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FORMULATION AND EVALUATION OF TAMSULOSIN HYDROCHLORIDE AS SUSTAINED RELEASE MATRIX TABLET

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Abstract: Prolonged, sustained or extended release systems, release the active ingredient slowly than conventional dosage forms similarly administered. Tamsulosin is a selective, potent and competitive α_1 – adrenoreceptor antagonist. It has a greater affinity for the α_{1A} – receptor subtype and is indicated to treat uretheral stone symptoms associated with benign prostatic hyperplasia. In the present work, attempt was made to develop an once daily sustained release matrix tablet of Tamsulosin hydrochloride. Hydroxy propyl methyl cellulose was used as a hydrophilic matrix polymer. The formulation showed acceptable pharmacotechnical properties and HPLC assay requirements. The present work also involves application of Higuchi's equation, Drug release kinetics, Korsmeyer's and Hixsen-crowell plots. In vitro drug release studies indicated a sustained release pattern.
Key words: Tamsulosin, BPH (Benign Prostatic Hyperplasia), Sustained release matrix tablet.

Introduction

Modified release dosage forms are preparations that regulate the rate and/or site of release of the active ingredient, in order to achieve specific therapeutic objectives, which cannot be achieved by conventional immediate release dosage forms, similarly administered. A prolonged or sustained release product is one in which the drug is initially made available to the body in an amount sufficient to produce the desired pharmacological response as rapidly as is consistent with the properties of drug and which provides for the maintenance of activity at the initial level for a desired number of hours[1]. Prolonged release systems release the active ingredient more slowly than conventional dosage forms. They generally contain higher dose of active ingredient compared to conventional dosage forms, and reduce administration frequency (or frequency of administration). Design of sustained release product is normally a very difficult task because of the interplay of the physico chemical and biological properties of the drug, pharmacokinetic behaviour of the drug, route of administration, disease state to be treated, and most importantly, placement of the drug in a dosage form that will provide the desired temporal and spatial delivery pattern for the drug.

Sustained release formulations enjoys several advantages (offers several advantages) like increased safety margin, reduced intensity of local or systemic side effects, improved patient convenience and compliance, reduction in personnel time to dispense, administer and monitor patients. At the same time, they suffer from few disadvantages like decreased systemic availability and poor in vitro – in vivo correlation and higher cost of formulation[2].

The tone of the human prostate smooth muscle is maintained primarily by noradrenaline released from adrenergic nerves and stimulating post-junctional α_1 – adrenoreceptors. This provides the rationale for the use of α_1 – receptor antagonists for lower urinary tract symptoms associated benign prostatic hyperplasia [3, 4].

Common uretheral stone symptoms are low back pain or flank pain, penile pain, sudden stoppage of urine flow during urinating, urinary retention and painful urination[5]. The most common enlarged prostate symptoms have to do with urination and include sudden and strong urge to urinate, a frequent need to urinate, pushing or straining to begin, weak stream and dribbling

after finishing[6]. Tamsulosin is a selective, potent and competitive α_1 – adrenoreceptor antagonist and has a greater affinity for these receptors, predominantly present in the human prostate. Chemically, Tamsulosin is 5 – [(2 R) – 2- [[2-(2-ethoxy phenoxy) ethyl] amino] propyl] – 2 – methoxy benzene sulfonamide hydrochloride. It is a white to slightly yellowish crystalline powder, freely soluble in methanol, ethanol and sparingly soluble in water. Literature survey reveals that, tamsulosin hydro chloride was developed as controlled release delivery system, pellets and oral controlled delivery system [(9-13)] and was estimated in pharmaceuticals and biological fluids by HPLC, HPLC – MS, LC – MS/MS methods [(14-17)]. These methods are too expensive and time consuming. In the present work, an attempt has been made to develop a simple, economical, accurate and reproducible method for formulation and evaluation of Tamsulosin hydrochloride as an once daily sustained release matrix tablet.

Material and Methods

Materials Used

Tamsulosin Hcl – Malladi drugs, Aarthi drugs, Lactose – DMV international, Dicalcium phosphate – Signet chemical corporation, MCC – Vijilak Pharma HPMCK 100 LV – CR – HPMC K 100 M – CR, HPMCK15 M – CR – Colorcon Asia Pvt. Ltd., Eudragit RS PO, L30, D55 from Degussa, Kollicoat MAE 100 P – BASF, Germany, Povidone K30 – Nanhang Industrial Corporation, EC – Asha Cellulose (I) Pvt. Ltd., Polysorbate 80 – Chemplast Sanmar, Propylene glycol – Manali Petro Chemicals, Magnesium stearate – Amishi Drugs, Colloidal silicon dioxide – Cabot, Sanmar, Purified talc – TiO_2 – Indian chemicals and mineral, Pot. dihydrogen – phosphate, Sodium hydroxide pellets, Sodium dihydrogen phosphate, Acetonitrile – Rankem RFCL, Ltd, Isopropylalchol – Shell, purified water – Fourrts (India) Laboratories Pvt. Ltd. were the materials used for the present work.

Equipments used

Weighing balance (AR 2140, Viper BC) Bulk density apparatus, IR moisture balance, Compression machine and stations(Accura) pH analyzer, Hardness Tester (Monsanto), Digital tablet dissolution test apparatus (Lab India disso. 2000) Sonicator, HPLC (Shimadzu SPA 20 & Agilent) HPLC Column C– 18 (Phenomonex), Membrane filter (0.22 µ) (Paul Life Sciences), Mechanical Stirrer (Remi Motors), Friability test apparatus (Electro Lab), Digital Caliper (Mitutoyo), Sieve analysis equipment (Electro Lab), Coating Pan 28" (Cadmach) & Spray gun (Bullows) were the equipments used for the present work.

Methods

Tamsulosin hydrochloride[18] was procured from Malladi drugs and excipients such as lactose, MCC, Povidone, HPMC, calcium phosphate, ethyl cellulose, magnesium stearate, purified talc, IPA, polysorbate 80, propylene glycol, polymetha crylates, TiO_2, where procured from Fourrts India Laboratories Pvt. Ltd and used for the formulation of sustained release Tamsulosin hydrochloride tablets. The first step in formulation activity is careful consideration of a complete physicochemical profile of the active ingredients available prior to initiating a formulation development activity. Pre formulation studies was performed first to provide a rational basis for the formulation approaches, to maximize the chances of success and ultimately to provide a basis for optimizing drug product quality and performance. Characteristics such as solubility, compatibility study of drug with excipients was performed by using the following procedure.

Solubility

Solubility of drug (Tamulosion Hcl Salt) were determined by shaking an excess of salt in the solvent (water and 0.1 m phosphate buffer pH 7.4 respectively) for 24 hours at room temperature. The resultant solution was centrifuged at 5000 rpm for 30 min in a temperature – controlled centrifuge. The supernatant liquid was diluted and analysed for drug by reversed phase HPLC (RP-HPLC). The results were tabulated in table No. 1.

Compatibility study of drug with excipients was performed and the results were tabulated in table No. 2.

From the study, suitable excipients were selected for development of formulation such that there is no interaction with active drug. Different excipients of same category / functionality were taken in same ratio as they all come under single category having same function.

Evaluation of Marketed product

The marketed product (Veltam – 0.4 mg) was evaluated for in-vitro drug release and assay. The samples were analyzed by HPLC method.

Instrumental conditions

Column – Phenomonex ODS, E-18 (250 x 46 mm) 5µ
Flow rate – 1 ml per minute
Detector wave length – 280 nm
Injection volume – 20 µl for assay and 100 µl for dissolution.
Mobile phase: Buffer solution: Acetonitrile (70:30)
Retention time: 6.9 min

Procedure:

Preparation of sodium dihydrogen orthophosphate buffer pH 6.0:

15.6 gm of sodium dihydrogen orthophosphate was dissolved in 1000 ml of water and the pH was adjusted to 6.0 $\pm$ 0.1 with dilute sodium hydroxide solution.

Preparation of mobile phase:
The mobile phase constitutes a moisture of 70% of buffer and 30% of acetonitrile. The mobile phase was used as diluent for assay standard and assay sample preparation.
Preparation of assay standard solution: 20 mg of drug was dissolved in 200 ml of the diluent by sonicating for 5 mts. 10 ml of above solution was transferred to a 25 ml volumetric flask and made up to volume with the same diluent.

Preparation of assay sample solution: The average weight of 20 tablets of Tamsulosin Hcl was determined and grounded to fine powder. The quantity of powder equivalent to 2 mg of Tamsulosin Hcl was taken and dissolved in 50 ml of diluents by sonicating for 15 mts. The assay was determined by using the formula.
Amount of drug =
Sample area/ std.area x 20/200x10/25x50/wt.equiv. to 2 mg x Average weight
% purity = (Amount / label claim x 100)
Label claim = 0.4 mg

In-vitro drug release study
This test serve 2 important functions. First, data from such tests are required as a guide for formulation during the development stage, prior to clinical testing, Second, in-vitro testing is necessary to ensure batch-to-batch uniformity in the production of a proven dosage form[20].

Dissolution parameters
Apparatus: USP Type – II (Paddle)
Speed: 100 RPM
Medium: 500 ml phosphate buffer pH 7.2
Sampling points: 1, 2, 3, 6, 8, 10 & 15 hrs
Temperature: 37°C $\pm$ 0.5°C
Volume drawn: 10 ml

Procedure:
Dissolution standard Preparation: 16 mg of drug was dissolved in 200 ml of the diluent by sonicating for 5 minutes. 1ml of above solution was transferred to a 100 ml volumetric flask and made up to volume with the same diluent.

Dissolution sample preparation
Dissolution study was carried out for a period of 15 hrs in phosphate buffer pH 7.2. Samples of 10 ml were collected at intervals 1, 2, 3, 6, 8 10 and 15 hrs and loaded in the HPLC.

The peak area of standard solution and sample collected at intervals 1, 2, 3, 6, 8, 10 and 15 hour was recorded and the percentage drug release was calculated by using the formula.
% drug released = (sample area / std. area x 16 / 200 x 1/100 x 500/ label claim x 100)
A graph was plotted using time (in x – axis) against percentage drug release (in y-axis).

Formulation of Tamsulosin Hcl once daily sustained release matrix tablets

The methods employed for the formulation process were wet granulation and direct compression. The trial formulations prepared by direct compression were named as I, II, III, IV, VII, VIII, IX, X and XII. The trial formulations prepared by wet granulation were named as V, VI and XI. The blend (or) granules obtained from the above trials were compressed using 5-5 mm steep concave punches fixed to 8-station compression machine and the average weight of the tablet was fixed at 75 mg / tablet except for trial XI for which the average weight was fixed at 90 mg / tablet.
The methods were explained as follows:

a. Direct compression method

Drug (Tamsulosin Hcl) passed through sieve # 200 and the excipients, polymers passed through sieve # 40. Then these were mixed in blender to give homogenous mixture of granules.

These granules were evaluated for bulk density, compressibility index, Hausner ratio and sieve analysis. Then these granules were subjected for lubrication and then gets compressed. The compressed tablets were evaluated for hardness, friability, assay, dissolution and stability study.

b. Wet granulation method

Drug (Tamsulosin Hcl) passed through sieve # 200 and the excipients, polymers passed through sieve # 40. Then these were mixed in blender with binders to give granules. These granules were dried in the tray drier and then passed through the sieve # 20. After that it was subjected for lubrication and compression. Then the compressed tablets were evaluated for hardness, friability, assay, dissolution and stability study.

Enteric coating for core tablets

60 grams Eudragit L-30 D55, propylene glycol (8.9g) TiO_2 (2.8g) Purified talc (14.2 g), purified water (390 g) were used for enteric coating process.

Procedure:
Required quantity of eudragit (L-30 D55) was added to purified water in SS vessel and stirred for 4 hours. Then add required quantity of propylene glycol and mixed well for 5 minutes .Required quantity of purified talc, TiO_2 were passed through 60 # and added to purified water and triturated thoroughly and added to above mixture through 200 # nylon cloth and stirred for 15 minutes. Core tablet about 500 g was coated using the above polymeric dispersion by setting the machine to the following coating parameters. Coating was continued till the coating solution was exhausted. Coated tablets were dried using air blower at 40°C to 50°C for about an hour with intermittent tumbling. Enteric coated tablets were collected in poly bag and stored well. This enteric coating was carried out for trial formulation XII.
Trial formulation details of Tamsulosin Hcl. SR tablet was tabulated in Table No. 3

DETAILS OF FORMULATION

Trial Batch I: This batch was containing 20% of HPMC K100 LV CR to that of tablet weight as rate controlling polymer and contains 79.82% directly compressible lactose as diluents and 0.67% of magnesium stearate as lubricant. The granules were compressed at a hardness of 4.5 kg / cm^2.

Trial Batch II: 40.68% directly compressible lactose, 38.2% MCC as diluents and 0.67% of magnesium stearate as lubricant. The granules were compressed at a hardness of 4.5 kg / cm^2.

Trial Batch III: 78.82% directly compressible lactose as diluents and 0.67% magnesium stearate as lubricant. The granules were compressed at a hardness of 5 kg / cm^2.

Trial Batch IV: 30% of HPMC K 100 MCR to that of tablet weight as rate controlling polymer and contains 78.82% directly compressible lactose as diluents and 0.67% magnesium stearate as lubricant. The granules were compressed at a hardness of 5.5 kg/cm^2.

Trial Batch V: 30% of HPM CK 100 MCR to that of tablet weight as rate controlling polymer and contains 67.48% directly compressible lactose as diluents 0.67% colloidal silicon dioxide as anti adherent and 0.67% of magnesium stearate as lubricant. Tamsulosin Hcl was solubilized using 0.7% polysorbate 80 and 0.26% propylene glycol in 0.03% H_2O and wet mass was prepared, dried and sieved. The granules were compressed at a hardness of 2-2.5 kg/cm^2.

Trial Batch – VI: The trial batch was containing 30% of HPMC K 100 MCR to that of tablet weight as rate controlling polymer and contains 67.48% directly compressible lactose as diluents, 0.67% colloidal SiO_2 as antiadherant and 0.67% of Magnesium stearate as lubricant. Tamsulosin Hcl was solubilized using 1.4% polysorbate 80 and 0.8% propylene glycol in 0.015% water and wet mass was prepared, dried and sieved. The granules were compressed at a hardness of 1.5-2.0 kg/cm^2.

Trial Batch – VII: The trial four batch size was increased from 250 tablets to 2500 tablets and maintaining 30% of HPMC K 100 MCR to that of tablet weight as rate controlling polymer and contains 78.82% directly compressible lactose as diluents and 0.67% Magnesium stearate as lubricant. The granules were compressed at a hardness of 5.5 kg/cm^2.

Trial Batch – VIII: The trial batch was containing 20% of HPMC K 15 MCR to that of tablet weight as rate controlling polymer and contains 78.13% directly compressible lactose as diluents, 0.67% colloidal SiO_2 as antiadherant and 0.67% of Magnesium stearate as lubricant. The granules were compared at a hardness of 4 kg / cm^2.

Trial Batch IX: 30% of ethyl cellulose to that of tablet weight and as rate controlling polymer contains 68.15% directly compressible lactose as diluents 0.67% colloidal SiO_2 as anti adherent and 0.67% of magnesium stearate as lubricant. The granules were compressed at a hardness of 4 kg/cm^2.

Trial Batch X: The trial batch was containing 20% of HPMC K 100 MCR, 10% of kollicoat MAE 100P to that of tablet weight as rate controlling polymer and contains 68.13% directly compressible lactose as diluents, 0.67% colloidal SiO_2 as antiadherant and 0.67% of magnesium stearate as lubricant. The granules were compressed at a hardness of 4.0 kg/cm^2.

Trial Batch XI: The trial batch was containing 20% of eudragit RSPO in wet granulation, 10% of eudragit RSPO in lubrication to that of tablet weight as rate controlling polymer and 2.25% of povidone as binder to that of tablet weight and contains 67% dicalcium phosphate as diluents and 0.56% of magnesium stearate as lubricant. The granules were compressed at a hardness of 5 kg/cm^2.

Trial Batch XII: The trial batch was containing 30% of HPMC K 100 MCR to that of tablet weight as rate controlling polymer and contains 78.82% directly compressible lactose as diluents and 0.67% of magnesium stearate as lubricant. The granules were compressed at a hardness of 5.5 kg/cm^2 and finally the tablet was coated with 12% enteric coated material to that of tablet weight.

Aerosil and magnesium stearate were used as antiadherant and lubricant respectively in all trial batches to avoid sticking of tablet to dies and easy ejection of tablet.

Evaluation of the formulation

The formulated tablets were subjected to various evaluation stages as follows:

(i) Physical evaluation of the granules
- (a) Bulk density
- (b) Compressibility index
- (c) Hausner's ratio
- (d) Sieve analysis

(ii) Evaluation of the formulated tablet
- (a) Friability
- (b) Hardness
- (c) Thickness
- (d) Weight variation
- (e) Uniformity of weight
- (f) Assay
- (g) Dissolution
- (h) Stability study

Evaluation of the Granules

(a) Bulk density[21]: An accurately weighed quantity of the granule was added to the cylinder with the aid of a funnel. Typically the initial volume was noted, and the sample was then tapped until no further reduction in volume was noted. The volumes before and after tapping were used on the standard equation to compute bulk and tapped density respectively.

(b) Flow properties of the powder

Compressibility index & Hausner's ratio[22]

The compressibility index and the closely related Hausner's ratio have become the simple,fast and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of materials. Both are determined by measuring both the bulk volume and tapped volume of a powder. The basic procedure is to measure the unsettled apparent volume V_0 and the final tapped volume, V_f, of the powder after tapping the material until no further volume changes occur.

The compressibility index and the Hausners ratio were calculated as follows:

Compressibility index = $100 \times (V_0 - V_F / V_0)$

Hausner's Ratio = (V_0 / V_F)

Alternatively, both may be calculated using measured values for bulk density and tapped density as follows:

Compressibility index =

$$= 100 \times \frac{\text{Tapped density - bulk density}}{\text{Tapped density}}$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

(c) Particle size determination[22]

Sieving method

50 gm of sample was weighed and placed on top sieve of the arranged sieves and mechanically shaken in mechanical sieve shaker. The sieves were then removed and the granule retained on each sieve was weighed. The percentage weight of powder retained on each sieve was calculated. The results were tabulated on table no 5.

Weight size = Mean size of sieve opening x % weight retained on smaller sieve

Particle size = weight size / 100.

Evaluation of the tablet

(a) Friability

Friability of uncoated tablets was determined by using Roche friabilator in the laboratory. A pre weighed tablet sample was placed in the friabilator, which was then operated for 100 revolutions. Then, the tablets were dusted and reweighed. Friability index was then calculated by using the formula,

Friability index = $(I - F/I) \times 100$

I → Initial weight

Limit for friability is < 1%

F → Final weight

(b) Hardness

Hardness of tablets was determined by using Monsanto Hardness tester in the laboratory. A pre weighed tablet sample was placed between two anvils of tester, force was applied to the anvils and the crushing strength that just causes the tablet to break was recorded.

(c) Thickness

The thickness was determined for 10 tablets from a batch using a vernier caliper and the reading was recorded in millimeters.

(d) Weight variation

Weights of individual 20 tablets were noted and their mean weight also calculated. The percentage deviation was calculated by using the following formula.

Percentage deviation = $[X - X^*/X] \times 100$

X = Actual weight of the tablet

X* = Average weight of the tablet

The official limit for weight variation is $\pm$ 10%

(e) Uniformity of weight

Content uniformity test was applied to assure uniform potency for tablets of low dose drugs. 10 tablets were selected at random and assayed individually. This was calculated by using the following formula.

Amount of drug = (Sample area / std area x 20 / 200 x 10/25 x 10/ one tablet)

% purity = (Amount / label claim x 100)

Label claim = 0.4 mg

(f) In vitro drug release studies

This in-vitro test for drug release serve two important functions. First, data from such tests were required as a guide for formulation during the development stage, prior to clinical testing. Second, in-vitro testing was necessary to ensure batch-to-batch uniformity in the production of a proven dosage form.

(g) Dissolution

Parameters:

Apparatus: USP type – II (Paddle)

Speed: 100 RPM

Medium: 500 ml phosphate buffer pH 7.2

Sampling points: 1, 2, 3, 6, 8, 10 and 15 hrs

Temperature: 37°C $\pm$ 0.5°C

Volume drawn: 10 ml

Dissolution standard preparation

16 mg of Tamsulosin hydrochloride was dissolved in 200 ml of the diluent by sonicating for five minutes. 1 ml of above solution was transferred to a 100 ml volumetric flask and made up to volume with the same diluent (buffer: acetonitrile, 70:30)

Dissolution sample preparation

Dissolution study for trial formulations I – XII was carried out for a period of first 2 hrs in pH 1.2 solution containing 0.0003% of polysorbate 80 and followed by phosphate buffer pH 7.2 up to 15 hours. Samples of 10 ml were collected at intervals 1, 2, 3, 6, 8, 10 and 15 hours and detected at 280 nm using RP – HPLC employing UV – detector. The peak area of standard solution and sample collected at intervals 1, 3, 5, 7, 10

and 12 hours was recorded and the percentage drug release was calculated by using the formula.

% drug released = (sample area / std area x 16/200 x 1/100 x 500/label claim x 100)

A graph was plotted using time (in x – axis) against cumulative percentage drug release (in y – axis)

Dissolution profile comparisons

It was carried out using model independent and model dependent methods.

Model independent method is most suitable for dissolution profile comparison when 3 – 4 or more dissolution time points are available.

$$f_1 = \{[\sum_{t=1} n[Rt-Tt]]/[\sum_{t=1} nR_t] \times 100$$

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

n $\Rightarrow$ number of time points

R $\Rightarrow$ Dissolution value of the reference (pre change) batch at time t

t $\Rightarrow$ Dissolution value of the test (post charge) batch at time t

$f_1 \Rightarrow$ difference factor

$f_2 \Rightarrow$ similarity factor

The dissolution profiles of two products of the test (post change) and reference (pre change) products was determined using the mean dissolution values from both curves at each time interval, the difference factor and similarity factor was calculated by using the above equations. For curves to be considered similar, f_1 values should be close to zero and f_2 values should be close to 100. f_1 values up to 15 (0 – 15) and f_2 values greater than 50 (50 – 100) ensures sameness (or) equivalence of the two curves and thus, of the performance of the test (post change) and reference (pre change) products.

(h) Stability studies

The stability studies was performed under the following three categories:

(i) Solid state stability of drug alone

(ii) Compatibility studies (stability in presence of excipients)

(iii) Solution – phase stability (including stability in gastrointestinal fluids and granulating solvents)

(i) Solid state stability: It covers both, physical as well as chemical stability.

(ii) Chemical stability: Investigation of stability must begin with an examination of the chemical structure, which gives some indication of the chemical reactivity.

(iii) Physical stability: Physical properties of the drug, such as its solubility, pKa, melting point, crystal form and equilibrium moisture content, also influence its stability.

Stability in presence of excipients

Stability of the drug in the presence of different excipients were studied for formulation studies, which will be used in the formulation of that particular drug and / or with other drugs.

The stability study was conducted for trial formulation XII which gives a dissolution profile as that of the marketed product (veltam). The tablets were exposed to 40°C / 75% RH for a period of one month and quality control test including assay and dissolution study was carried out by using the above mentioned procedure.

Results and Discussion

Both methods which were performed for the formulation of tamsulosin hydrochloride once daily sustained release matrix tablets had proven to be effective in controlling the drug release from the tablet. HPMC, eudragit RSPO and ethyl cellulose were used as the rate controlling polymer in this formulation. Various grades of HPMC and excipients in different percentage was employed.

Analytical method (HPLC) was employed for detection and quantification of drug. The proposed mobile phase (buffer : acetonitrile/ 70:30) was given better resolution and sensitivity. The average retention time for the drug was found to be 6.9 min.

The marketed product was evaluated for matching the drug release pattern of the tablets of tamsulosin hydro chloride. The amount of drug present in the SR tablet was calculated according to the formula described above and the percentage purity was determined to be 102.2%. The results were tabulated in the table 4.

A graph was also plotted.

Evaluation of Granules for pre-compression properties

The granules from trial batch XII were evaluated for bulk density, compressibility index, Hausner's ratio and particle size and the results were tabulated on Table No. 5, 6 & 7.

The compressibility index of the granules was 18.01 and Hausner's ratio was 1.21. So the granules will have fair flow.

The tablet parameters observed were given in table 8. The tablets were compressed at an average weight of 75 mg. The weight of tablets were $\pm$3.5%, which falls within the acceptable weight variation range of $\pm$ 10% as per USP. Hence the tablets of all trial batch passed the weight variation test. Hardness of all formulations were in the range of 2.0-5.5 kg / cm^2. Friability value for the trial batches was not more than 0.25%. The results of friability indicate that the tablets were mechanically stable and could handle the rigors of transportation and handling. The assay limit for the tablets is 90-110%.

The tablets of trial batch I to XII were found to be within specified limit for weight variation, hardness, thickness, friability and assay. The test for uniformity content was carried out only for the tablets of trial batch XII and the results were tabulated on table no. 9.

All ten tablets were found to contain the labeled amount of drug (0.4 mg), hence passes the test for content uniformity.

Dissolution study was carried out for a period of 2 hours and the drug release profile obtained showed significant variation compared to the marketed product. At the end of 2hrs 70.32% of the drug was released.

Dissolution study was carried out for a period of 10 hours and the drug release profile obtained showed that the drug release was more at intervals 1,2,3 and 6 hour compared to the marketed product. At the end of 10 hours 70.85% of the drug was released.

Dissolution study was carried out for a period of 10 hours and the drug release profile obtained showed that the drug release was more at intervals 1, 2, 3 and less at intervals 6, 8 and 10 hour compared to the marketed product. At the end of 10 hours 63.02% of the drug was released.

Trial Batch V: Dissolution study was not carried out since the trial was taken to solve the assay problem, but the problem was not rectified.

Trial Batch VI: Dissolution study was not carried out since the trial was taken to solve the assay problem, but the problem was not rectified.

Dissolution study was carried out for a period of 15 hours and the drug release profile obtained showed that the drug release was more at intervals, 1, 2, 3, 6, and 8 hours compared to the marketed product. At the end of 15 hours 94.13% of the drug was released.

Dissolution study was carried at for a period of 15 hours and the drug release profile obtained showed that the drug release was more at all intervals 1, 2, 3, 6, 8, 10 and 15 hours compared to the marketed product. At the end of 15 hours 99.42% of the drug was released.

Dissolution study was carried out for a period of 15 hours and the drug release profile obtained showed that the drug release was more at intervals 1, 2, 3, 6, and 8 hours compared to the marketed product. At the end of 15 hours 86.18% of the drug was released.

Dissolution study was carried out for a period of 15 hours and the drug release profile obtained showed that the drug release was more at intervals 1, 2, 3, 6, and 8 hours compared to the marketed product. At the end of 15 hours 91.80% of the drug was released.

Dissolution study was carried out for a period of 15 hours and the dissolution profile obtained matches with that of the marketed product and the deviation in % release at all intervals (1,2,3,6.8,10 and 15 hours) was found to be less. The (f_1) and (f_2) value when compared with the marketed product was determined to be 8.32 and 57.92 respectively. The trial formulation XII was manufactured two more times and analyzed. The In-vitro release profile of these batches was similar to the initial batch.

A comparison of the drug release profile of marketed product and trial formulation XII was desisted graphically on graph – 1.

Assay was carried out for the stability sample by the above mentioned procedure and was found to be 103.6%.

The stability sample of trial batch XII was found to be within specified limits for weight variation, hardness, thickness, friability and assay at the end of 1 month.

The drug release profile obtained for the stability sample was similar to the initial drug release profile obtained for trial batch XII. Based on the above observation the tablets were found to be stable at the end of first month.

Conclusion

The In – vitro release of the trial batch XII complies with the tolerance limit and matches with a reputed sustained release product in the market. The evaluation for drug release kinetics reveals that the drug release from the tablet follows first-order kinetics. The technique employed here was simple, highly adaptable for large scale production. The stability study of the tablets of trial batch XII revealed that it was stable at the end of 1st month at 40°C/75% RH. The stability study of the developed formulation will be continued in future.

COMPARISON OF IN-VITRO DRUG RELEASE PROFILE OF MARKETED PRODUCT & TRIAL BATCH 12

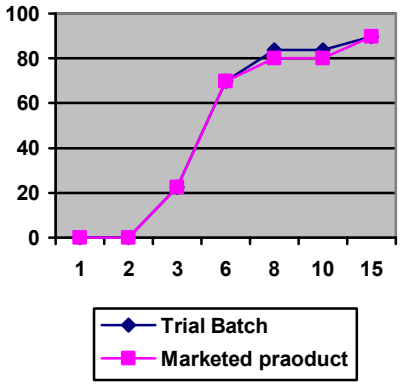

Table 1: Equilibrium Solubility of Tamsulosin Hydrochloride Slat

Tamsulosin salt	Solubility in water (final pH)	In 7.4 buffer (final pH)
HCL	8.7 (7.0)	7.5 (7.3)

Table 2: Compatibility Study of Tamsulosin Hcl with Excipients

S.No.	Excipients	D:E Ratio	Physical observation					
			First day		After one week		After 2 weeks	
			25°C/ 60% RH	40°C 75% RH	25°C/ 60% RH	40°C/75 % RH	25°C 60% RH	40°C 75% RH
1.	Lactose	1:10	NC	NC	NC	NC	NC	NC
2.	MCC	1:10	NC	NC	NC	NC	NC	NC
3.	DCP	1:10	NC	NC	NC	NC	NC	NC
4.	Kollicoat MAE 100 P	1:5	NC	NC	NC	NC	NC	NC
5.	EC	1:5	NC	NC	NC	NC	NC	NC
6.	PVPK 30	1:5	NC	NC	NC	NC	NC	NC
7.	HPMCK 100M	1:5	NC	NC	NC	NC	NC	NC
8.	Eudragit RSPO	1:5	NC	NC	NC	NC	NC	NC
9.	Polysorbate 80	1:5	NC	NC	NC	NC	NC	NC
10.	Na-CMC	1:5	NC	NC	CC	CC	CC	CC
11.	Polyethylene oxide	1:5	NC	NC	LF	LF	LF	LF
12.	Propylene glycol	1:0.5	NC	NC	NC	NC	NC	NC
13.	Aerosil	1:0.5	NC	NC	NC	NC	NC	NC
14.	Mag. stearate	1:0.5	NC	NC	NC	NC	NC	NC
15.	Talc	1:0.5	NC	NC	NC	NC	NC	NC

D:E – Drug excipient ratio N.C – No change
L.F – Lump formation CC – Colour change

Table No. 3

S. No.	Name of the ingredient	Trial 01	Trial 02	Trial 03	Trial 04	Trial 05	Trial 06	Trial 07	Trial 08	Trial 09	Trial 10	Trial 11	Trial 12
		Qty. / Tablet (mg)	Qt/T (mg)	Qt/T (mg)	Qt/T (mg)	Qt/T (mg)	Qt/T (mg)	Qt/T (mg)	Qt/T (mg)	Qt/T (mg)	Qt/T (mg)	Qt/T (mg)	Qt/T (mg)
	Dry mixing												
1.	Tamsulosin hydrochloride	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
2.	Lactose	59.1	30.5	59.1	51.6	50.36	49.45	51.1	58.6	51.1	51.1		51.1
3.	Dicalcium phosphate											60.05	
4.	Microcrystalline cellulose		28.6										
5.	HPMC K 100 LV-CR	15	15										
6.	HPMC K 100 M-CR			15	22.5	22.5	22.5	22.5			15		22.5
7.	HPMC K 15 M-CR								15				
8.	Ethyl cellulose									22.5			

9.	Kollicoat MAE 100P										7.5		
10.	Eudragit RS PO											9	
	Binder												
11.	Povidone K 30											2	
12.	Polysorbate 80					0.05	1.04						
13.	Propylene glycol					0.2	0.6						
14.	Isopropyl alcohol											0.05	
15.	Purified water					0.02	0.012						
	Lubrication												
16.	Eudragit RS PO											18	
17.	Colloidal silicondioxide					0.5	0.5	0.5	0.5	0.5	0.5		0.5
18.	Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
	Average weight per tablet	75	75	75	75	75	75	75	75	75	75	90	75
	Trial size taken	250 Tab	250 Tab	250 Tab	250 Tab	250 Tab	250 Tab	2500 Tab	2500 Tab	2500 Tab	2500 Tab	2500Tab	2500 Tab

Table No. 4: In-vitro drug release study for marketed product

S.No.	Time (Hrs)	pH of mediura	Mean area of peak	Amount of drug released (mg)	Percentage drug release
1.	1	1.2	0	0.00	0.00
2.	2	1.2	0	0.00	0.00
3.	3	7.2	9820	0.09	1.86
4.	6	7.2	25942	0.23	57.74
5.	8	7.2	32493	0.29	72.32
6.	10	7.2	37152	0.33	82.69
7.	15	7.2	39635	0.35	88.21

Table 5: Sieve Analysis

S.No.	Sieve Member	Mean size opening (3)	Weight retained on smaller sieve	% weight returned on smaller sieve	Weight size (3) x (5)
1.	Sieve 40/60	337.5	5.05	10.1	3408.75
2.	Sieve 60/80	215	8.7	17.4	3741
3.	Sieve 80/100	165	21.15	42.3	6979.5
4.	Pan	125	15.1	30.2	3775

Particle size = weight size / 100

Table 6: Scale of flowability[22]

Compressibility index (%)	Flow character	Hausner ratio
$\leq$ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
> 38	Very, very poor	> 1.60

Table 7

Granules	Bulk density	Tapped density	Compressibility index	Hausner's ratio	Particle size
Trial XII	0.563	0.686	18.01	1.21	157.5µ

Table 8: Evaluation of tablets for post compression properties

Preparation of tablet	Average thickness (mm)	Average hardness kg / cm^2	Friability (%)	Percentage weight variation limit ± 10%	Assay by HPLC
Trial batch – I	2.88-2.91	4.5	0.18	-2.81+3.12	81.84%
Trial batch - II	3.05-3.08	4.5	0.24	-2.92+2.90	82.60%
Trial batch – III	2.88-2.91	5.0	0.25	- 3.11-+2.87	83.71%
Trial batch-IV	2.88-2.9	2.5	0.16	-2.68-+3.45	81.64%
Trial batch-V	2.91-2.99	2.0	0.36	-2.91-+3.33	84.35%
Trial batch-VI	2.91-2.99	2.0	0.24	-1.87-+3.01	83.10%
Trial batch-VII	2.87-2.90	5.0	0.10	-2.02-+1.97	104.80%
Trial batch-VIII	2.89-2.92	5.0	0.15	-2.05-+1.99	100.85%
Trial batch-IX	2.87-2.90	4.0	0.22	-2.67-+3.40	101.20%
Trial batch-X	2.85-2.88	4.0	0.17	-2.88-+3.23	102.81%
Trial batch-XI	2.32-2.35	5.0	0.09	-3.01-+2.80	99.72%
Trial batch-XII	3.15-3.18	5.5	0.07	-2.12-+1.87	105.50%

Table 9

Tablet	Drug content (mg)	Assay %
1	0.41	102.97
2	0.38	95.52
3	0.40	99.35
4	0.41	102.74
5	0.39	97.56
6	0.40	100.18
7	0.39	98.19
8	0.41	103.26
9	0.41	101.76
10	0.42	105.38

In – Vitro Drug Release Study

Trial Batch – I: Table No: 10

S.No	Time (Hrs)	pH of medium	Mean area of peak	Percentage drug release
1.	1	1.2	17326	38.56
2.	2	12	31596	70.32

Trial Batch – III Table No: 11

S.No.	Time (Hrs)	pH of medium	Mean area of peak	Percentage drug release
1	1	1.2	11340	25.24
2	2	1.2	20098	44.73
3	3	7.2	22322	49.68
4	6	7.2	28195	62.75
5	8	7.2	29264	65.13
6	10	7.2	31834	70.85

Trial Batch – IV Table No: 12

S.No.	Time (Hrs)	pH of medium	Mean area of peak	Percentage drug release
1	1	1.2	6933	15.43
2	2	1.2	13362	29.74
3	3	7.2	15380	34.23
4	6	7.2	21167	47.11
5	8	7.2	24488	54.50
6	10	7.2	28316	63.02

Trial Batch – IV Table No: 12

S.No.	Time (Hrs)	pH of medium	Mean area of peak	Percentage drug release
1	1	1.2	6933	15.43
2	2	1.2	13362	29.74
3	3	7.2	15380	34.23
4	6	7.2	21167	47.11
5	8	7.2	24488	54.50
6	10	7.2	28316	63.02

Trial Batch – VII Table No : 13

S.No.	Time (Hrs)	pH of medium	Mean area of peak	Percentage drug release
1	1	1.2	10321	22.97
2	2	1.2	22722	50.57
3	3	7.2	28693	63.86
4	6	7.2	35658	79.36
5	8	7.2	37154	82.69
6	10	7.2	37316	83.05
7	15	7.2	42295	94.13

Trial Batch – VIII Table No : 14

S.No.	Time (Hrs)	pH of medium	Mean area of peak	Percentage drug release
1	1	1.2	7822	17.41
2	2	1.2	26901	59.87
3	3	7.2	39437	87.77
4	6	7.2	38813	86.56
5	8	7.2	23586	94.61
6	10	7.2	42510	86.18
7	15	7.2	46469	103.41

Trial Batch : IX Table No: 15

S.No.	Time (Hrs)	pH of medium	Mean area of peak	Percentage drug release
1	1	1.2	26281	58.49
2	2	1.2	33420	74.38
3	3	7.2	38709	86.15
4	6	7.2	38871	86.51
5	8	7.2	38983	86.76
6	10	7.2	42658	94.94
7	15	7.2	44671	99.42

Trial Batch X:Table No: 16

S.No	Time (Hrs)	pH of medium	Mean area of peak	Percentage drug release
1	1	1.2	14895	33.15
2	2	1.2	24825	55.25
3	3	7.2	34463	76.70
4	6	7.2	19981	80.15
5	8	7.2	36013	84.80
6	10	7.2	37199	82.79
7	15	7.2	38722	86.18

Trial Batch : XI Table No: 17

S.No.	Time (Hrs)	pH of medium	Mean area of peak	Percentage drug release
1	1	1.2	5.5	21.15
2	2	1.2	10.8	41.67
3	3	7.2	15.2	58.76
4	6	7.2	19.3	74.88
5	8	7.2	21.4	82.84
6	10	7.2	22.2	86.11
7	15	7.2	23.7	91.80

Trial Batch : XII Table No: 18

S.No.	Time (Hrs)	pH of medium	Mean area of peak	Amount of drug released	Percentage drug release
1	1	1.2	0	0.00	0.00
2	2	1.2	0	0.00	0.00
3	3	7.2	5.8	0.09	22.51
4	6	7.2	18.0	0.28	69.86
5	8	7.2	21.6	0.34	83.83
6	10	7.2	21.6	0.34	83.83
7	15	7.2	23.1	0.36	89.65

Stability Data for Trial Batch XII (40^0C / 75% RH) Table 19

S.No	Evaluation Test	Initial	End of 1st month
1	Average weight (mg)	87.6 $\pm$ 2	87.6 $\pm$ 2
2	Thickness (mm)	3.15 $\pm$ 0.02	3.15 $\pm$ 0.02
3	Hardness (kg /Cm^2)	5.5	5.5
4	Friability (%)	0.07	0.11

In – vitro Drug Release Study : Table No: 20

S.No.	Time (Hrs)	pH of medium	Mean area of peak	Amount of drug released(mg)	Percentage drug release
1	1	1.2	0	0.00	0.00
2	2	1.2	0	0.00	0.00
3	3	7.2	6.2	0.10	23.84
4	6	7.2	17.4	0.27	67.52
5	8	7.2	21.4	0.33	82.71
6	10	7.2	21.8	0.34	84.45
7	15	7.2	23.3	0.36	90.15

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