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Research Article

Development of Mouth Dissolving Tablets containing Tadalafil Hydroxypropyl β-Cyclodextrin Inclusion Complex

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ABSTRACT

The objective of the present study was to formulate mouth dissolving tablets of inclusion complex of tadalafil with improved aqueous solubility and dissolution rate. Tadalafil is a BCS class II drug having low aqueous solubility and therefore low oral bioavailability. In the present study, inclusion complex of tadalafil with hydroxypropyl-β-cyclodextrin were prepared by kneading method. Inclusion complex were characterized by differential scanning calorimetry (DSC), X-ray diffractometry (XRD), and ^{1}H NMR studies, and evaluated for in vitro dissolution, and phase solubility studies. DSC and XRD study demonstrated that there was a significant decrease in crystallinity of pure drug present in inclusion complex, which resulted in an increased dissolution rate of tadalafil and ^{1}H NMR studies strongly, confirmed that the inclusion complex has formed. Inclusion complexation results in improvement in solubility and dissolution rate have been used in preparation of mouth dissolving tablets using super disintegrants by direct compression method. A total of nine formulations were developed and the tablets prepared were evaluated for weight variation, friability, hardness and wetting time. *In vitro* disintegration and dissolution studies were also performed. On the basis of these results, mouth dissolving tablets of tadalafil- HPβCD inclusion complex may be considered as a promising alternative to conventional tablets with improved patient compliance.

INTRODUCTION

The oral route of administration is considered as the most widely used route. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patient incompliance particularly in case of pediatric and geriatric patients. Of all the orally administered dosage forms, tablet is most preferred because of ease of administration, compactness and flexibility in manufacturing. Because of changes in various physiological functions associated with aging including difficulty in swallowing, administration of intact tablet may lead to poor patient compliance and ineffective therapy. The pediatric and geriatric patients are of particular concern. Thus a new delivery system known as rapidly dissolving or disintegrating dosage forms is gaining importance. These systems dissolve rapidly in saliva and can be swallowed without the need of water [1].

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Tadalafil (TDF) is a potent and selective phosphodiesterase-5 inhibitor used for the treatment of erectile dysfunction which was recently approved by the FDA in November 2003 [2]. Compared to sildenafil and vardenafil, tadalafil 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 versus PDE6 [3,4]. However, it has the disadvantage of poor aqueous solubility. This may cause formulation problems and lead to highly variable blood levels, and irreproducible clinical response (therapeutic failure or exaggerated side effects). Therefore, it is important to introduce effective methods to enhance the solubility and dissolution rate of the drug aiming to improve its bioavailability, increase the predictability of the response and/or reduce the dose.

Complexation with CDs has been widely used to enhance the bioavailability of poorly soluble drugs by increasing the drug solubility, dissolution and/or permeability. The aim of this work was to study the interaction of tadalafil

with HP-β -CD in solid state, aiming to develop a soluble form of the drug as a primary step in the development of tadalafil tablet formulation.

Solid tadalafil–cyclodextrin inclusion complex were prepared using kneading method. DSC, XRD and NMR were used to evaluate the physicochemical properties of the prepared systems in order to clarify any interaction between the drug and the used carriers. In-vitro dissolution studies of all the prepared systems were carried out to investigate the effect of the molar ratio, on tadalafil dissolution. Mouth dissolving tablets of tadalafil- cyclodxtrin inclusion complex were prepared by direct compression technique using superdisintegrants.

MATERIALS AND METHOD

Materials

Tadalfil was received as a kind gift from Ami Life sciences Pvt. Ltd. Thane, India. HPβCD was obtained from Whokhart Pharma, Aurangabad, India, Sodium starch glycolate, cross carmellose sodium and mannitol were procured from Loba Chemie (Mumbai, India) and used as received. Flavour (Strawberry) was kind gift from Firmenich, Chennai. All other reagents used were of analytical grade.

Methods

Phase solubility studies

Phase solubility studies were performed according to the method reported by higuchi and Connors [5]. Excess of tadalafil (equivalent to 20mg) was added to 10 ml of distilled water containing various concentrations of HPβCD (0.02-0.1 mM), taken in series of test tubes covered with black paper and suspension were shaken for 48 hr on orbital shaker. The suspensions were equilibrated and filtered using Whatman filter paper (No 40). The filter sample were suitably diluted and assayed for Tadalafil content by UV analysis against blank prepared in same concentration of HPβCD. The experiments were performed in triplicate. The phase solubility diagram was constructed by plotting the dissolved tadalafil concentration against the respective concentration of HPβCD. The binding constant Ka was calculated from phase solubility diagram using its slope and intercept value. The apparent stability constant Kc was calculated from the initial linear portion of the phase solubility diagram, according to the equation:

$$Kc = \text{slope} / [\text{intercept} (1 - \text{slope})] \quad \ldots\ldots\ldots (1)$$

Preparation of tadalafil – HPβ-CD inclusion complex

Inclusion complex of tadalafil with hydroxypopyl-β-cyclodextrin were prepared by kneading method. Calculated amount of tadalafil and hydroxypopyl-β-cyclodextrin was triturated in a mortar with a small volume of water – methanol (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 pulverised and sieved through sieve no. 60. Store in cool place and in air tight container.

Physicochemical characterization of tadalafil–HPβCD inclusion complex

DSC thermograms, X-ray diffractograms and NMR spectra were recorded for pure tadalafil, pure HPβCD, and inclusion complex.

Differential Scanning Calorimetry (DSC)

DSC analysis was performed 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 diffraction patterns were recorded using Philips diffractometer (PW 1140) and Cu-Ka 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°.

^{1}H NMR studies

Nuclear magnetic resonance spectroscopy was carried out by using NMR spectrometer (Bruker Advance III, 400 MHz,). The tadalafil and inclusion complex dissolved in DMSO were scanned from 1 to 10 ppm range under the following measurement conditions: Magnet 9.4 tesla super-conducting Magnet; Probe-BBO 400 MHz, with Z-gradient, 2H lock; for observation of nuclei like 1H, 13C, 31P, 15N etc. with 1H decoupling, Any of these nuclei can be fully automatically selected and optimally tuned and matched.

In vitro dissolution studies

The dissolution of inclusion complex was carried out following the USP XXIV Apparatus 2 (paddle) method. The phosphate buffer (pH 6.8) used as media at 100rpm, bath temperature was

37±0.5°C. Inclusion complex containing drug equivalents to 5 mg was placed in dissolution bath container. Filter about 5 ml of aliquots collected up to 2 h at 15 min interval and analyzed spectrophotometrically at 284 nm (UV 1700, Shimadzu). Dissolution profile of tadalafil was also carried in similar manner.

Preparation of Tadalafil Mouth Dissolving Tablets

Mouth dissolving tablets were prepared by direct compression method according to formula given in the Table 1. Nine different formulations were prepared. All the ingredients were sieved separately through sieve no. 40 except magnesium stearate which was sieved through sieve no. 60 and collected. The weighed amount of inclusion complex equivalent to 5 mg of drug and other ingredients were mixed first and magnesium stearate was finally added and mixed thoroughly. The tablets were compressed in a ten station rotary punch tablet machine (Rimek Mini Press) using 8 mm punch.

Micromeritics of Powder Blend

Before final compression of tablets, powdered mixture was subjected to pre compression parameters such as bulk density, tapped density, angle of repose, powder compressibility and Hausner ratio. All the experiments were done in triplicates and expressed as mean± SD.

Bulk Density

Bulk density was determined by measuring the volume of the predetermined or preweighed mass of the powder blend according to the protocol described [6].

$$\text{Bulk Density (Db)} = (M) / (Vo) \quad \ldots\ldots\ldots (2)$$

Where, M = Mass or weight of the powder blend
Vo = Apparent volume of the powder blend into the cylinder

Tapped Density

Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder was mechanically tapped and volume readings were taken until little further volume change was observed. The mechanical tapping was achieved by raising the cylinder and allowing it to drop under its own weight from a specified distance

$$\text{Tapped density (Dt)} = (M) / (Vf) \quad \ldots\ldots\ldots (3)$$

Where, M = Mass or weight of the powder blend
Vf = Final volume of the powder blend into the cylinder.

Carr's Index or Compressibility Index (I)

This was calculated by the formula and expressed as percentage (%)

$$I = Dt - Db / Dt \times 100\% \quad \ldots\ldots\ldots (4)$$

Where, Db = Bulk density, Dt = Tapped density.

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula-

$$\text{Hausner Ratio} = Dt/Db \quad \ldots\ldots\ldots (5)$$

Where, Db = Bulk density, Dt = Tapped density.

Angle of Repose

The determination of angle of repose of powder blend was carried out by employing fixed funnel method

$$\text{Angle of Repose} = \tan^{-1}(H/R) \quad \ldots\ldots\ldots (6)$$

Where, H = height of the pile, R = radius of the pile.

Evaluation of Formulated Tablets

Thickness and Diameter

The thickness of individual tablets may be measured with a micrometer, which permits accurate measurement and provides information on the variation between tablets. The tablet thickness should be controlled within a ± 5% variation of a standard value.

Tablet Hardness and Friability

Tablets were evaluated for hardness and friability using Monsanto hardness Tester and Friabilator (Electro Lab, India) respectively [6].

Uniformity of weight

Weighed individually 20 tablets at random and average weight were calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table and none deviates by more than twice that percentage [7].

Wetting Time

A piece of tissue paper folded twice was kept in a culture dish (internal diameter 5.5 cm) containing ~6 mL of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the

upper surface of the tablet was recorded as the wetting time [8].

In vitro **Disintegration Time**

The *in vitro* disintegration time was determined using disintegration test apparatus (Electro Lab Disintegration test Apparatus). A tablet was placed in each of the six tubes of the apparatus and a disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no discernible mass remaining in the apparatus was measured [9, 10].

Disintegration in Oral Cavity

The time required for complete disintegration of tablet in oral cavity was obtained from six healthy volunteers, who were given tablets from all the formulations [11, 12].

In vitro **Dissolution studies**

In vitro dissolution studies will carry out by USP II (paddle type) dissolution test apparatus at 50 rpm. The dissolution medium consisted of 900ml of 6.8 pH Phosphate buffer. This is maintained at 37±0.5°C. Aliquots of 5 ml were withdrawn at specified time and equivalent amount of fresh dissolution medium is added. Aliquots withdrawn were filtered and analyzed at 284 nm spectrophotometrically [13].

RESULTS AND DISCUSSION

Phase solubility studies

The phase solubility diagrams of tadalafil with HP-β-CD in distilled water at 37 ± 0.5 °C are shown in Fig.1. The HPβCD solubility diagram shows a typical curve whose initial rising portion is followed by a plateau region; the apparent stability constant (Kc) 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 0.910. The stability constant (Kc) of tadalafil - HPβCD 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 [14]. 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 [15].

Preparation of Tadalafil- HPβCD complex

Inclusion complex of tadalafil with HP-β-CD were prepared using kneading technique. Based on the results obtained through the phase solubility studies, which proved the possibility of formation of higher order complexes between tadalafil and cyclodextrins, 1:4 (drug to HPβCD) molar ratio was chosen for the preparation of inclusion complex.

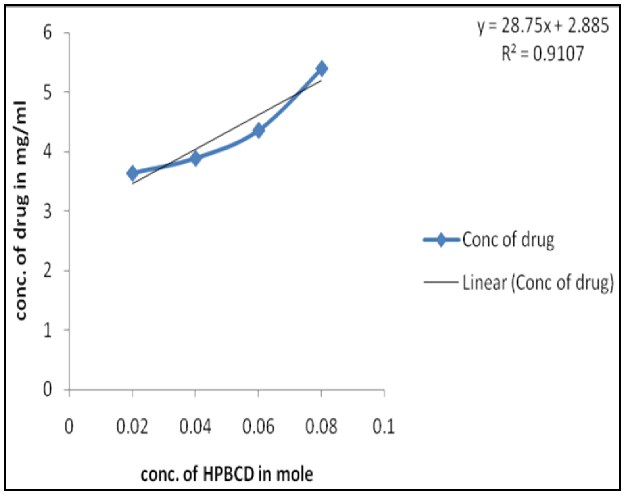

Figure 1: Phase solubility curve of tadalafil with HPβCD

Differential scanning calorimetry (DSC)

The DSC spectra of tadalafil (A) and inclusion complex containing hydroxyl propyl-β-cyclodextrin prepared by kneading method are depicted in Fig. 2. 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-β-CD. This could indicate amorphous solid dispersion or molecular encapsulation of the drug into the cyclodextrin cavity [16].

X-Ray Diffraction (XRD)

The diffraction pattern of pure tadalafil Fig 3 showed that the drug was of crystalline nature, as demonstrated by numerous distinct peaks at 2θ of 16.31°, 18.79°, and 19.96°, 22.90° respectively (a). (Fingerprint region), however, the intensity of the peaks in inclusion complex prepared by kneading method was reduced when compared to that of the drug and hence absent(c). Intensity of peak sharpness was greater in physical mixtures of TDF-HPβCD than in kneaded products (b). The results indicate that the drug in kneading method was amorphous as compared to the pure drug; hence the dissolution of the drug was improved.

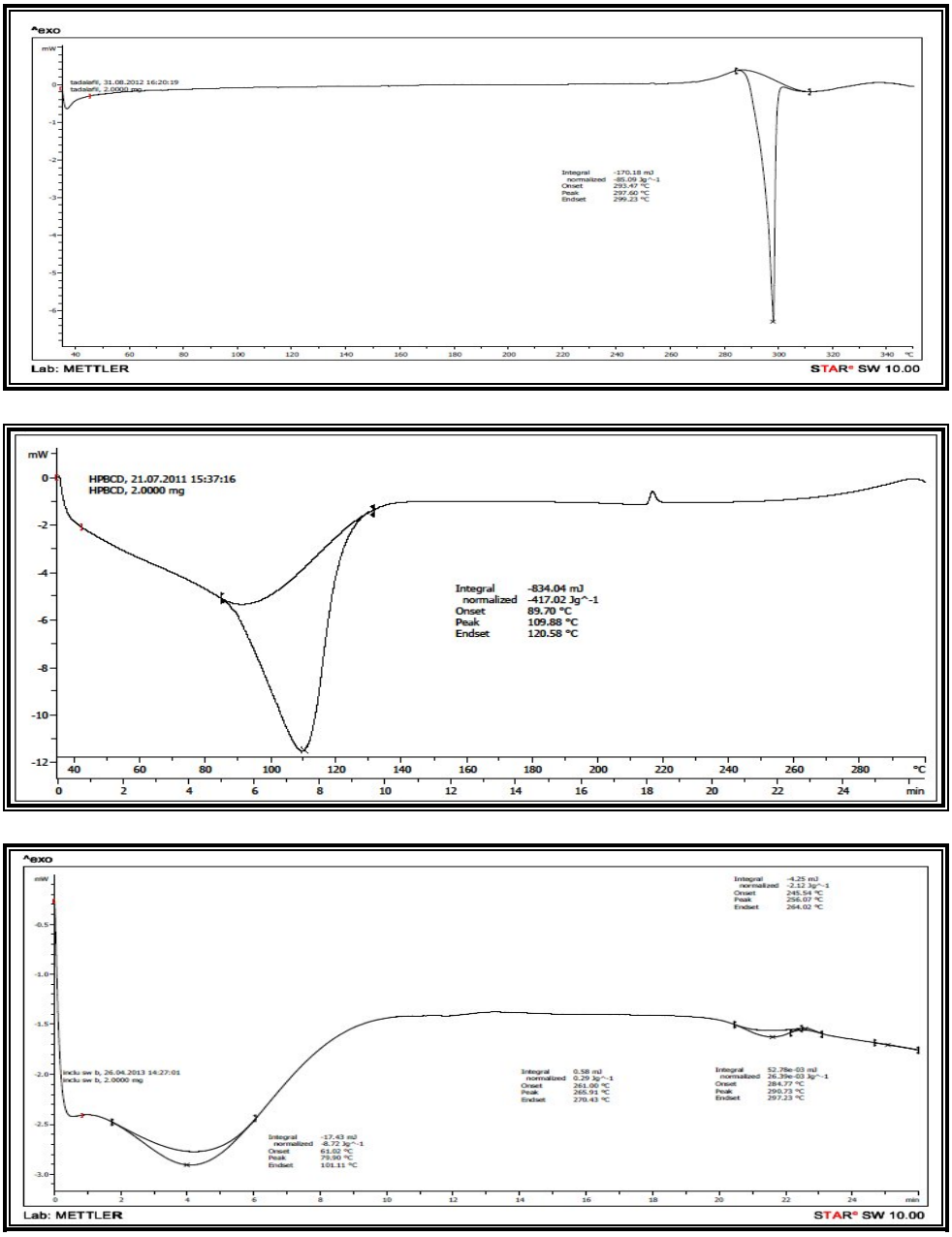

Figure 2: DSC thermpgram of tadalafil, HPβCD and inclusion complex.

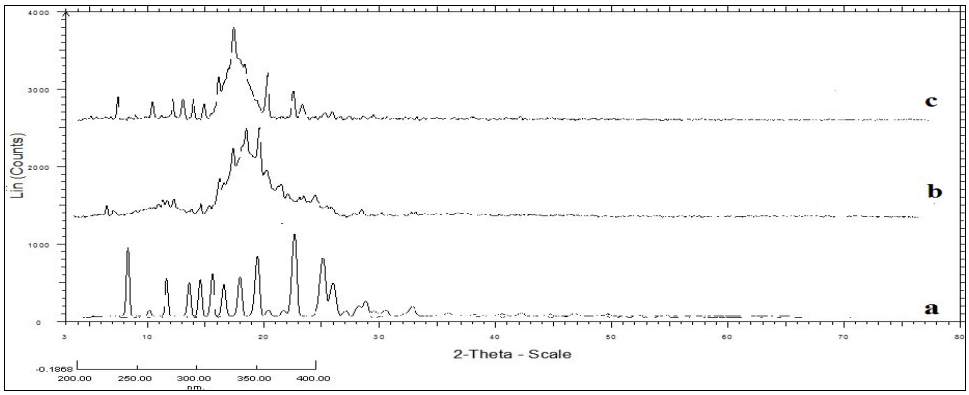

Figure 3: X-ray powder diffractogram of a.Tadalafil, b. HPβCD, c. inclusion complex.

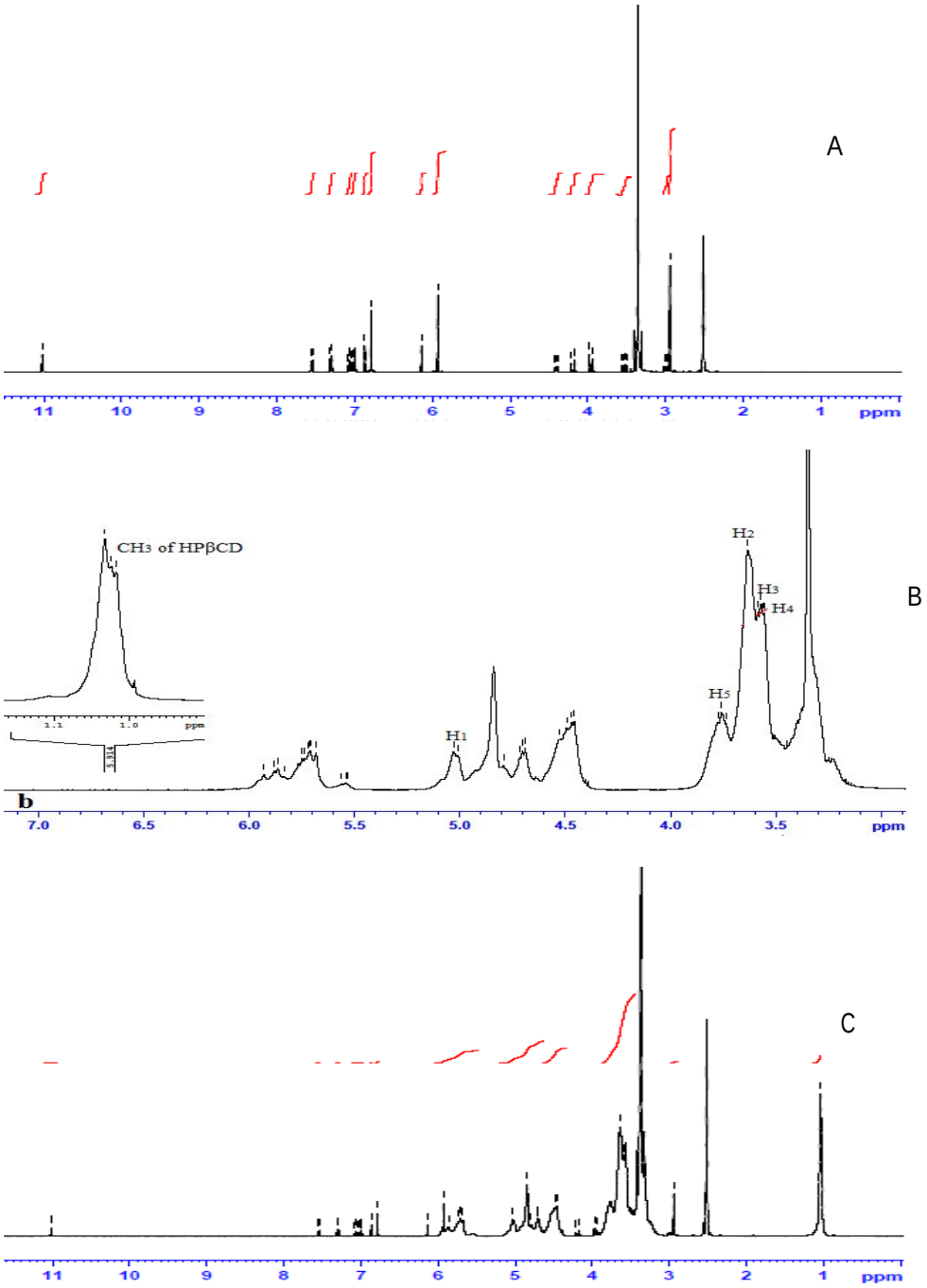

Figure 4: ^{1}H NMR spectrum of a. tadalafil b. HPβCD c. tadalafil- HPβCD inclusion complex.

Table 1: Composition of different formulations of tadalafil tablets

Ingredients (mg)	S1	S2	S3	S4	S5	S6	S7	S8	S9
Inclusion complex containing 5mg of Tadalafil	5	5	5	5	5	5	5	5	5
Sodium starch glycolate (SSG)	10	20	30	-	-	-	-	-	-
Crosspovidone XL		-	-	10	20	30	-	-	-
Cross Carmellose Sodium (CCS)	-	-	-	-	-	-	10	20	30
Mannitol	80	70	60	80	70	60	80	70	60
Strawberry Flavour	2	2	2	2	2	2	2	2	2
Aerosil	3	3	3	3	3	3	3	3	3
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5

Table 2: Tablet characteristics

Formulations	Hardness (kg/cm2)±S.D	Friability (%) ± S.D	Disintegration time (Sec) ± S.D	Wetting time (sec) ± S.D	Thickness (mm) ± S.D	Weight variation(mg) ±S.D
S1	3.6±0.1	0.28±0.01	73±3	83±3	4.2±0.15	185.8±1.31
S2	3.2±0.1	0.53±0.01	60±2	71±2.5	4.4±0.2	186.1±1.33
S3	3.1±0.15	0.53±0.01	50±2	67±2.5	4±0.1	183.7±1.11
S4	3±0.15	0.41±0.05	60±3	80±4	3.9±0.15	186.3±1.81
S5	2.8±0.1	0.66±0.06	47±3	72±2.08	3.5±0.32	186.4±1.10
S6	2.5±0.1	0.98±0.05	36±1	45±1.52	4±0.15	185.6±1.13
S7	4.3±0.25	0.32±0.05	83±2	75±1.52	4.3±0.2	187.2±1.26
S8	3.6±0.25	0.64±0.1	67±2	72±2.08	4.1±0.15	183.7±1.37
S9	3.2±0.3	1.5±0.07	55±2	58±2.51	4.3±0.15	186.3±1.30

^{1}H NMR studies

In order to explore the possible inclusion mode of the HPβCD-TDF complex, we compared the ^{1}H NMR spectra of HPβCD in the absence and presence of TDF (Fig. 4). The ^{1}H resonances of HPβCD were assigned according to the reported method. As illustrated in Fig.4, After inclusion complexation with TDF , the H-3 proton of HPβCD shifted 0.010 ppm and the H-5 proton of HPβCD shifted 0.02 ppm . Both H-3 and H-5 protons are located in the interior of the Cyclodextrin cavity, with H-3 protons near the wide side of cavity and H-5 protons near the narrow side. These results may indicate that TDF should be included in the HPβCD cavity from the wide side. Fig.4 shows the 1H NMR spectra of TDF (4a), HPβCD (4b), and HPβCD – TDF complex (4c) in DMSO. In the ^{1}H NMR spectrum of the HPβCD- TDF inclusion complex, the presence of hydrogen atom signals belonging to both HPβCD and TDF molecules strongly confirmed that the inclusion complex has formed. Thus Almost all the peaks were same as in the ^{1}H NMR spectra of TDF except a few peaks arrised of HPBCD.In the structure of HPBCD it is an cyclodextrin which contain cyclic aliphatic structure all peaks appered in downfield region. Pyranose ring contain -CH_2-OH proton appered as a singlet at 1.034 ppm. The ring contains all hydroxyl groups appeared as sharp singlet peak appered at 2.939 ppm. As per the ^{1}H NMR sectra of drug polymer inclusion complex there is no chemical interaction between the drug and polymer; Hence TDF is fully intact inside the structure of HPBCD.

In vitro dissolution studies

The dissolution profiles of tadalafil and optimized inclusion complex (1:4) are shown in Fig.5 About 70% of the inclusion complex of tadalafil dissolved in 30 min and complete dissolution occurred in 60 min. However only 50% of untreated tadalafil dissolved in 60 min and achieved complete dissolution up to the end of 120 min testing period. The increase in dissolution rate of the drug in the presence of HPβCD may be attributed to both an improvement in drug wettability and the formation of a readily soluble complex. Furthermore, the TDF-HPβCD complex shows a markedly higher dissolution rate this is a consequence of increasing the drug-carrier contact surface. This result agrees with the previously reported data regarding the high affinity of HPβCD for drugs.

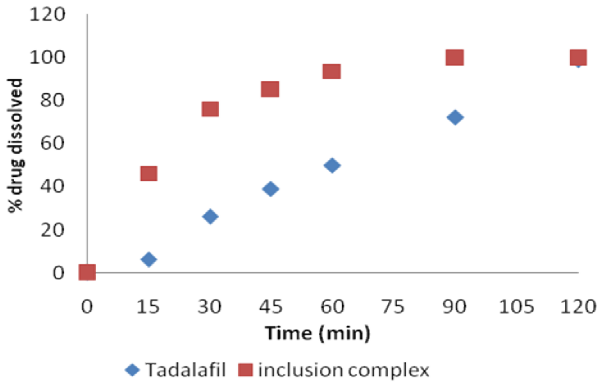

Figure 5: Dissolution profile of pure drug (tadalafil) and inclusion complex in water

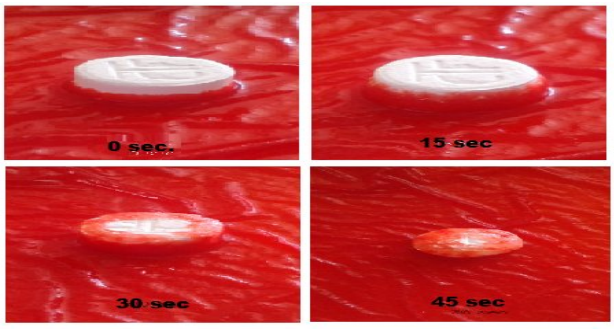

Figure 6: Observation of the wetting time for optimised tablets (S9)

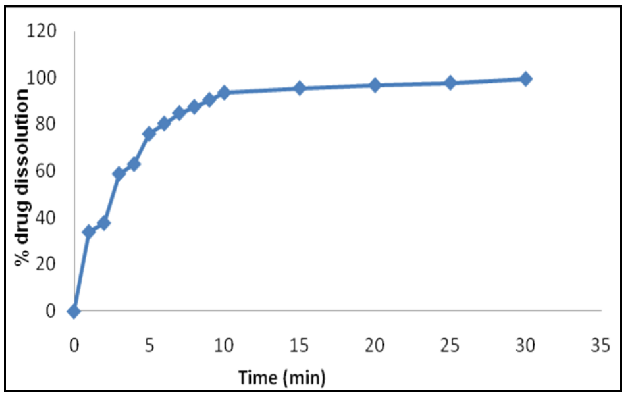

Figure 7: Dissolution profile of tadalafil from mouth dissolving tablets

Study of Micromeritics of Powder Blend

In the present study, tadalafil mouth dissolving tablets were prepared by using cross povidone, croscarmellose sodium and sodium starch glycolate as super disintegrants (Table 1). A total number of nine formulations were prepared and tablets were made by direct compression technique.

The pre formulation study of the TDF blend shown that it has low Hausner`s ratio (< 1.2), compressibility index (< 16.8 %), angle of repose (< 35.3) values indicate a fairly good flow ability of powder mixture. As the powder blend posses free flowing properties hence tablets so produced has uniform weight.

Tablet Characteristics

The data obtained from post compression parameters such as hardness, friability, weight variation, thickness are shown in Table 2. The hardness was found to be in the range of 2.5±0.1 to 4.3±0.25 kg/cm^2 for all the tablets from all the formulations indicating that these formulations confer adequate mechanical strength to withstand physical and mechanical stress during handling of the tablets. In all the formulations, the friability values were less than 1% except S9 which met the pharmacopoeial limits. All the tablets passed weight variation test as the percent weight variation was within the pharmacopoeial limits. The weight of all the tablets was found to be uniform with low standard deviation values (183.7±1.11 to 187.2±1.26) indicating that mixing of drug, disintegrants and excipients was efficient and homogenous.

The results obtained from wetting and disintegration were found to be within the acceptable limits and the criteria for mouth dissolving tablets (Table 2). *In vitro* wetting time was in the range of 55.00 ±1.52 to 83.00 ±3 s while the *in vitro* disintegration time was 36.00±1 to 83.00±2 s (Table 2). From above results, it can be concluded that increasing the concentration of crosspovidone and decrease in concentration mannitol,resulted into decrease in disintgration time of tablets. Although there is increase in the hardness of the tablet disintegration time remains 36 sec due to increase in the concentration of crosspovidone.

Among all 9 batches formulations prepared with crosspovidone i.e. Batch S6 showed ideal disintegration time and micromeritics parameters of S6 were found to be satisfactory and complies with official specification. Hence, S6 was considered as optimized formula for preparation of tadalafil mouth dissolving tablets. The faster disintegration of tablets attributed to rapid weeting of tablets. Fig 6 shows wetting behaviour of the tablets with respect to time demonstrating complete wetting of tablet within 45 sec. The time required for disintegration in oral cavity is 46 sec with good organoleptic properties reported by volunteers.

Fig 7 demonstrate dissolution profile of tadalafil form mouth dissolving tablet, more than 80% of drug get dissolved within 5 min. Since mouth dissolving tablets are expected to dissolve in least possible time.

CONCLUSION

Inclusion complex of tadalafil with HPβCD were prepared using kneading techniques in 1:1, 1:3 and 1:4 (drug: CD) molar ratios. From the above results, it is possible to conclude that HPβCD able to form true inclusion complexes with tadalafil at a molar ratio of 1:4 using the kneading technique. The dissolution of tadalafil was markedly enhanced. Therefore, the inclusion complex system of tadalafil with HPβCD prepared at a molar ratio of 1:4 could be chosen for the formulation of tadalafil mouth dissolving tablets due to the well-documented safety profile of HPβCD. Based on our results of tablet characterization it can be concluded that mouth dissolving tablets of tadalafil can be prepared using S6 formula as they satisfy the criteria of a mouth dissolving tablet and would be the alternative to the currently available conventional tablets for geriatric patients. Due to development of inclusion complex with HPβCD there is marked improvement in solubility and dissolution along with organoleptic properties leads to increase in patient acceptance especially elderly patients.

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