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Research Article

DEVELOPMENT AND *IN VITRO* CHARACTERIZATION OF TAMSULOSIN HYDROCHLORIDE PELLETS USED FOR BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

Tamsulosin hydrochloride was a commonly used drug in benign prostatic hyperplasia belongs to BCS class I with greater than 90% bioavailability. But, its interaction with food causes fluctuations in its bioavailability. The objective of the present study was to develop delayed release tamsulosin hydrochloride pellets with an extended drug release property. The pellets were prepared by extrusion spheronization technique with Eudragit L30D55 and calcium stearate after preformulation studies. The pellets were evaluated for various pharmacopeia tests like micromeritic properties, assay and dissolution. Preformulation studies such as fourier transform infrared spectroscopy confirmed the drug excipint compatibility. Micromeritic properties of pellets revealed their flowability and compactibility. The drug content was in the range of 94.5%-99% and cumulative percent drug released after 2 hours was found in the range of 3.7±0.3% to 25.6 ± 5.74 and 100 % drug release was observed after 8 hours in all formulations. The pellets of upturned formulation (F7) were filled into capsules and evaluated for in vitro drug release characteristics, differential scanning calorimetry and short term stability studies. The selected formulation showed similar drug release with USP specifications and innovator drug Flomax capsules. The similarity factor and difference factor between F7 and Flomax were 81.3 % and 0% respectively. The compatibility between drug and polymers in the drug-loaded pellets was confirmed by FT-IR studies. Stability studies and differential scanning calorimetry indicated that the pellets were stable. Finally it was concluded that tamsulosin hydrochloride pellets possessed similar drug release properties as that of innovators product and stable.

Keywords: Tamsulosin hydrochloride, Eudragit L30D55, Calcium stearate Extrusion-Spheronization.

INTRODUCTION

The prostate gland that surrounds urethra gets bigger and cause problems during urination. This condition is called benign prostatic hyperplasia (BPH). It is a common disorder in almost all men when they age. Tamsulosin HCl is a selective antagonist at alpha -1A and alpha – 1B adrenoceptors in the prostate and relaxes the smooth muscles in the bladder neck and prostate. Thus it decreases the urinary outflow resistance in men and hence used in the treatment of BPH. Because, it belongs to BCs class I it is freely soluble and highly permeable drug. Its oral bioavailability in fasting conditions is 90% and T_{max} is reached in 4 to 5 hrs and its elimination half life is 5 to 7 hrs. Its absorption during fed state is hindered due to its interaction with food and therefore the T_{max} in fed state is 6 to 7 hrs[1-2]. Multiparticulate drug delivery systems are utmost accepted dosageforms recently as they offer many benefits over unit dosage forms like improved bioavailability, reduced inter subject variation and transportation and reduced chances of dose dumping. Pelletization using extrusion spheronization is one of the most promising techniques for the multi particulate drug delivery systems[3-4]. Extrusion spheronization involves blending, extrusion, spheronization, coating and final drying. Dry mixing produces uniform blend and wet massing produce a sufficient plastic mass. Extrusion is used to produce rod shaped particles of uniform diameter. Spheronization

shapes the rod shaped particles into uniform spherical ones and desired moisture content can be achieved by drying.

Extrusion spheronization has several advantages such as higher levels of active components can be incorporated, two or more active ingredients can be combined in any ratio in the same unit, physical characteristics of active ingredients can be modified and narrow sized particles with smoother surface can be produced[5-9]. The objective of the present investigation is to develop enteric coated pellets of tamsulosin hydrochloride with extended release properties using extrusion spheronization technique and *in vitro* evaluation.

MATERIALS

Tamsulosin HCl was obtained as a gift sample from Divis laboratories, Hyderabad, India. Microcrystalline cellulose was purchased from FMC Bio polymer, Eudragit L30D55 was received as a gift sample from Alphamed PVT Ltd, Hyderabad, India. All other materials were purchased from SD Fine chemicals limited, Hyderabad, India.

Methodology

Pre formulation testing is the first step in the rational development of pharmaceutical drug delivery systems. It involves the study of physicochemical properties of a drug substance alone and when combined with excipients. These studies yield necessary information about the nature of the drug substance and aid in the development of suitable dosage form to obtain the better therapeutic outcome.[10-11]

Organoleptic properties and solubility measurement

The physical state, color, odor and taste were observed and the results were noted.[12]

Analytical method establishment for the determination of Tamsulosin HCl

A simple RP HPLC method was established using Schimadzu chromatograph with UV detector and Hypersil BDS C8 150×4.6 mm, 5µm column. Mobile phase consists of buffer: Acetonitrile in the ratio (70:30) with a flow rate of 1.0 ml/minutes and the injection volume was 50 µL. The total run time was 10 minutes. Accurately weighed quantity of Tamsulosin HCl was taken and stock solution was prepared in water to produce 1 mg/ml solution. From the stock solution calibration curve standards were made using mobile phase. The standard solutions were injected into HPLC.

Solubility studies

The solubility of the drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of the drug release into the dissolution medium, consequently the therapeutic effect of the pharmaceutical product. The solubility of the material usually determined by the equilibrium solubility method, which employs a saturated solution of the material, obtained by stirring an excess of material in the solvent for a prolonged period until equilibrium is achieved. The aqueous solubility of tamsulosin HCl was checked in water.[13]

Sieve analysis and determination of moisture content

The main aim of sieve analysis is to determine the different size of drug particles present in a powder/powder mix. The sieves of standard are stacked one above the other so that sieves with large pore size (less sieve number) occupy top position followed by sieves with smaller pore size (greater sieve number towards the bottom). A series of sieves were arranged in the order of their decreasing pore diameter (increasing sieve number) such as the sieve number 20, 30, 40, 60, 80,100 and 50 grams of drug was weighed accurately and transferred to sieve number 20 which were kept on top. The sieves were shaken for about 5-10 minutes .then the drug retained on each sieves was taken, weighed separately and amount retained was expressed in terms of percentage. The moisture content was determined using Karl Fischer apparatus.

Drug excipient compatibility studies

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation. Drug is mixed with excipients in 1:1 ratio. These mixtures were kept in a 5ml glass flint colored vials and packed properly. These vials are exposed to 1) room temperature 2) 40˚C / 75% RH. Observations for physical appearance are made at initial, 2 weeks, 3 weeks and 4 weeks. The samples were withdrawn and observed for physical appearance.[13]

Fourier transfer infrared spectroscopy (FTIR)

FTIR studies were carried out for drug and a mixture of drug and excipients. Sample about (1 mg) was mixed with (1 mg) of potassium bromide IR powder and compacted under

vaccum at a pressure of about 12 psi for 3min. The IR spectrum was recorded between 600 to 4000 cm^{-1} and the resultant spectra were compared for any spectral changes.

Formulation development

Tamsulosin HCl pellets were prepared by extrusion spheronization method. Initially weighed quantity of Tamsulosin HCl, a portion of purified talc and calcium stearate were sifted through ASTM # 80 mesh as first step. In the second step specified quantity of microcrystalline cellulose PH 101 and remaining quantities of purified talc and calcium stearate were co sifted through ASTM # 30 mesh. Then powder mixtures in step 1 & 2 were co sifted through ASTM # 30 mesh in order to distribute the drug uniformly throughout the powder mix. Binder solution was prepared by dispersing the polymer in water. The powder mix was loaded into rapid mixer granulator and mixed for 20 minutes with impeller at slow speed and chopper off. The powder mix was then granulated by adding binder solution at a slow speed over a period of 3 minutes. The wet granules were discharged into a double lined polybag by opening the discharge port. The wet granules thus prepared were transferred into an extruder fitted with 1.0 mm screen and extruded at 80-126 RPM. The extrudates were loaded into spheronizer fitted with 2 mm friction plate and spheronization continued for 5 to 6 minutes to get the desired shape pellets. The wet pellets were placed into fluidized bed dryer bowl and air dried the wet pellets for 10-15 minutes. The inlet temperature was set at 50 ± 5°C and product temperature at 45 ± 5°C. The dried pellets were collected from container walls by scrapping and without disturbing the shape of the pellets. The integrity of fluidized bed drier filter bag and bowl screen before and after use was checked. The collected pellets were then sieved through vibro-sifter ASTM # 16 mesh and collected into a double lined polybag and evaluated for various physicochemical properties. All the tried compositions were listed in the **table 1** The pellet of selected composition equivalent to 0.4 mg of tamsulosin HCl was filled into hard gelatine capsules and the dissolution profile was compared with innovator's product**.**

Evaluation of Tamsulosin HCl core pellets

Micromeritic Properties of Tamsulosin hydrochloride core pellets

Bulk density

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. A pre weighed quantity of pellets was placed into a graduated cylinder and the volume was noted. The bulk density was calculated using the following formula

$$\text{Bulk Density} = \frac{\text{weight of the pellets}}{\text{bulk volume of pellets}}$$

Bulk density was expressed in g/ml

Tapped density

Tapped density is determined by placing a graduated cylinder containing a known mass of material and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. A pre weighed quantity of pellets was placed into a 100 ml graduated measuring cylinder and the initial volume was noted. The cylinder was secured in its holder in a settling apparatus which is capable of producing 250±15 taps from a height of 3±0.2mm in 1 minute. The cylinder was tapped until little change in volume i.e., less than 2 ml was observed. The tapped volume was noted and the tapped density was calculated using the following formula.

$$\text{Tapped density} = \frac{\text{weight of the pellets}}{\text{tapped volume of pellets}}$$

Compressibility index and Hausner Ratio

Compressibility characters of the materials can be determined using compressibility index and Hausner ratio and calculated using the following formulas:

$$\text{Compressibility index} = \frac{\text{bulk volume} - \text{tapped volume}}{\text{tapped volume}} \times 100$$

$$\text{Hausner ratio} = \frac{\text{bulk volume}}{\text{tapped volume}}$$

Angle of repose

The manner in which stresses are transmitted through a bead and the beads response to applied stress are reflected in the various angles of friction and response. The method used to find the angle of repose is to pour the powder in a conical heat on a level, flat surface and measure the included angle with the horizontal.

$$\textbf{Tan } \theta = h/r$$

Where, h= height of the heap
r= Radius of the heap

***In vitro* drug release studies**

In vitro dissolution studies of tamsulosin HCl core and enteric coated pellets were carried out by using USP type 2(paddle) dissolution

apparatus and operated in 500 ml of 0.1 N HCl for first 2 hours, next 8 hours in 500 ml of phosphate buffer pH 6.8. The dissolution medium was kept in thermostatically controlled water bath at 37±0.5 ºC. The paddle was rotated at 50 rpm, at different time intervals, 10 ml of aliquots were withdrawn, and same amount of the fresh dissolution medium was replaced into the dissolution flask. The samples were filtered, degassed and analyzed using above given RP HPLC method. From the dissolution data the rate of drug release and mechanism of drug release were determined with mathematical models.

Comparison of dissolution profiles of pellets filled capsules with innovator's product

Dissolution profile of tamsulosin HCl pellets were compared with innovator's product by calculating the similarity and difference factors. The FDA and EMEA defined similarity factor as a "logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the test and the reference products". It represents closeness of two comparative formulations. Generally similarity factor in the range of 50-100 is acceptable according to US FDA. It was calculated according to the following equation.

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} \left(R_t - T_t \right)^2 \right]^{-0.5} 100 \right\}$$

Where, f_2 = similarity factor
n= number of dissolution time points
R_t = reference profile at time points t
T_t= test profile at the same point t

Difference factor describes the relative error between two dissolution profiles. It is approximately the percentage error between curves. The percent error is zero when the test and reference profiles are identical and increases in proportionality with the dissimilarity between the two profiles. Dissimilarity factor or difference factor (F1) was calculated from the following equation. Difference factor of 0-15 is acceptable.

$$f_1 = \frac{\sum_{t=1}^{n} \left(R_t - T_t \right)}{\sum_{t=1}^{n} R_t} 100$$

Where, f_1 = difference factor
n= number of dissolution time points
R_t = reference profile at time points t
T_t= test profile at the same point t

Stability studies

The upturned formulation after filling into capsules was subjected to short term stability studies. A sample of tamsulosin HCl was stored in humidity chamber at 40ºC±2^{0}C and 75±5% RH conditions. The pellets were withdrawn for 3 months periodically, and analyzed for their physical appearance, drug content and *in vitro* drug release.

RESULTS

Pre formulation studies

The investigation was done systematically. Initially, organoleptic properties like physical state, color, odor of tamsulosin HCl were observed and found that tamsulosin HCl was a white to offwhite powder, freely soluble in water. The moisture content and loss on drying were determined as 2.84% and 1.83% respectively. The micromeretic properties such as bulk density, tapped density, Carr's index and Hausners ratio of tamsulosin HCl were obtained as 0.1034 gm/ml, 0.1132 gm/ml, 8.65 and 1.15 respectively. The procured and used sample of tamsulosin HCl in the study had a melting point in the range of 138°C - 140°C. The sample purity was checked by RP HPLC and found to be 99.1%. The sieve analysis showed that the drug sample was passed through ASTM # 80 and retained on ASTM # 100. The average particle diameter was determined as (0.177 + 0.149) / 2 = 0.163 mm or 163 µm.

Analytical method

A RP HPLC method was established for the determination of tamsulosin HCl content in the developed formulations and also for analyzing the dissolution samples. The standard curve was linear in the concentration range 200 to 1000 ng. From the result table, the retention time, peak asymmetry and theoretical plates (USP) were noted as 9.285 min, 1.134 and 8222.

Drug excipient compatibility Studies

Drug excipient mixtures were stored at room temperature and at 40°C/75% RH for four

weeks. The physical state of the mixture and any appearance or disappearance of color was observed. The results were bestowed in **table 2.** The chemically stability was determined by FTIR and the spectra were showed in **Figure - 1a and 1b.**

Evaluation of Tamsulosin HCl pellets

Micromeritic Properties of Tamsulosin hydrochloride pellets

The pellets were evaluated for their flowability and compressibility characteristics and the results were given in **table 3.** The results indicated that the pellets were flowable and compactable.

***In vitro* drug release studies**

In vitro drug release data was given in **figures 2A & 2B**. The cumulative percent drug released after 2 hours was found in the range of 3.7±0.3% to 25.6 ± 5.74 and 100 % drug release was observed after 8 hours in all formulations. More than 50 % of drug release was obtained at 3hrs indicating a burst release effect.

Differential scanning colorimetric and stability studies

DSC thermograms were showed in **figures 3A and 3B** and dissolution profiles after stability studies were given in **figure 4.**

DISCUSSION

Pre formulation studies showed that the drug was crystalline, white to off white powder. It was freely soluble in water and dimethyl formamide. Further its high melting point also revealed its crystalline nature. Loss on drying (LOD) and moisture content values were discussed in results**.** It was observed that the LOD was less than the moisture content. These values revealed that, there are no any additional volatile impurities in the drug sample and during the measurement of LOD the bound moisture was not released. Flow properties (bulk density and tapped density) and compressibility were interrelated parameters. Tamsulosin HCl powder is low dense, high bulk volume with excellent cohesive properties. A sieve analysis was conducted on a sample of drug powder. The sample was passed through 80 mesh screen and was retained by 100 mesh screen. The average particle diameter was determined as 163µm indicating that the powder is fine and particle size distribution is uniform[14]. In order to understand the drug excipient compatibility at room temperature and at 40˚C / 75% RH, mixtures of drug and excipient in 1:1 ratio were kept and examined visually for change in physical state or color. But no change in physical state or color was observed during and after four weeks of drug excipient compatibility studies.

FT-IR studies revealed that there was no physicochemical interactions between Tamsulosin hydrochloride and other excipients and spectra were showed in (Fig 6.1 and 6.2). The pure drug Tamsulosin hydrochloride showed characteristic absorption peaks at 3394.59 cm^{-1} due to N-H bend, 1538 cm^{-1} due to C=C stretching, 1296.35 cm^{-1} due to S=O stretching, 1257.21 cm^{-1} due to C-O stretching, 1166.72 cm^{-1} due to C-C stretching, 667.30 cm^{-1} due to C-S stretching. All these peaks were remained unaltered in the IR spectrum of physical mixture of drug and excipients. IR spectrum revealed that there was no chemical interaction of drug with the excipients.

The FT-IR spectral analysis showed that there was no change of any characteristic peaks of pure drug Tamsulosin hydrochloride and excipients. The FTIR studies and drug excipient compatibility studies conformed that the chemical interactions between drug and excipients were absent. RP HPLC method was established for the estimation of tamsulosin HCl. The retention time was 9.285 minutes, peak was symmetric and the USP theoretical plates were 8222.

Extrusion spheronization produces uniform spherical, free flowing granules or pellets. High drug loading efficiency is possible and the process is simple. Therefore this technology has gained worldwide importance. Tamsulosin HCl belongs to BCS class I (highly soluble and highly permeable class) and high potent drug with low therapeutic index. Though it absorbs 90% into systemic circulation after its oral administration it is highly variable due to the interaction with food[15]. Therefore in present investigation enteric coated pellets were prepared using extrusion spheronization technique to achieve more uniform drug absorption and drug blood levels. Eudragit L30D55 is an enteric film former and most widely used enteric polymer in solid dosage forms. It is non toxic, resistant to gastric juice and dissolves readily at above pH 5.5. Calcium stearate was used as drug release retardant and to obtain the sustained release effect. Microcrystalline cellulose was used for its binding and diluent properties. Total 7 trials were made and the 7^{th} was selected and reproduced as batch 8 and evaluated.

Micromeritic properties of powders describe their bulking properties, flow ability and compressibility. A comparison of bulk and tapped densities can give a measure of interparticulate interactions. The interparticulate interactions influence powder

flow and bulking characteristics. Therefore, all micromeretic properties of pellets were determined and it was observed that the bulk density and tapped density were closer in value. Compressibility index and Hausner's ratio values were between 11±0.2 to 13±0.4 and 0.9±0.4 to 1.2±0.3 respectively[16]. These results confirmed that the pellets had good flowable and compressible characteristics. Drug content was within the USP limits and the results were showed in **table 3**

***In vitro* drug release studies**

In the present work efforts have been made to develop Tamsulosin Hydrochloride delayed release capsules as an approach to bypasses the stomach and retain the drug release in the intestine using enteric release polymer. The results showed that the release of the drug depends on concentration of excipients used in formulations. The formulations F1, F2 and F3 showed that the cumulative percent drug released at two hours was below the USP specifications i.e., 13-34% because of high polymer concentration. In F4 2nd hour results were satisfactory then optimized the formulation for 4th hour dissolution point. In F5 all the physical parameters are satisfactory, 2nd and 4th hour release was within the limits but 5th hour release not in limits due to the decreased concentration of calcium stearate concentration. In F6 all the physical parameters are satisfactory, 5th and 8th hour release was within the limits and results were satisfactory. Trial was taken for reproducibility as F7 and all the physical parameters are satisfactory, results were within the limits of the USP specifications. The regression coefficient values were found to be between 0.686 to 0.969 and -0.14 to 0.964 in zero order and first order respectively. However, in trial F6 and reproducible formulation F7 the r^2 values were greater first order plot compared to zero order plot. Therefore it is confirmed that the rate of drug release in up turned formulation followed first order drug release. Higuchi and Korsmeyer peppas plots were also constructed and the dissolution data was not fit into these models indicating that the mechanism of dissolution does not follow either Higuchi or Korsmeyer peppas models. This is because there was no matrix forming polymer in the formulation. The dissolution data also revealed that an extended drug release up to 8 hours was obtained. The drug release retardation was due to the presence of high concentration of calcium stearate.

The dissolution profile of upturned formulation was also compared with innovators product by calculating the similarity and difference factors. The results confirmed that both the upturned formulation and innovators products are similar in their dissolution profiles

DSC is a fast and reliable method for understanding polymorphic transitions when screening drugs and polymers for compatibility, obtaining information about possible interactions. It was evident from the DSC profile figure shows that Tamsulosin Hcl exhibited a sharp endothermic peak at 233°C, which corresponds to the drug crystallinity whereas formulation F8 is thrashing its sharpness at its endothermic peak at 121.48°C. It appears that there is a significant reduction of drug crystallinity in the pellets. The absence of detectable crystalline domains in drug loaded pellets clearly indicates that drug was dispersed completely in the formulation, thus modifying the pellets to an amorphous, disordered-crystalline phase.

The stability testing confirmed that there were no physical or chemical changes in the formulation. During stability testing at 40ºC / 75% RH%, samples were withdrawn at a predetermined time intervals, dissolution study was performed. The dissolution profiles were not changed after 3 months of the stability study.

Table 1: Composition of Tamsulosin hydrochloride delayed release capsules

S.no	Ingredients	Quantity per capsule (mg)							
		F1	F2	F3	F4	F5	F6	F7	F8
1.	Tamsulosin hydrochloride	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
2.	Avicel pH 101	20	20	20	20	20	20	20	20
3.	Talc	85.6	85.6	85.6	85.6	35	25	25	25
4.	Calcium stearate	44	52	57.0	62.0	109.6	118.6	119.6	119.6
5.	Eudragit L30D55*	50	45	40.0	35.0	35	35	35	35
6.	Total weight	200	200	200	200	200	200	200	200

Table 2: Drug excipient compatibility study results

S. No	Name of the Excipient	Ratio API: Excipients	Initial Observation	Final observation 40°C/75% RH			Conclusion
				2nd week	3rd week	4th week	
1	API (Tamsulosin Hydrochloride)	---	Off white	NCC	NCC	NCC	Compatible
2	API+ Avicel pH 101	1 :1	Off white	NCC	NCC	NCC	Compatible
3	API + Talc	1 : 1	Off-white	NCC	NCC	NCC	Compatible
4	API + Calcium stearate	1 : 1	Off-white	NCC	NCC	NCC	Compatible
5	API + Eudragit L 30 D55	1 : 1	Off-white	NCC	NCC	NCC	Compatible

Table 3: Micromeretic properties and drug content Tamsulosin Hydrochloride pellets

Property /code	F1	F2	F3	F4	F5	F6	F7
BD	0.68±0.2	0.66±03	0.83±0.3	0.68±0.5	0.68±0.6	0.68±0.5	0.69.±0.3
TD	0.7±0.5	0.69±0.5	0.85±0.2	0.69±0.4	0.7±0.2	0.7±0.4	0.68±0.5
CI	12.6±0.6	12±0.9	13±0.4	12±0.2	11.9±0.3	12.2±0.5	11±0.2
HR	1.2±0.3	0.9±0.4	1±0.2	0.9±0.3	1.1±0.3	1.1±0.4	1.01±0.02
AR	22.2±2.9	23.5±1.3	24.3±2.7	24.8±2.4	24.8±2.1	25.6±2.6	23.9±1.9
DC	22.2±2.9	23.5±1.3	24.3±2.7	24.8±2.4	24.8±2.1	25.6±2.6	23.9±1.9

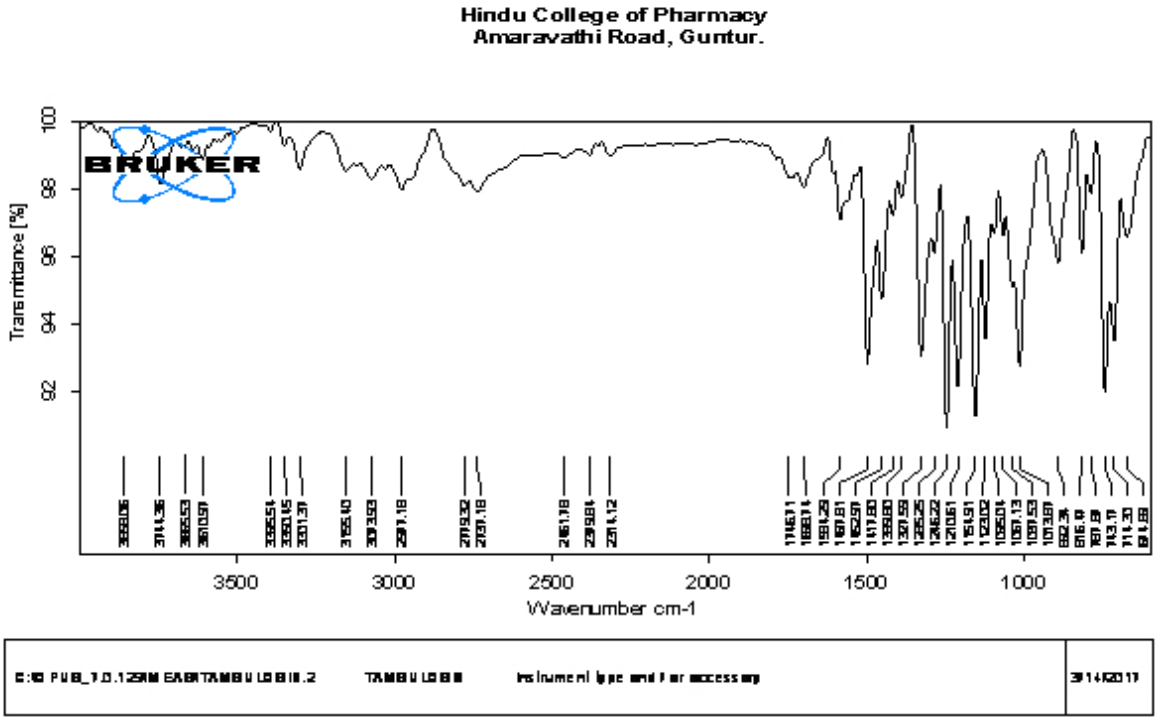

Fig. 1A: FTIR spectrum of Tamsulosin Hydrochloride

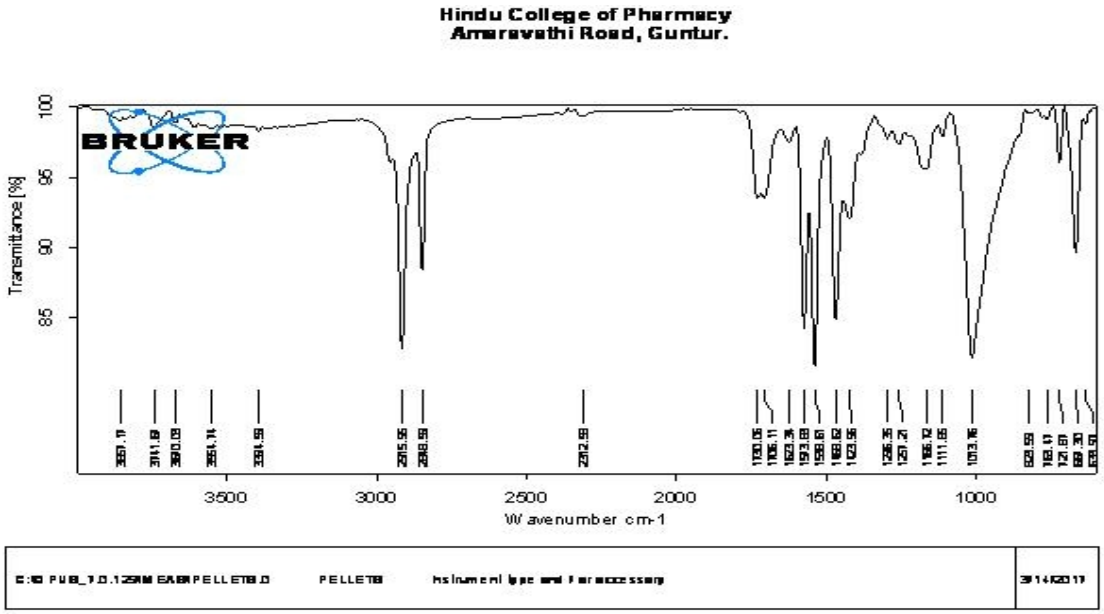

Fig. 1B: FTIR spectrum of optimized formulation

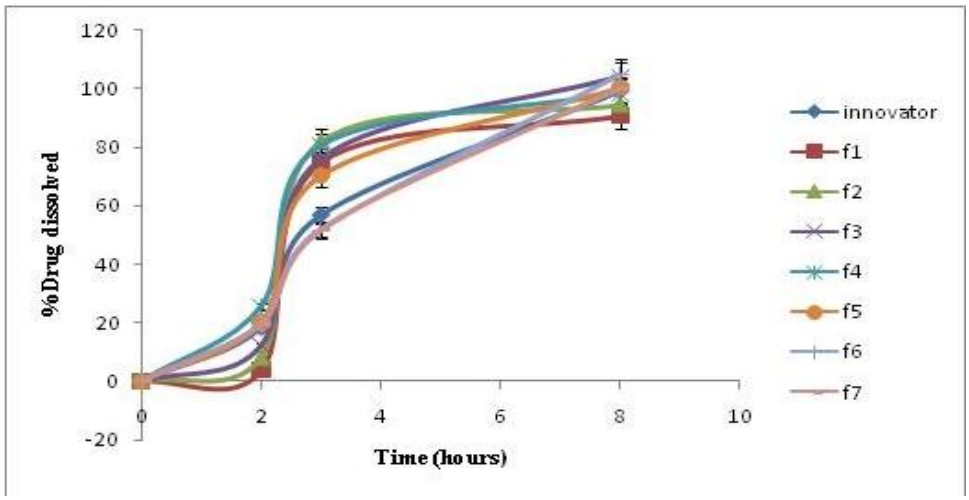

Fig. 2A: Cumulative %Drug released vs Time

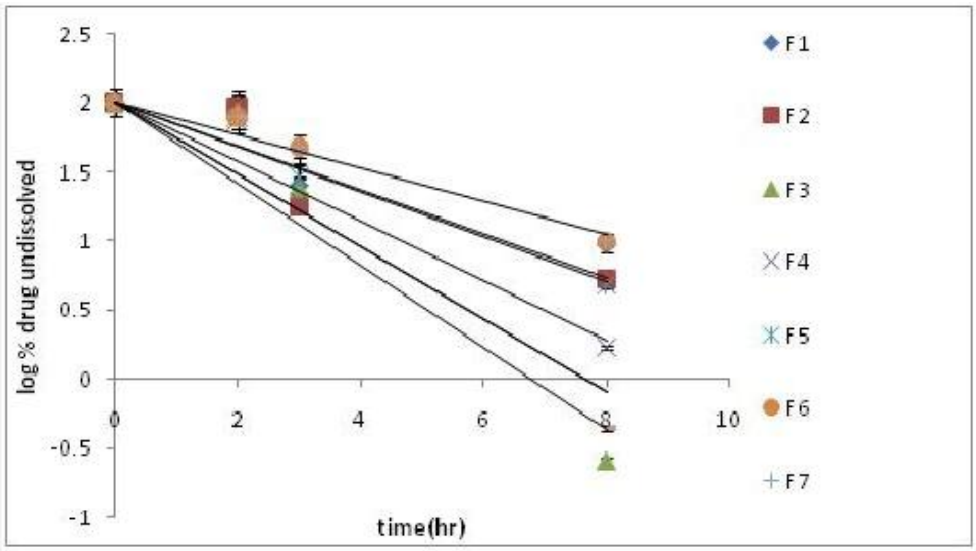

Fig. 2B: log % Unreleased vs Time

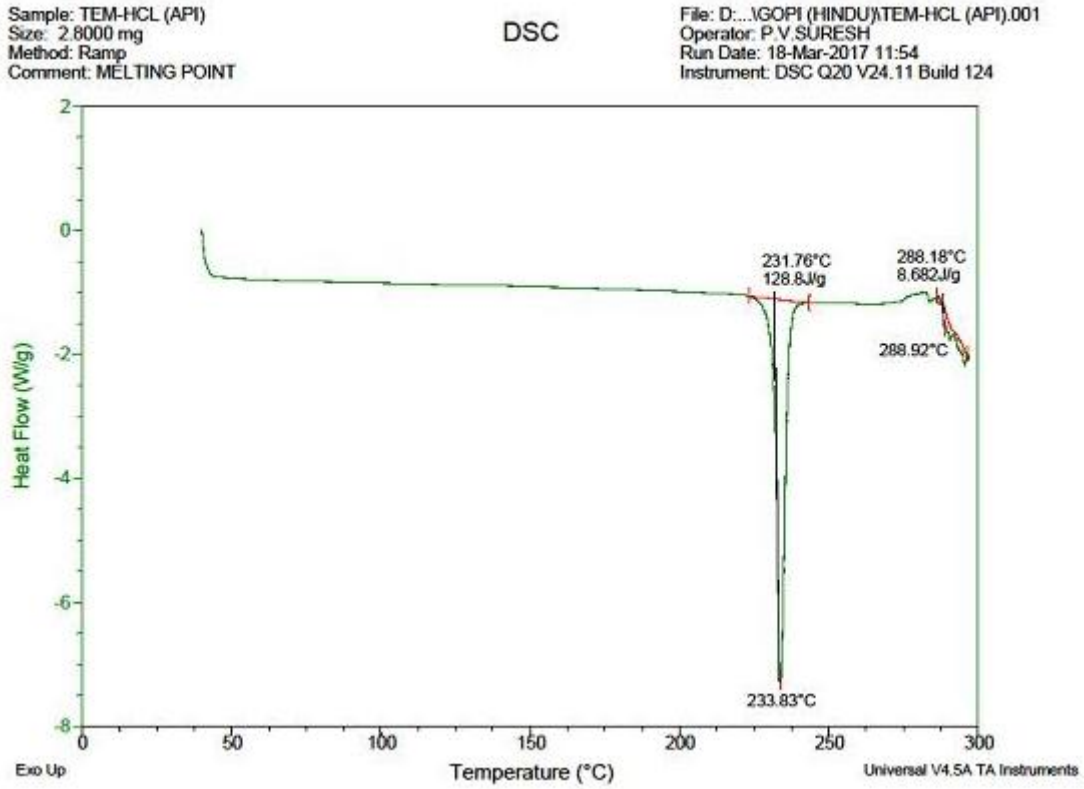

Fig. 3A: DSC Thermogram of Tamsulosin Hydrochloride

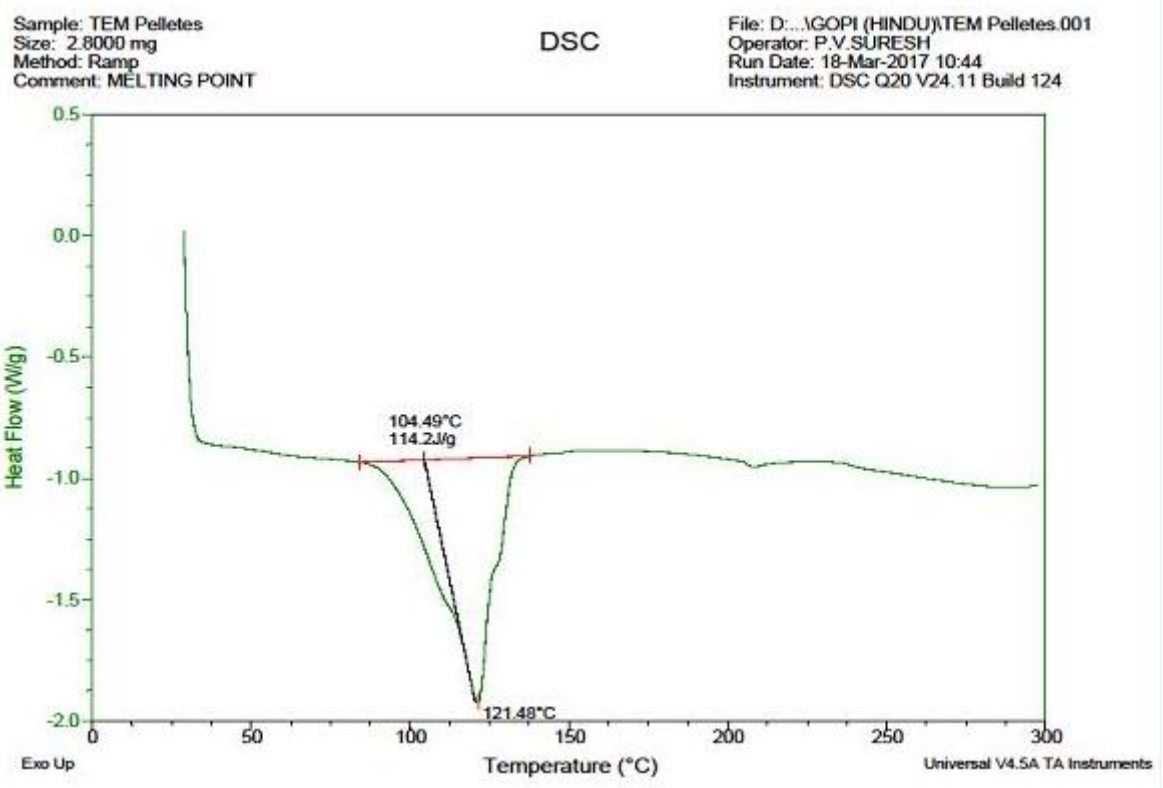

Fig. 3B: DSC Thermogram of Tamsulosin Hydrochloride pellets of F7

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