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Formulation and In-vitro Evaluation of Tolterodine Tartrate Tablets by Using High Performance Liquid Chromatographic (HPLC)

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Abstract

Tolterodine tartrate, is a new, potent and competitive muscarinic receptor antagonist in clinical development for the treatment of urge incontinence and other symptoms of unstable bladder. The purpose of this study is to formulation and invitro evaluation of Tolterodine tartrate by high performance liquid chromatography with ultraviolet detection (HPLC-UV). A simple, rapid, and sensitive high-performance liquid chromatographic method was developed and evaluated for invitro formulation of Tolterodine tartrate Tablets. Tablets were analysed by measuring different parameters: lubricated granules content of Tolterodine tartrate having bulk density, tap densities and angle of repose And flim coated Tolterodine tartrate tablets having friability, thickness, hardness, weight variation, invitro dissolution,

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content uniformity, assay and related substances. Separation of Tolterodine tartrate was achieved within a single chromatographic run on 5µm 4.6x250mm with UV detection at 280 nm, under isocratic conditions, using Acetonitrile and A mixture of 65 volumes of buffer solution prepared by mixing 2.2 ml of orthophosphoric acid to 1000 ml with water, adjusted to pH 3.0 with triethylamine in 35:65 ratio with a flow rate of 1.5 ml/min. From the results, it was clear that designed formulations among f7 displayed drug release in the range of 55.66% to 102.067% in 10 min, which showed improved invitro dissolution rate compared to other formulations as well as others parameters were found to be good as compared to other formulations. Similarly, the average content of formulation f7 was found to be 104.58% and Related substances should comply the test. Assays of f_7 were found to be 96.04%, the limit is 90% - 110% of the label claim having weight variation range from 82.50 mg-91.50 mg**.**

Keywords: Tolterodine tartrate; HPLC; Assay; Dissolution.

1. Introduction

The new potent and competitive muscarinic receptor antagonist in the form of Tolterodine tartrate,(R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanaminel-hydrogen tartrate , is armour of clinical development for the treatment of urge incontinence and other symptoms of unstable bladder (1-3). Tolterodine builds tolerability profile in case of the low frequency of bothersome dry mouth; As It has high affinity and specificity for muscarinic receptors in vitro and exhibits the selectivity for the urinary bladder over salivary glands in vivo (4). A major pharmacologically active metabolite, 5-hydroxymethyl derivative is formed after telterodine is metabolized in liver following the oral administration [5]. The proper dosage form of the drug is required to ensure it's optimum therapeutic effect. Solubility is an important characteristic for the drug as systemic absorption is affected by dissolution since only dissolved drug can pass the gastrointestinal membrane. Oral administration of any drug is the simplest, most common and easiest route, because of small bulk, stability, ease in manufacturing as well as ingesting and maintenance of accurate dosage as per required. Poorly water soluble drugs with slow drug absorption assists to inadequate as well as variable bioavailability and gastrointestinal mucosal toxicity. Designing the oral dosage forms is an uphill task due to poor oral bioavailability of the drug. Low solubility, low dissolution of the drug is the main reason of poor oral bioavailability of the drug instead of pervasion of drug through epithelia of gastrointestinal tract [6]. Poor aqueous solubility and poor membrane pervasion of drug molecule contributes to limitation of drug absorption from Gastrointestinal tract. Oral intake of an active agent should first dissolve in gastric and/or intestinal fluids before it permeates GI tract membranes onto system circulation. Enhancement of solubility and dissolution rate alongside permeability of poorly water soluble drugs is a major challenge pharmaceutical field in improvement of oral bioavailability of active agents. Thus, most of the under development chemical entities are targeted to be used in the form of solid dosage as an effective reproducible in vivo plasma concentration under oral administration [7]. In this study, we describe a comparative study of tablet with marketed drug by using high performance liquid chromatography for the determination of stable Tolterodine tartrate Tablets.

2. Materials and Methods

Tolterodine tartrate (AR No.Poo12456 TOl, C26H37NO7, and MicroCrystalline Cellulose, 102 Lactose monohydrate, Calcium Hydrogen Phosphate Dihydrate, Sodium Starch glycollate, Magnesium Stearate, colloidal anhydrous silica and Filmcoat universal were obtained from Time Pharma Pvt. Ltd. as a gift sample were provided by our Shree Medical and Technical College, Bharatpur-12, Chitwan.

2.1 Method of Preparation of film coated tablets

The direct compression method was employed to prepare film coated tablets of tartrate using different excipients, such as Microcrystalline cellulose 102, lactose monohydrate, 100 and Carbopol-940, in different ratios.

2.2 Preparation

MCC 102 was sieved through mesh # 80 and mix with Tolterodine tartrate. The calcium hydrogen phosphate dehydrate, sodium starch glycollate and lactose monohydrate were sieved through # 60 and mix with the above mixer of Tolterodine tartrate and MCC p 102 and the mixer was sieved through #60 for two times. The content was lubricated with already sieved mixer of Magnesium stearate and Colloidal silicon dioxide through #60 mesh size for 5 min in RMG. The moisture content was measured which was found to be 5.78%. And compression of the tablet was done at 85 mg tablet to a hardness of 6-11 kg/cm^2 using a 6.5 mm punch according to SOP and finally the compressed tablets were coated by preparing coating solution of Flimcoat Universal which was dissolved in purified water passing through # 60 mesh size, the coating solution was allowed to soak for 20 minutes. Finally the filmcoated tablet of Tolterodine tartrate was obtained.

2.3 Evaluation of Lubricated content of Tolterodine tartrate

All the prepared tablets were evaluated for the following parameters.

2.4 Bulk density and Tap densities

Exactly 50 gm of powder blend were weighed on a chemical balance and transferred into a 100 ml measuring cylinder. The cylinder was dropped on a wooden plat form from a height of 2.5 cm three times at 2 second intervals. The volume occupied by the granules was recorded as the bulk volume. The cylinder was then tapped on the wooden platform until the volume occupied by the powder blend remains constant. This was repeated three times for the blend. The data generated was used in calculating Carr's compressibility index and Haunser's ratio [5].

$$\text{Bulk density} = \frac{\text{Mass}}{\text{Untapped volume}}$$

$$\text{Tapped density} = \frac{\text{Mass}}{\text{Tapped volume}}$$

2.5 Angle of repose

Fifty grams of powder blend was placed in a plugged glass funnel that had a distance of 10 cm from the flat surface. The blend was then allowed to flow through the 8 mm funnel orifice by removing the cotton plug from the funnel orifice. The height of the heap (h) formed as well as the radius of the heap (r) was noted [5].

$$\text{Tan}\,\theta = \frac{h}{r}$$

where,

'θ' is the angle of repose

'h' is height of pile

'r' is the radius of the base of the pile

Carr's Index

The compressibility index of the granules was determined by Carr's index. Carr's index can be calculated by using the following formula [8]:

$$\text{Carr's Index} = \left(1 - \frac{\text{Tapped volume}}{\text{Fluppy/Bulk volume}}\right) * 100$$

2.6 Hausners Ratio

The Hausners ratio is the indication of the compressibility of a power. The Hausners ratio of the mixed powder was calculated by the following formula [8]:

$$\text{Hausners Ratio} = \frac{100}{100 - \text{Carr's index}}$$

3. Evaluation of Flim coated Tolterodine tartrate tablets

Friability

Friability is the measure of tablet strength. A Roche-type friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed, and the percentage loss was determined [12].

$$\% \text{ loss} = \frac{(\text{Initial weight} - \text{final weight})}{} * 100$$

Initial weight

Hardness

Hardness was measured using a Campbell (HT-100TP) hardness tester. For each batch, three tablets was tested [7].

Thickness

Three tablets were selected randomly from each batch, and thickness was measured by using a vernier caliper [7].

4. Weight Variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets were calculated. The batch passed the test for the weight variation test if not more than two of the individual tablet weights deviated from the average weight by more than the percentage shown in Table No. 3 and none deviated by more than twice the percentage shown [7].

Table 1: Percentage deviation allowed under the weight variation test

S.N	Average wt. of Tablets (mg)	Percentage
1.	130 or less	10
2.	130-324	7.5
3.	More than 324	5

In vitro dissolution studies

The release of the drug from the Tolterodine tartrate tablet was determined using a IP dissolution apparatus, and the dissolution rate was studied using 900 ml of gastric juice artificial prepared by dissolving 2 g of sodium chloride in 80 ml of 1M hydrochloric acid and dilute to 1000 ml with water [IP 2018].

Assay

4.1 Chromatographic Condition

Table 5

Mobile phase	A mixture of 65 volumes of buffer solution prepared by mixing 2.2 ml of orthophosphoric acid to 1000 ml with water, adjusted to pH 3.0 with triethylamine and 35 volumes of acetonitrile
Flow rate:	1.5 ml/minute
Wavelength:	280 nm
Column:	4.6mm*25cm; 5µm,C18
Injection volume :	20µl

4.2 Test solution

Weight and powder 20 tablets. Disperse a quantity of powder containing 10 mg of tolterodine tartrate in 70 ml of mobile phase with the aid of ultrasound for 20 minutes and dilute to 100.0 ml with the mobile phase, filter.

4.3 Reference Solution

A 0.01 percent w/v solution of tolterodine tartrate RS in the mobile phase.

4.4 Procedure

Inject the reference solution, the test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 percent

Inject the reference solution and test solution.

4.5 Related substances

Solvent mixture: Equal volumes of mobile phase A and mobile phase B

Test solution: disperse a quantity of powdered tablets containing 10 mg of tolterodine tartrate in 1 ml of methanol 5 ml of the solvent mixture with the aid of ultrasound and dilute to 10 ml with the solvent mixture, filter

4.6 Reference solution

(a) A 0.001 percent w/v solution of tolterodine tartrate RS prepared by dissolving in methanol and dilute with the solvent mixture.
(b) A 0.03 percent w/v solution of tartaric acid in the solvent mixture.

Table 6

Mobile phase	Dissolve 6.8 g of potassium dihydrogen orthophosphate in 1000 ml water, adjusted to pH 3.5 with orthophosphoric
Flow rate:	1 ml/minute
Wavelength:	215 nm
Column:	4.6mm*25cm; 5µm,C_{18}
Injection volume :	20µl

Table 7

Time (in min)	Mobile phase A(percent v/v)	Mobile phase B(percent v/v)
0	65	35
5	65	35
20	50	50
40	30	70
50	65	35

Inject the reference solution a the test is not valid unless the column efficiency is not less than 2000 theoretical plates and the ailing factor is not more than 2.0 Inject the reference solution (a), (b) and the test solution. in the chromatogram obtained with the test solution the area of the principal peak in the chromatogram obtained with the reference solution (a) (1 percent) the sum of the areas of all the secondary peaks is not more than twice the area of the principal peak in the chromatogram obtained with the reference solution (a) (2.0 percent) . Ignite the peak due to tartaric acid corresponding to the peak in the chromatogram obtained with reference solution (b)

Table 1: Composition of different formulations

Ingredients mg/tablet	Formulation code						
	F1	F2	F3	F4	F5	F6	F7
Tolterodine tartrate	1.005	1.005	1.005	1.005	1.005	1.005	1.005
MCCp 102	62.12	74	76	…	….	….	(A)
Lactose monohydrate	12.00	….	….	77	67	75.415	(B)
Calcium hydrogen phosphate dehydrate	4.98	4.98	2.915	3.80	5.00	4.98	4.98
Sodium starch glycollate	4.795	4.915	4.915	3.095	11.895	3.50	3.50
Colloidal anhydrous silica	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Magnesium stearate	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Total	85(mg)	85(mg)	85(mg)	85(mg)	85(mg)	85(mg)	85(mg)

5. Results

Evaluation of active Tolterodine tartrate

Moisture content

Moisture content was found to be 5.78%.

Assay

Assays of f_7 were found to be 96.04%, the limit is 90% - 110% of the label claim according to IP.

Evaluation of the developed formulation

The powder blend of the formulated product was checked for particle size distribution,

<150 μ= 56.20, 150-250μ = 44.80, >250μ = 0

Evaluation of Tolterodine tartrate tablets

Physiochemical Properties

The weight, thickness, hardness, and friability of the tablets of furosemide were determined. The hardness was in the range of 5 to 11 kg/cm^2. Friability was in the range of 0.32 to 0.67% less than 1%, indicating good mechanical strength to withstand the rigors of handling and transportation, and thickness was in the range of 2.9 mm to 3 mm. The weights of the film coated tablets were found to be in the range of 82.5 to 91.5 mg. which were showed in table 2

Table 2: Evaluation of both Granules of Tolterodine Tartrate Tablets and Formulated Tolterodine Tartrate Tablets

Formulation code	Angle of Repose	Hardness (Kg/cm^2)	Friability	Thickness	Assay	Weight variation
F_1	**25**	**9.5**	**0.27**	**2.5**	**80.99**	**70.09-65.77**
F_2	**24**	**4.4**	**0.23**	**2.3**	**79.77**	**80.00-69.02**
F_3	**28**	**5.7**	**0.22**	**2.1**	**68.09**	**77.9-80.00**
F_4	**27**	**7.1**	**0.47**	**2.8**	**76.09**	**79.54-80.10**
F_5	**23**	**8.3**	**0.39**	**2.9**	**88.98**	**70.10-79.00**
F_6	**30**	**9.7**	**0.50**	**2.9**	**89.23**	**60.98-77.98**
F_7	**28**	**10**	**0.67**	**3.0**	**96.04**	**82.50-91.50**

In-Vitro Dissolution Study

The cumulative percentage of drug released from the different formulations was given in Table 3.

Table 3: Dissotution Profile of Formulated Tolterodine Tartrate Products

			Cumulative % drug release				
Time	F1	F2	F3	F4	F5	F6	F7
10 min	76.11	55.66	60.38	69.05	78.92	89.051	102.067

Content Uniformity

Uniformity of Content of Tolterodine tartrate tablets of different formulations were recorded in table 4, formulation f_7 was found to be good, the average content of formulation 7 was 104.58%.

Table 4: Uniformity of content of different formulations

			Different Formulations				
Average (content of Tolterodine tartrate)	F1	F2	F3	F4	F5	F6	F7
	76.11	78.66	69.38	70.05	78.12	80.051	104.58

Related Substance

The individual impurity was found to be 0.0111% and total impurity was reported 0.0200% for the formulation f_7

6. Discussion

Tablets of Tolterodine tartrate were prepared by the direct compression method using different excipients such as MCCP 102, Lactose, Dicalcium Hydrogen Phosphate Dihydrate, Sodium starch Glycollate etc in different ratios. According to the work plan, the tablets were evaluated for their appearance, thickness, hardness, friability, weight variation, content uniformity, and related substances and in vitro release. The results of granule evaluation suggest that all the granules exhibit good flow properties, as the angle of repose values was less than 30. The weights of the tablets were found to be uniform. The hardness was in the range of 5 to 11 kg/cm3, Friability was in the range of 0.32 to 0.67% less than 1%, indicating good mechanical strength to withstand the rigors of handling and transportation, and thickness was in the range of 2.9 mm to 3 mm. The weights of the film coated tablets were found to be in the range of 60.98 to 91.5 mg from the above result the formulation f7 was good due to all the tablet parameters of hardness thickness weight variation as compare to other formulations. In vitro release studies were carried out in IP tablet dissolution test appratus-I employing a paddle at 50 rpm and 900 ml of gastric juice artificial as dissolution medium. The in vitro dissolution data of all the designated formulations are shown in tables 3 from dissolution data, it was evident that designed formulations displayed drug release in the range of 55.66% to 102.067% in 10 min. In vitro drug release data showed that formulation f_7 good in percentage drug release and drug dissolution profile and also better in content uniformity

as compare to other formulations.

7. Conclusion

From the present study, the following conclusions can be drawn: Filmcoated tablets of Tolterodine tartrate can be prepared by the direct compression method using MCCP 102 and lactose in definite ratio Magnesium stearate and colloidal anhydrous silica act as lubricating agent, which showed acceptable hardness of the prepared tablets. All the prepared tablet formulations were found to be good without capping and chipping. As the amount of lactose and MCCP 102 indefinite proportion showed the good parameters of tablet formulations, tablets were coated with Filmcoat Universal coating solution prepared by soaking with purified water for 20 minutes.

8. Limitation of the study

- Accelerated and real time study of the formulation was not done.
- Comparative study with marked product was not done

9. Recommendation for future work

- Stability study of the formulated product can be conducted.
- Optimization of formulations.
- Comparison with marked product can be conducted

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