissolution flask to keep the volume of dissolution medium constant. The dissolution profiles were represented graphically in (Fig. 6).

In vitro dissolution kinetics [16]: The *in vitro* drug release data was fitted into kinetic models to plot dissolution profiles (cum% drug dissolved *Vs* time) and first order plots (log% drug undissolved ***Vs*** time) as per the following equations.

$$\textit{Zero order: } Q_t = Q_0 + K_0 t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \textit{Eq. No. (9)}$$

$$\textit{First order: } \log Q_t = \log Q_0 - K_1 t / 2.303 \quad \ldots\ldots\ldots\ldots\ldots \textit{Eq. No. (10)}$$

Where *Qt* is the amount of the drug dissolved in time *t*, Q_0 is the initial amount of drug in the solution, K_0 & K_1 refers to the rate constants of zero & first order respectively. Dissolution Efficiency at 5 min (DE_5) by Trapezoid Rule [17]; and time for 50 % drug release (t_{50}) were calculated from dissolution profiles. Equations for calculating DE_5:

$$[AUC]_{t1}^{t2} = \frac{1}{2}(C_1+C_2)\ (t_2-t_1) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \textit{Eq. No. (11)}$$

$$[AUC]_0^5 = [AUC]_0^1 + [AUC]_1^2 + [AUC]_2^3 + [AUC]_3^4 + [AUC]_4^5 \ \ldots\ldots \textit{Eq. No. (12)}$$

$$DE_{10} = \frac{[AUC]_0^5}{Total\ area\ at\ 5\ min} \times 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \textit{Eq. No. (13)}$$

Where, $[AUC]_{t1}^{t2}$ = Area under curve between time points t_1 to t_2

Total area at 5 min = 5 X 100 = 500 cm^2

First order dissolution rate constant (K_1) and regression coefficient (r^2) of first order profiles were calculated from first order plots. The consolidated *in vitro* dissolution kinetic parameters of PH ODT were tabulated in (Table 5).

Accelerated stability studies of the optimized formulation [18]**:** F6 was carried; by placing 20 tablets each with a 10 CC HDPE bottle; according to International Conference on Harmonization (ICH) guidelines in a humidity chamber (NSW-175, Narang Scientific work, India) maintained at 45°C ± 2 °C and 75 % ± 5 % RH up to 3M. At the end of 1M, 2M and 3M the respective samples were withdrawn and evaluated for post compression studies. The chemical stability of drug in the 3M-accelerated stability sample of formulation F6, was compared with the drug alone by FT-IR studies (Shimadzu, FTIR 8700), recorded in the region of 400-4000 cm^{-1}, by direct sampling method**.** The consolidated results of post compression studies on accelerated stability samples of formulation F6; except friability test were carried out in triplicate and the results as mean±SD were tabulated in (Table 6).

FT-IR spectra of pure TDF & 3M-accelerated stability sample of formulation F6 were represented in (Fig.4). *In vitro* dissolution profiles of accelerated stability samples of formulation F6 were represented graphically in (Fig. 5).

RESULTS AND DISCUSSION

The standard calibration curve of TDF in pH 6.8 phosphate buffer: Based on the measurement of absorbance at λ_{max} of 284 nm in pH 6.8 phosphate buffer in the conc. range of 5-30µg/ml, a straight line with an equation, y = 0.0048 x + 0.0012 and a r^2 of 0.998 was obtained (Fig. 1).

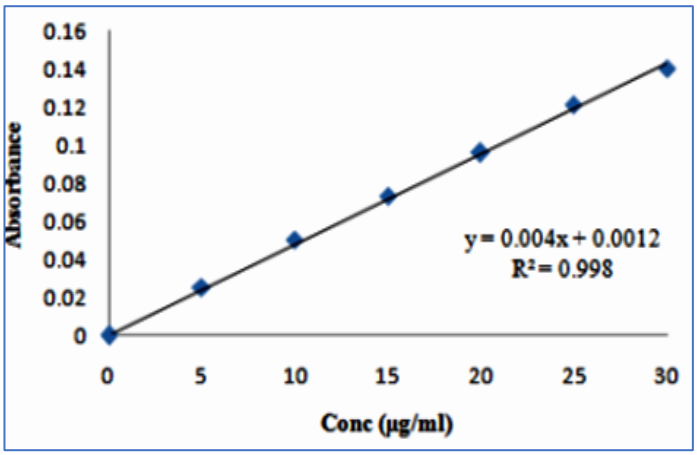

Fig. 1: Standard calibration curve of TDF in pH 6.8 phosphate buffer.

Phase solubility studies: The phase solubility diagrams of tadalafil with βCD in distilled water at 37 ± 0.5°C are shown in Fig.2. The βCD solubility diagram shows a typical curve whose initial rising portion is followed by a plateau region; the apparent stability constant (K_c) was calculated from the straight-line position of solubility diagram, assuming that 1:4 M complex was initially formed. The coefficient of regression value was 0.9985. The stability constant (K_c) of TDF-βCD inclusion complex was found to be 309.65M^{-1}.

The solubility of tadalafil increased as a function of the CDs concentrations due to the formation of inclusion complexes [19]. However, other interactions may be involved, such as aggregation of cyclodextrins and their complexes into water soluble aggregates that are capable of solubilizing water insoluble drugs via non-inclusion complexation or micelle-like structure [20].

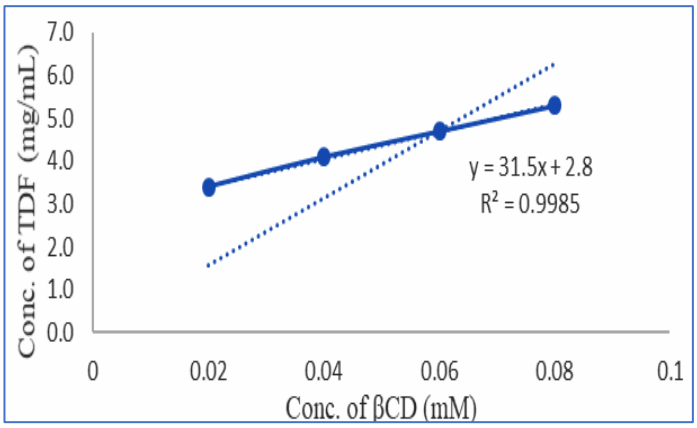

Fig. 2: Phase solubility curve of Tadalafil in β-Cyclodextrin.

Preparation of TDF-βCD complexes: Inclusion complexes of TDF with βCD were prepared using a kneading technique. Based on the results obtained through the phase solubility studies, which proved the possibility of formation of higher order complexes between TDF and βCD, (1:4 respectively) molar ratio was chosen for the preparation of inclusion complexes.

Physicochemical characterization of TDF-βCD inclusion complex:

Differential scanning calorimetry (DSC) studies: The DSC spectra of tadalafil (A) and TDF-βCD inclusion complex prepared by kneading method are depicted in Fig. 3. The DSC thermogram of tadalafil was typical of a crystalline substance, exhibiting a sharp endothermic peak at 297.60°C, corresponding to the melting point of the drug. The drug endothermic melting peak completely disappeared in the DSC thermograms of the inclusion complex prepared using HP-βCD. This could indicate the amorphous solid dispersion or molecular encapsulation of the drug into the cyclodextrin cavity [21].

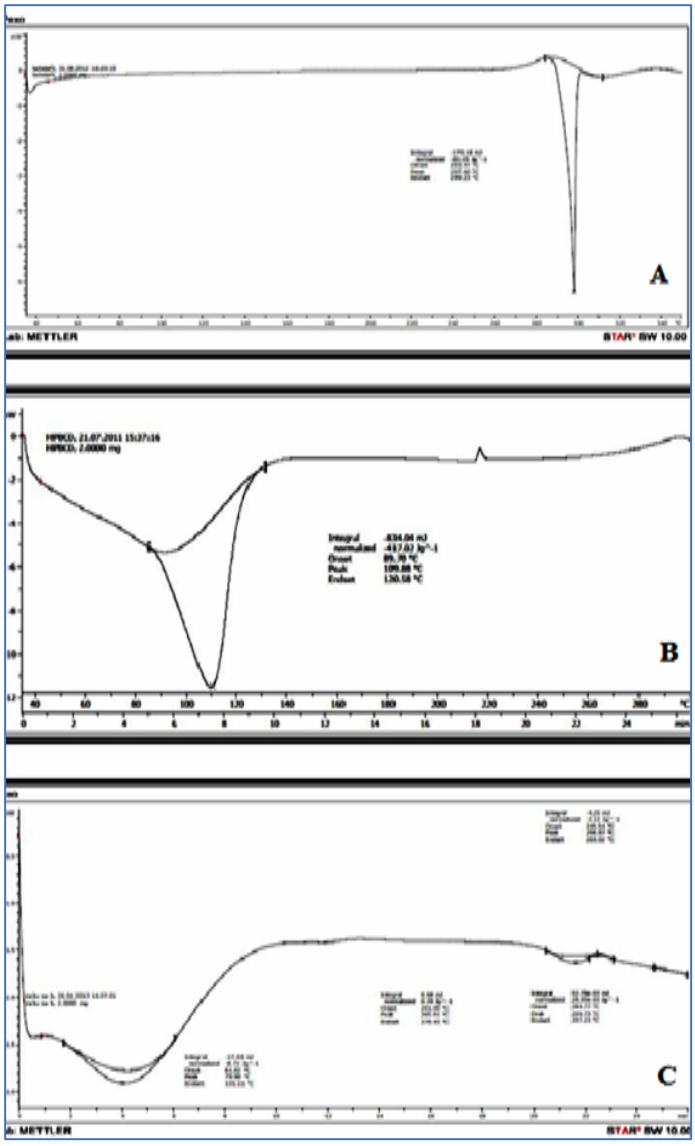

Fig. 3: DSC thermograms of A) TDF, B) βCD and C) TDF-βCD inclusion complex

X-ray diffraction (XRD) studies: The diffraction pattern shown in Fig.4 of pure tadalafil, confirms the crystalline nature of drug, as demonstrated by numerous distinct peaks at 2θ of 16.31°, 18.79°, and 19.96°, 22.90° respectively (A); (i.e. Fingerprint region). However, the intensity of the peaks in βCD inclusion complex prepared by kneading method (C) was reduced when compared to that of the pure drug. The results indicate that the drug in HP-βCD prepared by kneading method was amorphous as compared to the pure drug; hence the dissolution of the drug was noticeably improved [21].

Drug-excipient compatibility (FT-IR) studies: The FT-IR spectrum of TDF (Fig. 5A) is characterized by principal absorption peaks of –NH stretching band at 3,328 cm^{-1}, in addition to aromatic C–H stretch at 3,092 cm^{-1} and aliphatic C–H stretch at 2,905 cm^{-1} of Tadalafil, was apparently masked in all the prepared systems by the broad intense band corresponding to the OH vibration at 3,350 cm^{-1} and by C–H stretching at 2,890 cm^{-1} [22].

Comparison of FT-IR spectra of pure drug with the drug: polymers (1:4 ratio) samples indicate the absence of chemical interaction between TDF and polymers used in the study (Fig. 5A-I).

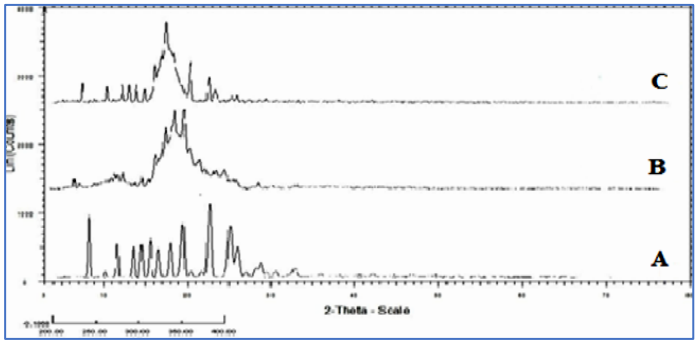

Fig. 4: X-ray diffractograms of: A) TDF, B) βCD and C) TDF- βCD inclusion complex

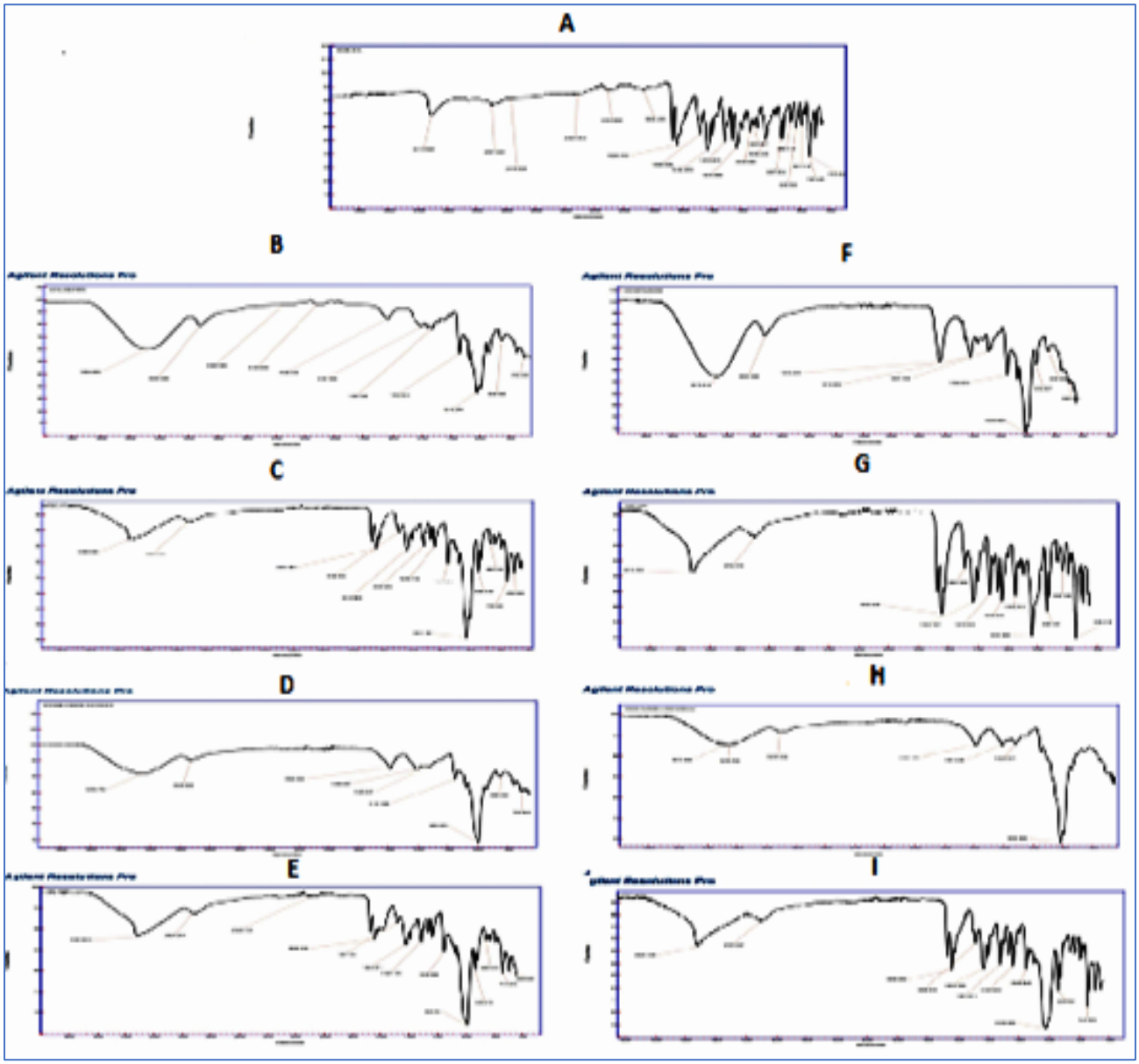

Fig. 5: FT-IR spectra of A) TDF, B) βCD, C) TDF+βCD, D) SSG E) TDF+SSG, F) CPV G) TDF+CPV H) CCS & I) TDF+CCS

Table 2: Results of pre-compression studies of TDF ODT

F. Code	Angle of repose (˚)	BD (g/cm^3)	TD (g/cm^3)	CI (%)	HR
F1	28.1±0.09	0.559±0.01	0.666±0.02	18.59±1.56	1.23±0.09
F2	25.8±0.06	0.585±0.05	0.646±0.03	21.73±1.64	1.25±0.02
F3	24.8±0.32	0.580±0.04	0.796±0.02	20.64±3.04	1.23±0.09
F4	25.8±0.01	0.559±0.02	0.733±0.02	21.73±1.64	1.25±0.02
F5	25.8±0.15	0.561±0.03	0.710±0.02	20.51±2.82	1.23±0.02
F6	29.8±0.15	0.564±0.04	0.693±0.01	20.51±2.82	1.23±0.02
F7	29.8±0.15	0.564±0.04	0.693±0.01	20.51±2.82	1.23±0.02
F8	28.4±0.21	0.552±0.01	0.746±0.03	17.28±0.53	1.13±0.03
F9	27.5±0.09	0.585±0.05	0.646±0.03	17.05±0.68	1.13±0.02

Post-compression studies: Of all the TDF ODT, reveals that the Avg. wt. of tablets of was found to be 118.1 to 120.7 mg. The Avg. thickness of tablets was found to be 3.9 to 4.3mm. The Avg. hardness of the tablets ranges between 3.2 to 4.1 Kg/cm^2, indicating satisfactory mechanical strength. The % Wt. loss in the friability test ranges from 0.28 to 0.58 %, which was NMT 1 % as per pharmacopeia limits indicating a good mechanical resistance of tablets. Assay of all the prepared batches is within 94.24 to 98.72 % of the labelled content, indicating the content uniformity of all the formulations. The disintegration results show CPV achieved the fastest disintegration (<30 sec), as it produces the highest tablet breaking force at a given compression force [23] and croscarmellose sodium provided the slowest disintegration (>1 min). The wetting time of all the formulations was obtained in the range of 45 to 83 Sec.

As the conc. of superdisintegrant increases, there is a significant decrease in the wetting time and *in vitro* disintegration time. Wetting is related to the inner structure of the tablets, hydrophilicity of the components and swelling mechanism of superdisintegrant. The water absorption ratio was also related to the hydrophilicity of the matrix. The ODT's with CPV were fully hydrated and soft throughout because CPV quickly wicks water into the tablet [24]. Meanwhile, the centres of the tablets made with SSG and CCS remained dry and hard. Although the tablet with SSG swelled, the outer edge appeared with gel like consistency. The order of superdisintegrant's efficiency was observed as CPV > SSG > CCS. The formulation F6 (with 6 %w/w of CPV) which shows min wetting time of 45 Sec and min *in vitro* disintegration time of 36 sec, is considered as an optimal TDF ODT (Table 3).

Table 3: Results of post-compression studies of TDF ODT

F Code	Avg. Wt. (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	DT (Sec)	WT (Sec)	Assay (%)
F1	119.8±1.31	4.2±0.15	3.6±0.11	0.28	73±0.32	83±0.35	99.98±0.01
F2	118.1±1.33	4.2±0.21	3.2±0.12	0.53	60±0.24	71±0.25	101.2±0.13
F3	120.7±1.11	4.0±0.12	3.3±0.15	0.53	50±0.22	67±0.25	99.98±0.04
F4	118.3±1.81	3.9±0.12	3.4±0.15	0.41	60±0.31	80±0.41	100.1±0.05
F5	120.4±1.10	4.1±0.32	3.2±0.12	0.46	47±0.35	72±0.48	99.95±0.06
F6	119.6±1.13	4.0±0.15	3.5±0.14	0.58	36±0.19	45±0.52	101.2±0.05
F7	118.2±1.26	4.3±0.22	4.1±0.15	0.32	83±0.24	75±0.49	99.34±0.05
F8	120.7±1.37	4.1±0.15	3.6±0.12	0.54	67±0.26	72±0.38	98.35±0.11
F9	119.3±1.30	4.3±0.14	3.2±0.13	0.45	55±0.21	58±0.51	99.79±0.07

* Except friability test all other were performed as n=3 and the values are given as mean±SD.

***In vitro* dissolution studies:** Dissolution profiles are represented graphically in (Fig. 6) indicate that, the release rate increases with an increase in concentration of superdisintegrant.

Based on the values of first order dissolution rate constant (K_1); the order of superdisintegrants in enhancing the dissolution rate of TDF from its ODT is CPV > SSG >CCS. Formulation F6 (with 6% CPV) released 73.21 % of drug within 5 min compared to others, it was considered as an optimal TDF ODT (Fig. 6).

In vitro dissolution kinetics: Formulation F6 had the highest DE_5 (39.55 %); K_1 (0.105min^{-1}) with r^2 (0.9844) and lowest t_{50} (4 min). Hence it is an optimal TDF ODT (Table 4).

Table 4: *In vitro* dissolution kinetics of TDF ODT

F. Code	t_{50} (min)	DE_5 (%)	K_1 (min^{-1})	r^2
F1	6	22.38	0.0879	0.8959
F2	5	26.50	0.0888	0.9258
F3	5	30.81	0.0900	0.9486
F4	5	26.33	0.0856	0.9530
F5	4	31.72	0.0959	0.9691
F6	4	39.55	0.1052	0.9844
F7	6	23.32	0.0804	0.9248
F8	5	26.17	0.0874	0.9455
F9	5	28.71	0.0932	0.9514

Accelerated stability studies of the optimized formulation: There was no significant differences in post compression and *in vitro* dissolution profiles of initial and accelerated stability samples of optimized formulation F6 up to 3 months, hence it passes the test for stability as per ICH guidelines.

FT-IR spectrum of 3M-accelerated stability sample of optimized formulation (F6), shows the same functional groups at the corresponding frequencies as that of pure drug. Thus, indicates no significant chemical interaction and change in functional groups of TDF had occurred during the 3M accelerated stability period (Table 5); (Fig. 7) & (Fig. 8).

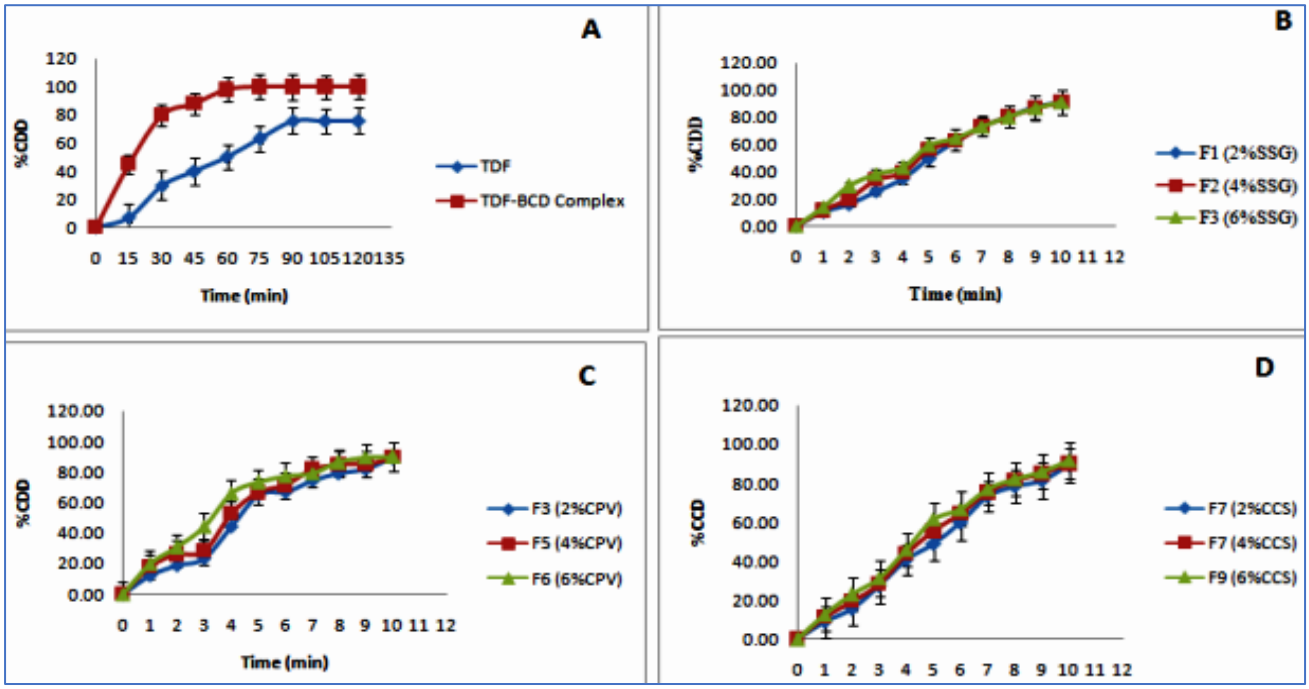

Fig. 6: *In vitro* dissolution profiles of A) TDF & TDF-βCD complex B) TDF ODT with SSG C) TDF ODT with CPV & D) TDF ODT with CCS

Table 5: Results of post-compression studies on accelerated stability samples of opt. formulation, F6

Parameter	Initial	45°C / 75% RH-1M	45°C / 75% RH-2M	45°C / 75% RH-3M
Avg. Wt. (mg)	119.6±1.13	120.6±1.02	119.9±1.12	119.0±0.92
Hardness (kg/cm^2)	3.5±0.14	3.6±0.05	3.6±0.06	3.7±0.07
Thickness (mm)	4.0±0.15	4.1±0.03	4.1±0.06	4.1±0.05
*Friability (%w/w)	0.58	0.59	0.61	0.65
DT (S)	36±0.19	38±0.07	36±0.04	38±0.09
Wetting time (S)	45±0.52	48±0.52	48±0.02	47±0.12
Assay (%)	101.2±0.05	100.2±0.02	99.98±0.05	100.2±0.15

* Except friability test all other were performed as n=3 and the values are given as mean±SD.

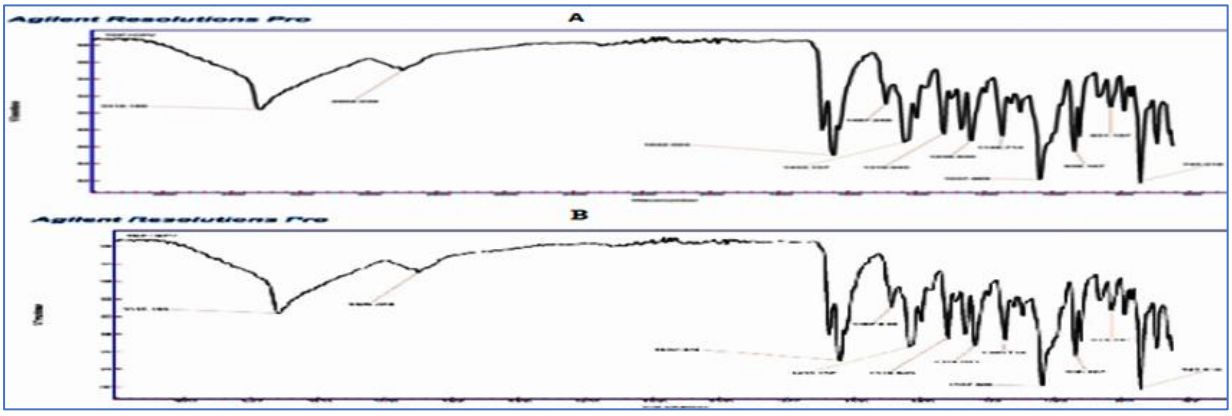

Fig. 7: FT-IR spectra of A) TDF & B) 45°C / 75% RH-3M sample of optimized formulation F6

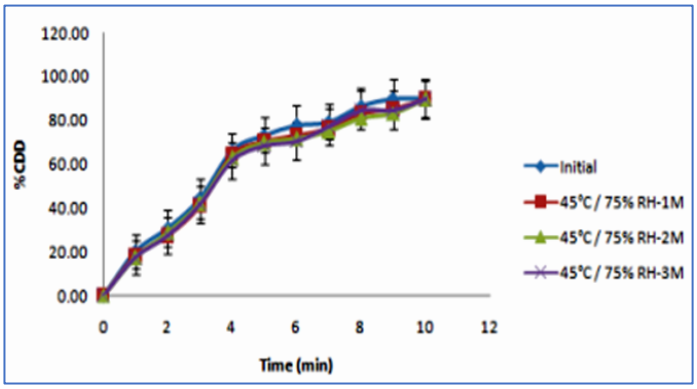

Fig. 8: Dissolution profiles of accelerated stability samples of optimized formulation F6

CONCLUSION

In the view of the above findings, there is drug-excipient compatibility between TDF and polymers used in the study. The formation of higher order complexes between TDF: βCD (1:4 respectively), was confirmed by the phase solubility studies, this molar ratio was chosen for the preparation of TDF-βCD inclusion complexes. Physico-chemical characterization of TDF-βCD inclusion complexes was done by DSC and XRD studies. Results of DSC studies indicate formation of amorphous solid dispersion or molecular encapsulation of the drug into the cyclodextrin cavity. XRD results indicate that the drug in βCD prepared by kneading method was amorphous as compared to the pure drug; hence the dissolution rate of TDF was improved in the *in vitro* dissolution studies drastically.

All the formulations passed the pre- & post- compression evaluation parameters. The release rate of TDF from ODT increases as the concentration of superdisintegrants increases. The order of superdisintegrants in enhancing the dissolution rate of TDF is CPV > SSG > CCS. Formulation F6 (with 6 % CPV) had the highest DE_5 (39.55 %); K_1 (0.1052 min^{-1}) with r^2 (0.9844) & lowest t_{50} (4 min), was considered as the optimal ODT. Accelerated stability studies on optimized formulation, F6 in the final 10 cc HDPE pack up to 3 months, indicate it passes the test for stability as per ICH guidelines.

Therefore, an effective TDF ODT for treating erectile dysfunction was formulated by the direct compression technique with disintegration attained by 6%w/w CPV as superdisintegrant. This will fasten the onset of action and thereby enhances the bioavailability of TDF in comparison to its conventional tablets.

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