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# Formulation development and evaluation of Tamsulosin Hydrochloride and Dutasteride in tablet dosage form

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**ABSTRACT**

*The purpose of the study was to develop tablet in tablet (compression – coated tablets) having different release pattern, which is indicated for the treatment of Benign Prostate Hyperplasia. The study was planned in three stages. In the first stage, five batches ($T_1$,$T_2$,$T_3$,$T_4$,$T_5$) of matrix tablet of Tamsulosin hydrochloride were prepared by wet granulation method, enteric coated and evaluated. Among the five batches, batch $T_3$ was taken up for further studies. In the second stage, three batches ($T_6$,$T_7$,$T_8$) of Dutasteride granules were prepared and evaluated. All three batches showed good flow property and drug content and taken up for further studies. In the third stage, three batches ($T_9$,$T_{10}$,$T_{11}$) of compression – coated tablets were prepared, film coated and evaluated. Among three batches, batch $T_{11}$ showed desirable properties and drug release. Hence batch $T_{11}$ was considered as an optimized batch. The stability studies was determined for the optimized batch. This design of dosage form will open a new era for repeat action tablets.*

**Key words:** Compression – coated tablets, Tamsulosin hydrochloride, Dutasteride, HPMC

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## INTRODUCTION

Prostate enlargement is the common part of ageing in men [1] [2] [3]. It can be treated by α adrenergic blockers and 5 α reductase inhibitor (5 ARI). Medical therapy of prostate symptoms (MTops) established the role of combination of α – blockers and 5 ARI in the management of Benign Prostate Hyperplasia (BPH), which is treated by Tamsulosin hydrochloride and Dutasteride to produce safe, effective and tolerable effect.

To improve patient compliance and reduce the side effects these drugs can be formulated as compression – coated tablet, which has two parts. The outer part (outer tablet) release the drug

immediately and inner part (inner tablet) release the drug in the intestine in a prolonged manner for a specific period of time (8 hours).

The aim of the study was to develop enteric coated matrix tablet of Tamsulosin hydrochloride and Dutasteride immediate release tablet as compression – coated tablet [4] [5] [6].

## MATERIALS AND METHODS

The following materials were obtained from Burgeion Ltd as gift sample. They were Tamsulosin hydrochloride, Dutasteride, Hydroxy Propyl Methyl Cellulose (HPMC), starch, Tween 80, Polyvinyl pyrolidone, Magnesium stearate, Isopropyl alcohol (IPA), Microcrystalline cellulose powder (MCCP), Colloidal silicon dioxide, Opadry white, Methylene dichloride, Acryl-EZE, Demineralised (DM) water

### Methods of Preparation

The study was planned in three stages

1. Formulation of enteric coated matrix tablets of Tamsulosin hydrochloride, and evaluation
2. Formulation of Dutasteride granules and evaluation.
3. Formulation of compression – coated tablets(tablet in tablet) using Dutasteride granules (outer layer) and enteric coated Tamsulosin hydrochloride(inner layer) followed by film coating and evaluation[6].

1. In the first stage, five batches ($T_1$,$T_2$,$T_3$,$T_4$,$T_5$) of matrix tablet of Tamsulosin hydrochloride which contains HPMC in different ratios were prepared and the formula was given in the **table.1**

For this preparation required quantity of polyvinyl pyrrolidine (PVP) in demineralised water, tween 80, tamsulosin hydrochloride, hydroxyl propyl methyl cellulose (HPMC) and starch were accurately weighed and stirred well and transferred to mass mixer [7][8]. Then the mass mixer allowed to run to granulate, and the granules were lubricated with magnesium stearate finally compressed by using 7/32 punch. Then it was enteric coated with Acryl – EZE and evaluated [9] [10]

**Table .1: Formula for Matrix tablets of Tamsulosin hydrochloride**

| S. No. | Ingredients | Batch | | | | |
|---|---|---|---|---|---|---|
| | | $T_1$ (%w/w) | $T_2$ (%w/w) | $T_3$ (%w/w) | $T_4$ (%w/w) | $T_5$ (%w/w) |
| 1 | Tamsulosin hydrochloride | 0.44 | 0.44 | 0.44 | 0.44 | 0.44 |
| 2 | Starch | 84.89 | 79.89 | 74.89 | 69.89 | 64.89 |
| 3 | HPMC | 10 | 15 | 20 | 25 | 30 |
| 4 | Tween 80 | 0.67 | 0.67 | 0.67 | 0.67 | 0.67 |
| 5 | Polyvinyl pyrolidone | 3.33 | 3.33 | 3.33 | 3.33 | 3.33 |
| 6 | Demineralised water | Q.S | Q.S | Q.S | Q.S | Q.S |
| 7 | Magnesium stearate | 0.67 | 0.67 | 0.67 | 0.67 | 0.67 |

2. In the second stage three batches ($T_6$,$T_7$,$T_8$) of Dutasteride granules which contains MCCP in different ratios were prepared and the formula was given in the **table.2**

For this preparation required quantity of PVP, Isopropyl alcohol, Tween 80, Dutasteride and starch weighed and stirred and transferred to mass mixer and allowed to run to granulate. Then the granules were lubricated with starch, MCCP, colloidal silicon dioxide and magnesium stearate and evaluated [11] [12]

**Table.2: Formula for Dutasteride granules**

| S. No. | Ingredients | Batch | | |
|---|---|---|---|---|
| | | $T_6$ (%w/w) | $T_7$ (%w/w) | $T_8$ (%w/w) |
| 1 | Dutasteride | 0.14 | 0.14 | 0.14 |
| 2 | Starch | 48.86 | 38.86 | 28.86 |
| 3 | Tween 80 | 0.14 | 0.14 | 0.14 |
| 4 | PVP | 0.86 | 0.86 | 0.86 |
| 5 | Isopropyl alcohol | Q.S | Q.S | Q.S |
| 6 | MCCP | 20 | 30 | 40 |
| 7 | Magnesium stearate | 0.86 | 0.86 | 0.86 |
| 8 | Starch | 28.57 | 28.57 | 28.57 |

3. In the third stage, three batches ($T_9$,$T_{10}$,$T_{11}$) of compression coated tablet were prepared and the formula was given in **Table.3 and Table.3.1**

In the third stage, inner tablets were prepared first in one turret. For preparing final tablet bigger die cavity in another turret was used in which 50% of weighed quantity Dutasteride granules was filled and then the optimized batch of enteric coated Tamsulosin hydrochloride tablets were transferred and the remaining space was filled with 50% of Dutasteride granules and finally compressed to produce compression – coated tablets. The compression coated tablets were film coated with opadry white and evaluated. [13]

**Table.3: Formula for Tablet in tablet(compression – coated tablet) Tamsulosin hydrochloride(Inner layer)**

| $T_9$, $T_{10}$, $T_{11}$ | | |
|---|---|---|
| **S. No.** | **Ingredients** | **(%w/w)** |
| 1 | Tamsulosin hydrochloride | 0.44 |
| 2 | Starch | 74.89 |
| 3 | HPMC | 20 |
| 4 | Tween 80 | 0.67 |
| 5 | Polyvinyl pyrolidone | 3.33 |
| 6 | Demineralised water | Q.S |
| 7 | Magnesium stearate | 0.67 |

**Table.3.1: Dutasteride(Outer layer)**

| S. No. | Ingredients | Batch | | |
|---|---|---|---|---|
| | | $T_9$ (%w/w) | $T_{10}$ (%w/w) | $T_{11}$ (%w/w) |
| 1 | Dutasteride | 0.14 | 0.14 | 0.14 |
| 2 | Starch | 48.86 | 38.86 | 28.86 |
| 3 | Tween 80 | 0.14 | 0.14 | 0.14 |
| 4 | PVP | 0.86 | 0.86 | 0.86 |
| 5 | Isopropyl alcohol | Q.S | Q.S | Q.S |
| 6 | MCCP | 20 | 30 | 40 |
| 7 | Magnesium stearate | 0.86 | 0.86 | 0.86 |
| 8 | Starch | 28.57 | 28.57 | 28.57 |

**Methods of Evaluation**
**Procedure for the determination of content uniformity by HPLC**[14]

**Mobile phase A Buffer:** 8.5ml of perchloric acid (70%) in 200ml of distilled water.

**Mobile phase B:** Acetonitrile

**Diluent:** Prepared a mixture of buffer and acetonitrile in the ratio of 65:35.

**Standard preparation:** Weighed accurately and transferred about 15mg of Tamsulosin hydrochloride working standard into a 200ml volumetric flask. Sufficient amount of 0.1 N methanolic sodium hydroxide was added to produce 200ml. 5ml of this solution was diluted to 100ml with 0.1N methanolic sodium hydroxide. 5ml of this solution was again diluted to 20ml with diluent.

**Sample preparation:** 1 tablet transferred was in to a 100 ml of volumetric flask. 75ml 0.1N Methanolic sodiumhydroxide was added. Sonicated for 20 minutes and diluted upto the mark with 0.1 N methanolic sodium hydroxide. Further diluted 5ml to 20ml with diluent.

**Chromatographic system:**
The liquid chromatograph is equipped with a 215nm detector and a 4.6mm X 25cm inertsil column that contains packing C 18, maintaining the peak responses as directed for procedure. The relative standard deviation for 5 replicate injections was not more than 2%.

**Procedure:** Separately injected equal volume (100µl**)** of the blank, standard preparation and sample preparation into the chromatograph, recorded the chromatograms and measured the responses for major peaks.

**Calculations:**

$$\frac{\text{Spl area x Std. Wt.(mg)x5x5x100x20xPurity of std x 100}}{\text{Std area x 200 x100 x20 x1 x5 x 100 x L.A.}}$$

***Invitro* Drug Release Studies**
**Stage I:** Gastric buffer stage: **Stage II:** Intestinal buffer pH6.8

**Apparatus:** USP type II

**Medium:** 500ml of gastric buffer (Preparation: 7ml HCl/2g NaCl in one liter of water).

**Speed:** 100 rpm

**Time: Stage I** -2 hours **;** : **Stage II:** 2, 4, 8 hours

**Temperature**: $37^0C \pm 0.5\ ^0C$

**Mobile phase A Buffer:** 8.5 ml of perchloric acid (70%) in 200ml of distilled water.

**Mobile phase B**: Acetonitrile

**Chromatographic system:**
The liquid chromatograph is equipped with a 215nm detector and a 4.6mm X 25cm inertsil column that contains packing C 18, maintaining the peak responses as directed for procedure. The relative standard deviation for 5 replicate injections was not more than 2%.
**Standard preparation:** Weighed accurately and transferred about 15mg of Tamsulosin hydrochloride working standard into a 200ml volumetric flask. Sufficient amount of 0.1 N methanolic sodium hydroxide was added to produce 200ml. 2ml of this solution was again diluted to 20ml with dissolution medium

**Sample preparation:** Transfer 1 tablet in a 500 ml of dissolution medium. At the end of specified time remove 10ml aliquot. Filter through whatmann filter paper No.41.

**Procedure:** Separately injected equal volume (100µl**)** of the blank, standard preparation and sample preparation into the chromatograph recorded the chromatograms and measured the responses for major peaks.

**Calculations:**

$$\% \text{ released} = \frac{\text{Spl area} \times \text{Std. Wt.(mg)} \times 2 \times 500 \times \text{Purity of std} \times 100}{\text{Mean Std area} \times 200 \times 200 \times 1 \times 100 \times \text{L.A.}}$$

**Limit:** Not more than 10% of the labeled amount is released in 2 hours in 0.1M HCl
**Limit:** Percentage release of tamsulosin hydrochloride in intestinal buffer pH 6.8
$2^{nd}$ hour – between 40 to 70%
$4^{th}$ hour – NLT 65%
$8^{th}$ hour – NLT 80%

## RESULTS

In the first stage, five batches ($T_1$,$T_2$,$T_3$,$T_4$,$T_5$) of enteric coated Tamsulosin hydrochloride were evaluated for average weight, hardness, content uniformity, disintegration test and dissolution. The results given in the Table 4, Table 5 and Table 6.

**Table 4.Physicochemical evaluation of formulated enteric coated Tamsulosin hydrochloride**

| Batch | Average weight | Hardness ($Kg/Cm^2$) | Content uniformity (% w/w) | Disintegration Test Acid(2 hrs) |
|---|---|---|---|---|
| $T_1$ | 100.20 | 3.5 | 97.15 | ▼ |
| $T_2$ | 100.24 | 3.5 | 97.26 | ▼ |
| $T_3$ | 100.04 | 3.5 | 97.70 | ▼ |
| $T_4$ | 100.28 | 4 | 96.23 | ▼ |
| $T_5$ | 100.28 | 4.5 | 97.41 | ▼ |
| ▼*-All the five batches of tablets remains intact in an acid medium.* | | | | |

**Table 5. *Invitro* drug release of the formulated enteric coated Tamsulosin hydrochloride tablets in acid medium**

| Batch code | Time in hours | Cumulative percentage release in acid medium |
|---|---|---|
| $T_1$ | 2 | 2.75 |
| $T_2$ | 2 | 2.95 |
| $T_3$ | 2 | 1.00 |
| $T_4$ | 2 | 1.25 |
| $T_5$ | 2 | 0.70 |

**Table 6. *Invitro* drug release of the formulated enteric coated Tamsulosin release in buffer pH 6.8**

| Batch code | Time in hours | Cumulative percentage release in pH 6.8 |
|---|---|---|
| $T_1$ | $2^{nd}$ | 86.84 ±0.62 |
| | $4^{th}$ | 89.75±0.58 |
| | $8^{th}$ | 97.62±0.35 |
| $T_2$ | $2^{nd}$ | 82.39±0.57 |
| | $4^{th}$ | 87.35±0.75 |
| | $8^{th}$ | 96.98±0.28 |
| $T_3$ | $2^{nd}$ | 47.45±0.37 |
| | $4^{th}$ | 76.02±0.64 |
| | $8^{th}$ | 95.61±0.55 |
| $T_4$ | $2^{nd}$ | 38.24±0.61 |
| | $4^{th}$ | 58.56±0.71 |
| | $8^{th}$ | 76.84±0.76 |
| $T_5$ | $2^{nd}$ | 22.35±0.81 |
| | $4^{th}$ | 45.22±0.59 |
| | $8^{th}$ | 68.75±0.53 |

*Mean ± Standard deviation (n = 3)*

**Table 7.Physicochemical evaluation of the formulated Dutasteride granules**

| Batch code | Angle of repose | Bulk density (%w/w) | Tap density (%w/w) | Hausner ratio | Carr's index (%) | Water Content (%w/w) | % Drug content |
|---|---|---|---|---|---|---|---|
| $T_6$ | $22^0 7$" | 0.7607 | 0.8656 | 1.14 | 12.12 | 1.23 | 98.67 |
| $T_7$ | $22^0 7$" | 0.7608 | 0.8656 | 1.14 | 12.13 | 0.98 | 99.44 |
| $T_8$ | $22^0 7$" | 0.7813 | 0.8656 | 1.14 | 12.50 | 0.78 | 100.20 |

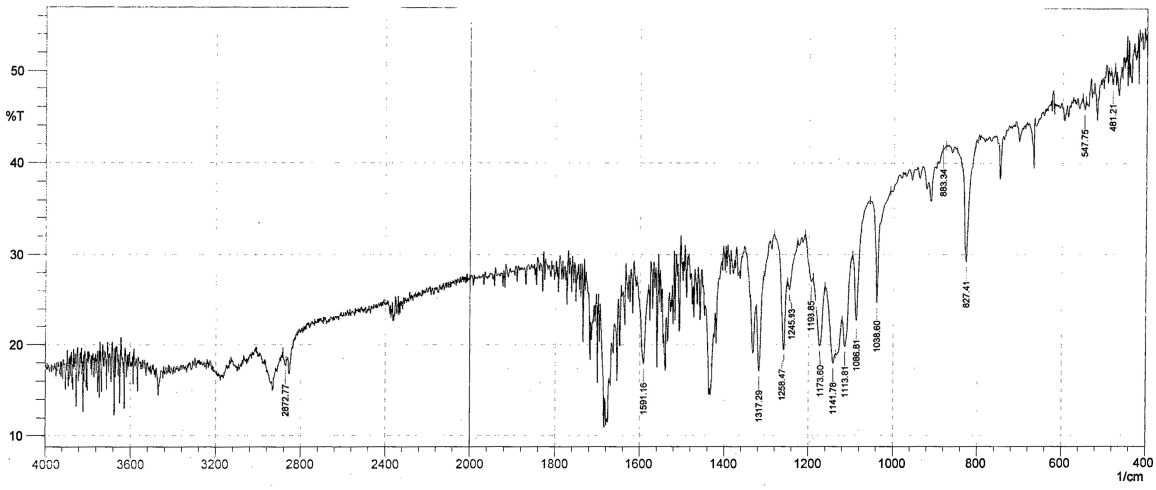
**Table 8. Physicochemical evaluation of formulated compression – coated tablets**

| Parameters | | Batch code | | |
|---|---|---|---|---|
| | | $T_9$ | $T_{10}$ | $T_{11}$ |
| Average weight (mg) | | 459.36 | 459.55 | 459.65 |
| Hardness ($Kg/Cm^2$) | | 8 | 8.5 | 8 |
| Disintegratation test | | 7'20" | 8'40" | 9'10" |
| Content Uniformity (%w/w) | Dutasteride | 92.57 | 93.25 | 95.22 |
| | Tamsulosin hydrochloride | 95.38 | 96.85 | 98.75 |
| Assay (%w/w) | Dutasteride | 98.67 | 99.04 | 99.86 |
| | Tamsulosin Hydrochloride | 99.05 | 99.66 | 100.56 |

In the second stage, three batches ($T_6$,$T_7$,$T_8$) Dutasteride granules were evaluated for angle of repose, bulk densitiy, tapped density hausner ratio,carr's index, water content and drug content . The results were given in the Table 7.

In the third stage, three batches ($T_9$,$T_{10}$,$T_{11}$) of compression – coated tablets were evaluated for average weight, hardness, disintegration test, content uniformity, assay and *invitro* drug release. The results were given in the Table 8 and Table 9, Table 9.1 and Table 9.2.

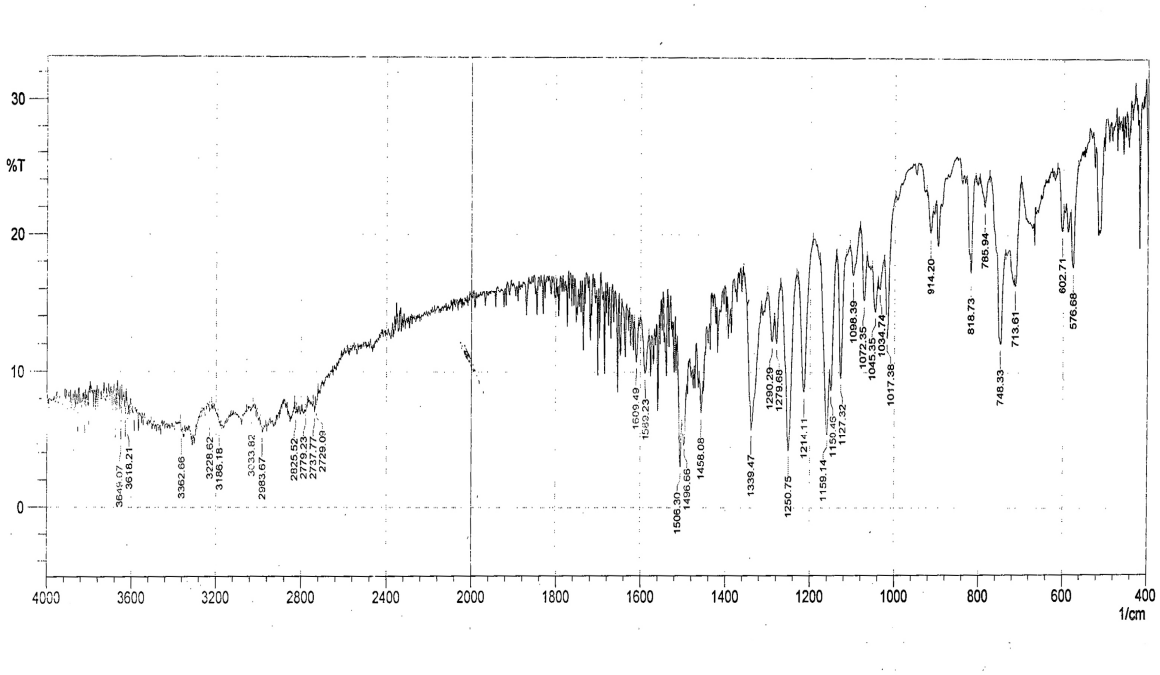
**Fig.1.IR Spectrum of Dutasteride and Tamsulosin hydrochloride**




DUTASTERIDE SPL

Resolution; 2 [1/cm]

Apodization; Happ-Genzel

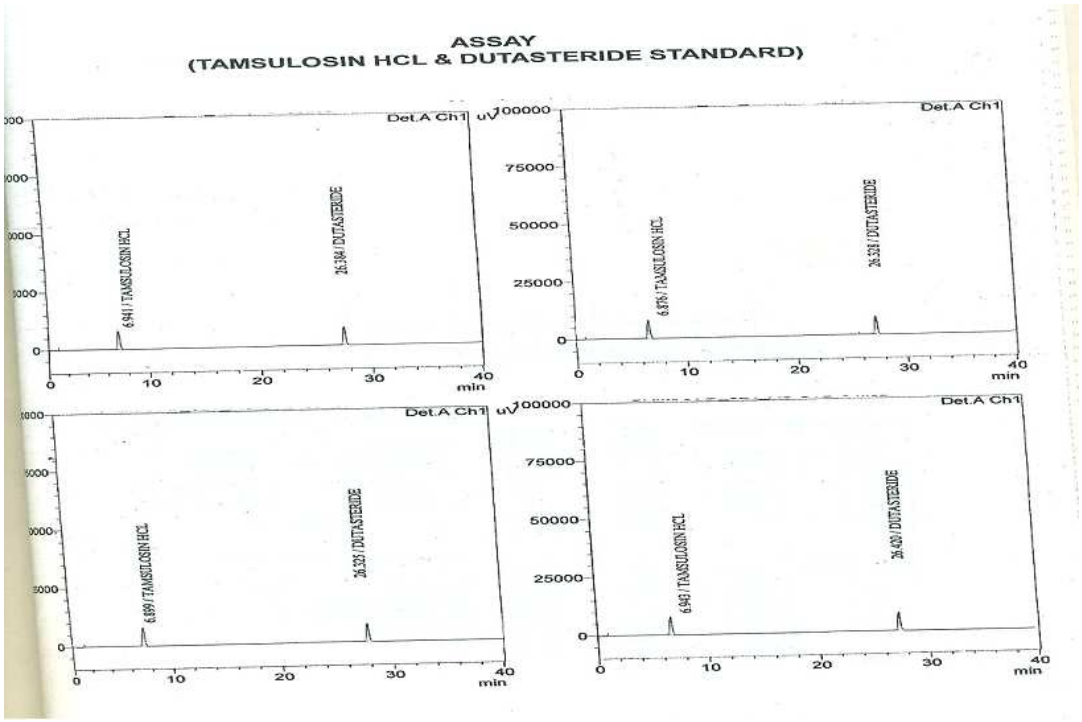


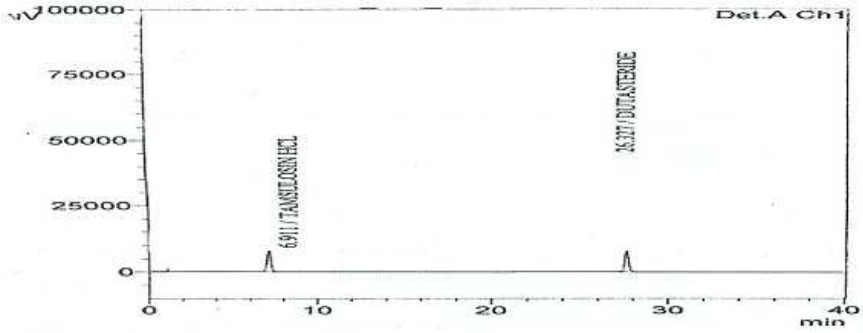

TAMSULOSIN HCL SPL

Resolution; 2 [1/cm]

Apodization; Happ-Genzel

**Fig.2. Assay HPLC chromatogram for Dutasteride and Tamsulosin hydrochloride(Standard)**




<< Detector A >>
ID#1 Compound Name: TAMSULOSIN HCL

| Vial# | Title | Ret. Time | Area | oretical Pla | ailing Facto |
|---|---|---|---|---|---|
| 22 | TAMSULOSIN HCL_024_AS-STD-05.lcd | 6.941 | 124269 | 5172.7 | 1.10 |
| 22 | TAMSULOSIN HCL_024_AS-STD-06.lcd | 6.876 | 125137 | 5224.7 | 1.11 |
| 22 | TAMSULOSIN HCL_024_AS-STD-07.lcd | 6.899 | 125149 | 5268.4 | 1.10 |
| 22 | TAMSULOSIN HCL_024_AS-STD-04.lcd | 6.943 | 124343 | 5146.0 | 1.11 |
| 22 | TAMSULOSIN HCL_024_AS-STD-01.lcd | 6.911 | 123440 | 5106.6 | 1.12 |
| | Average | 6.914 | 124468 | 5183.7 | 1.11 |
| | %RSD | 0.410 | 0.571 | 1.233 | 0.413 |

ID#2 Compound Name: DUTASTERIDE

| Vial# | Title | Ret. Time | Area | oretical Pla | ailing Facto |
|---|---|---|---|---|---|
| 22 | DUTASTERIDE_024_AS-STD-05.lcd | 26.384 | 133621 | 155074.5 | 1.17 |
| 22 | DUTASTERIDE_024_AS-STD-06.lcd | 26.328 | 138728 | 150998.3 | 1.19 |
| 22 | DUTASTERIDE_024_AS-STD-07.lcd | 26.325 | 137864 | 151557.5 | 1.17 |
| 22 | DUTASTERIDE_024_AS-STD-04.lcd | 26.420 | 136496 | 153404.9 | 1.18 |
| 22 | DUTASTERIDE_024_AS-STD-01.lcd | 26.327 | 134481 | 153307.8 | 1.14 |
| | Average | 26.357 | 136238 | 152868.6 | 1.17 |
| | %RSD | 0.164 | 1.593 | 1.063 | 1.544 |

**Fig.3. Assay HPLC chromatogram for Dutasteride and Tamsulosin hydrochloride(Sample)**

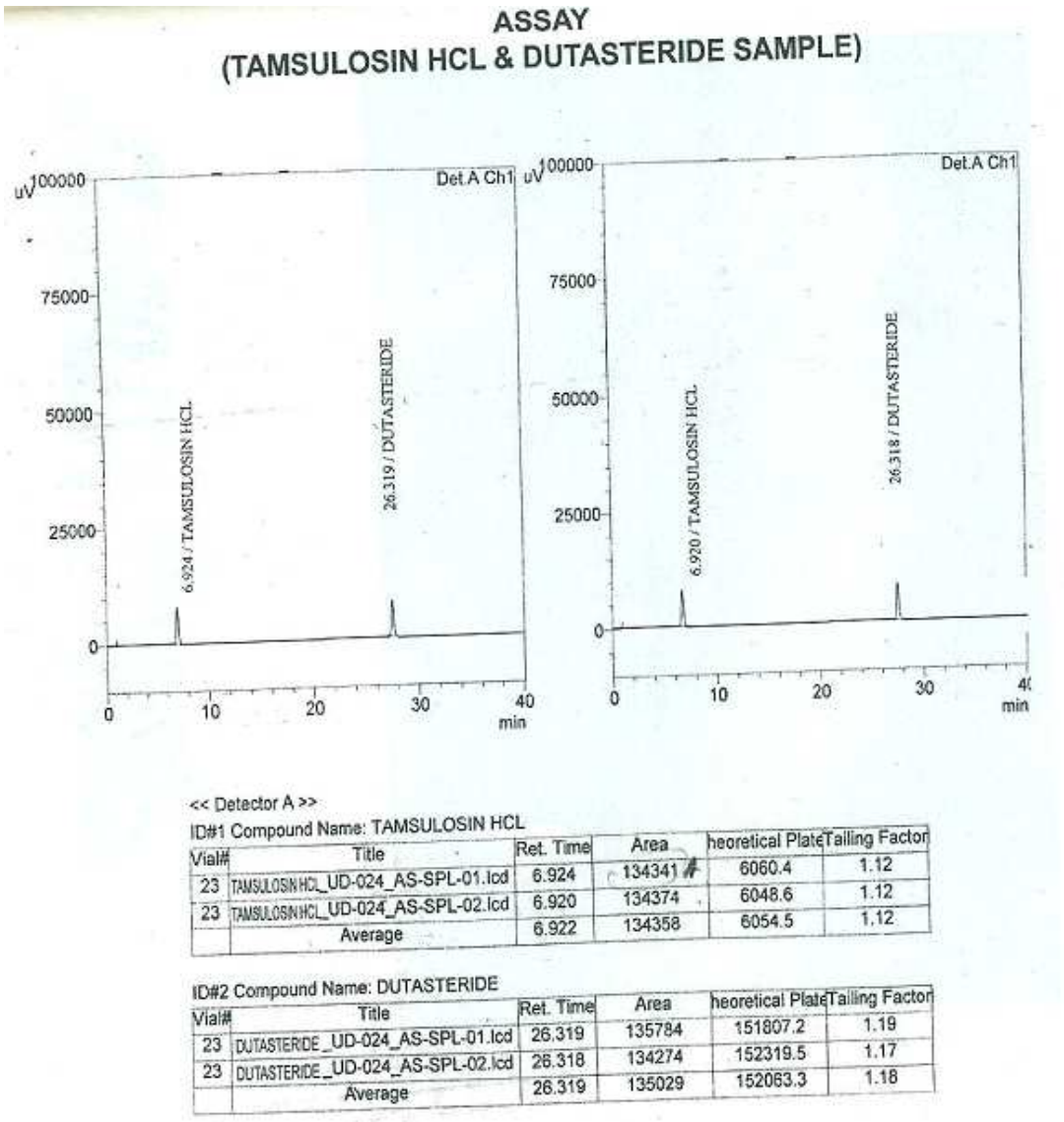



**Table 9: *Invitro* drug release of the formulated compression coated tablets DUTASTERIDE**

| Batch code | Time in minutes | Cumulative percentage release |
|---|---|---|
| $T_9$ | 30 | 97.88 |
| $T_{10}$ | 30 | 97.43 |
| $T_{11}$ | 30 | 98.88 |

**Table 9.1: TAMSULOSIN HYDROCHLORIDE**

| Batch code | Time in hours | Cumulative percentage release in acid medium |
|---|---|---|
| $T_9$ | 2 | 1.0 |
| $T_{10}$ | 2 | 1.2 |
| $T_{11}$ | 2 | 0.7 |

**Table 9.2**

| Batch code | Time in hours | Cumulative percentage release in pH 6.8 |
|---|---|---|
| $T_9$ | $2^{nd}$ | 45.63 ±0.46 |
| | $4^{th}$ | 72.54±0.68 |
| | $8^{th}$ | 94.85±0.72 |
| $T_{10}$ | $2^{nd}$ | 46.07±0.63 |
| | $4^{th}$ | 73.71±0.81 |
| | $8^{th}$ | 95.46±0.41 |
| $T_{11}$ | $2^{nd}$ | 48.40±0.25 |
| | $4^{th}$ | 77.20±0.38 |
| | $8^{th}$ | 96.70±0.57 |

*Mean ±Standard deviation (n = 3)*

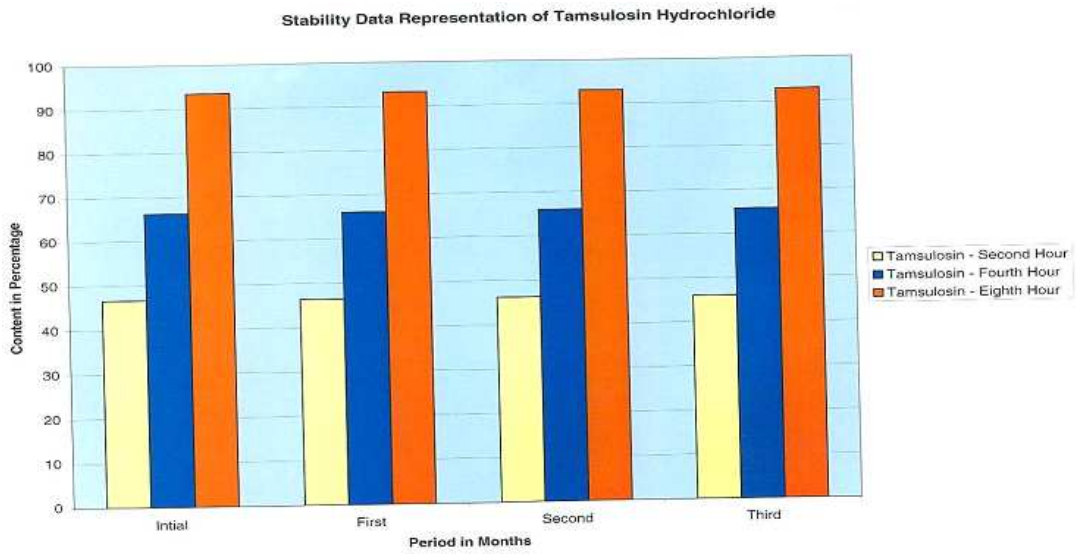
## STABILITY STUDIES:

The stability study was done for the optimized batch (batch $T_{11}$ ) as per ICH guideline at 40ºC ± 2ºC and RH 75 ± 5 % and the results were given in Table10

**Table 10**

| Tests | Storage time (Months) | | |
|---|---|---|---|
| | **After 1month** | **After 2 months** | **After 3 months** |
| Average weight (mg) | 459.66 | 459.36 | 459.26 |
| **Dissolution** | **% Release** | **% Release** | **% Release** |
| Dutasteride | 89.60 | 89.52 | 89.32 |
| Tamsulosin hydrochloride in acid medium | 2.16 | 2.52 | 2.90 |
| At pH 6.8 Time in hrs | **% Release** | **% Release** | **% Release** |
| $2^{nd}$ | 48.48 | 48.10 | 48.00 |
| $4^{th}$ | 77.80 | 77.72 | 77.40 |
| $8^{th}$ | 96.92 | 96.82 | 96.24 |
| Assay for Dutasteride | 99.94 | 99.86 | 99.54 |
| Assay for Tamsulosin hydrochloride | 100.62 | 100.43 | 100.28 |

**Fig.4.Sability data for Dutasteride and Tamsulosin hydrochloride**




## DISCUSSION

The average weight, hardness, content uniformity for the batches $T_1$,$T_2$,$T_3$,$T_4$,$T_5$ were within the limit. Batches $T_1$,$T_2$ had faster initial drug release, whereas batches $T_4$,$T_5$ had slow initial drug release than the normal. But batch $T_3$ had optimized drug release and release was similar with that of the marketed formulation. Hence batch code $T_3$ was taken up for further studies. In this optimized concentration for HPMC was found to be 20%w/w

The drug content and water content for batches $T_6$, $T_7$, $T_8$ were within the limit and the angle of repose, bulk density, tap density, Hausner ratio, Carr's index showed that all batches ($T_6$, $T_7$, $T_8$) had good flow property. Hence all three batches taken up for further studies

The average weight, hardness, disintegration test, content uniformity, assay for batches $T_9$, $T_{10}$, $T_{11}$ were within the limit. The batches $T_9$, $T_{10}$ had slow *invitro* drug release for Dutasteride [15][16][17].. But batch $T_{11}$ only exhibited more *invitro* drug release for Dutasteride and for Tamsulosin hydrochloride when compared to $T_9$, $T_{10}$.

The stability study showed that the batch $T_{11}$ was stable throughout the stability period

## CONCLUSION

Based on the observation, it was concluded that batch $T_{11}$ exhibited desirable properties and optimized drug release .The *invitro* drug release of batch $T_{11}$ was similar with that of the marketed formulation. Hence batch $T_{11}$ was considered as a desirable batch. The results demonstrated the effective use of compression – coated tablets of Tamsulosin hydrochloride and dutasteride as a ideal drug release formulation for treatment of Benign Prostate Hyperplasia.

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