AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Formulation of Tolterodine Tartrate Controlled Release MUPS Tablets by Using Novel Core and Studying the Effect of Protective Plasticizer

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ABSTRACT

Tolterodine is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. Tolterodine tartrate having side effects mainly dry mouth and other side effects like constipation ,headache ,stomach pain hence controlled release formulation is prefer for tolterodine tartrate and this controlled release formulation is also reduced the frequency of dosing. In market control release capsules dosage form is available, we have planned, new controlled release tablet dosage form which is prepared by using multi unit particulate drug delivery system. Tolterodine Tartrate controlled release MUPS tablets were formulated by using insoluble inert starting seed or core which was prepared by using extrusion spheronization technique. use of water soluble material combined with tolterodine create greater amount of osmotic pressure causing the controlled release pellets burst and dump the drug. Hence water insoluble core pellets were used in this formulation the controlled release formulation comprised of a) water insoluble insert core b) Drug loading layer comprising of tolterodine c) Controlled release coating surrounding drug layer d) pellets mixed with conventional tablet excipients compressed into tablets. The aim of this study focused on the introduction of new alternative core for formulation of control release MUPS tablets and also studied the effect of protective plasticizer coating layer on extended release pellets prior to compression into MUPS tablets.

Keywords: Tolterodine tartrate, overactive bladder, Extrusion and speronization, FBP, Insoluble core, MUPS, Protective plasticized layer.

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Received 19May 2016, Accepted 27 May 2016

Please cite this article as: Borra SP *et al.*, Formulation of Tolterodine Tartrate Controlled Release MUPS Tablets by Using Novel Core and Studying the Effect of Protective Plasticizer. American Journal of PharmTech Research 2016.

INTRODUCTION

Tolterodien tartrate capsules available in market as once a day formulation but this formulation showing high intra subject variability (Detrol LA 4mg) [1], Researchers Various approaches have been adopted to formulate tolterodine tartrate once a day formulations like once a day sustained release coated tablets[2], HPMC-based sustained release tablets[3],muco adhesive microspheres[4], silicon adhesive matrix tolterodine patches[5],PLGA microspheres[6] and hydrogel matrixes[7]. Multiple Unit Pellet Systems, widely known as MUPS, are Tablet dosage form consisting of spherical, granular subunits (pellets), These tablets disintegration into the single subunits or individual pellets immediately after administration[8], they transit shortly in stomach and promptly disperse across the huge surface area of the small intestine stabilizing the overall bioavailability and reducing the risk of dose dumping and local irritations. If until two decades ago pellets were exclusively filled into hard Gelatin capsules, they represent nowadays the ideal subunits for multi particulate tablets. In fact, MUPS present all the advantages of the production of tablets compared to capsules: higher production rates, reduced risk of tampering, lower tendency of adhering to oesophagus during swallowing and better patient compliance[9].

In fact, the compression of coated pellets into MUPS is a challenging process, in which subunits like the pellets or granules undergo structural deformation or even rupture. This may profoundly modify the drug release profile of the subunits and/or circumvent the tablet disintegration because of enhanced cohesion between pellets. If pellets are break during compression it may create batch to batch and tablet to tablet variation. to prevent the breakage of these subunits, pellets, coating material, excipients which used for compression have certain crushing strength to with standard the compressional forces. Some concepts like Moisture plasticization[10] will also produce elastic nature to pellets but during aging this concept may not stable. Introduction of new protective Plasticizer coating layer on the controlled release pellets will provide elastic strength So that controlled release pellets will not get deformed or ruptured during compression.

The embedding excipients should also deformable than the core excipients, as they should cushion the pellets by absorbing the mechanical stress during compression, they should build a supporting structure in which the subunits may be homogeneously dispersed.

MATERIALS AND METHOD

Tolterodine Tartrate reference samples (Detrol LA) 4 mg tablets were obtained from Pharmacia &Upjohn Manufactured by Pharmacia & Upjohn (which were being procured for Hetero Labs Ltd, Unit-III, and Hyderabad, India), Tolterodine tartrate drug substance was gifted by Hetero Drugs

Ltd, Hyderabad, India. Microcrystalline cellulose, grade Ceolus KG-1000 was gifted by Asahi kasei, USA. Dibasic calcium phosphate anhydrous (calipharm A) from Rhodia. Hypromellose 2910 5 CPS (Methocel E5 LV Premium) from Dow chemicals. Dehydrated alcohol (Ethanol) from Jiangya Huaxi Inernational Trade Co.Ltd. Aqous Ethylcellulose dispersion (Surelease) from colorcon. Hydroxypropyl cellulose (Klucel LF) from Aqualon Hercules. Polyethylene glycol (Polyglycol 6000 P), from clariant chemicals (India) Ltd. Crospovidone (Kollidon CL) from BASF and magnesium stearate (Ligamed-MF-2-V) from peter greven. All other Polymers and solvents used were of analytical grade.

Preparation of Tolterodine tartrate control release MUPS tablets:

The manufacturing process involves below steps for preparation of Tolterodine tartrate control release MUPS tablets

1. Manufacturing of inert Core by using extrusion spheronization
2. Drug loading of tolterodine tartrate on core pellets
3. Extended release coating on tolterodine tartrate drug loaded pellets
4. Protective plasticizer coating on tolterodine tartrate control release pellets
5. Blending or prelubrication
6. Lubrication
7. Compression
8. Film coating

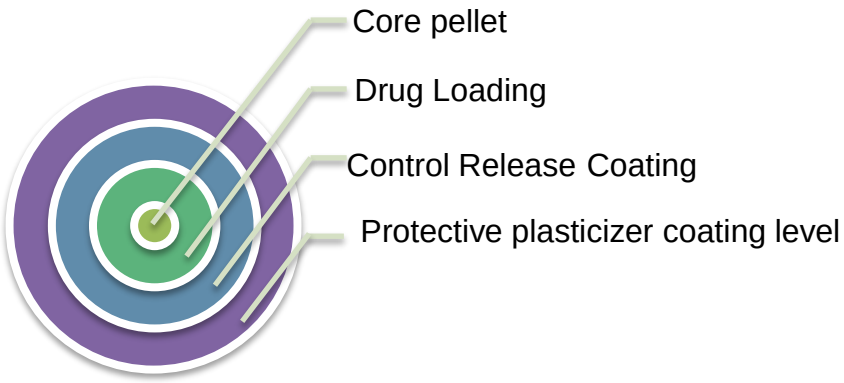

Figure 1: Final Tolterodine tartrate control release pellet

Preparation of Inert core for Tolterodine tartrate control release MUPS tablets:

Inert core is prepared by using extrusion spheronization technique, the material used in core manufacturing are Microcrystalline Cellulose, (Avicel PH 101), Dibasic calcium phosphate Anhydrous, (Calipharm A), Ethyl Acrylate and Methyl Methacrylate Copolymer dispersion (Eudragit NE 30D) and purified water.

Table 1: Composition of inert core

S.no	Ingredient	Function	Qty mg/unit		
			CP1	CP2	CP3
1	Microcrystalline Cellulose, USP/NF (Avicel PH 101)	Diluent	35	70	105
2	Dibasic calcium phosphate Anhydrous USP(Calipharm A)	Diluent	105	70	35
3	Ethyl Acrylate and Methyl Methacrylate Copolymer dispersion, USP/NF (Eudragit NE 30D) #	Binder	9.0	9.0	9.0
4	Purified water	Solvent	54	54	54
5	Purified water (Additional water)	Solvent	36	36	36

Manufacturing of inert Core by using extrustion spheronization:

Step1: Sifted Microcrystalline Cellulose, (Avicel PH 101), Dibasic calcium phosphate Anhydrous, (Calipharm A) through #20 mesh and transferred the sifted material into Rapid mixer granulator (Make: Gansons; Capacity: 2 Liters; Model: HSMG2) and mix these two excipients 10 min with impeller slow speed and chopper off and granulate the dry mix by using eudragit NE 30 D and followed by purified water. Below process parameters are used to prepare wet mass for extrusion and spheronization.

Table2: Granulation Parameters

S.no	Time in min	Impeller	Chopper
Dry mixing	10 min	Slow	Off
Granulation			
Binder addition	1 min	Slow	off
Purified water	1 min	Slow	slow
Kneading	30 sec	Slow	slow

Step 2: Pass the wet mass of Step No. 1through extruder (Make: Umang Pharmateck Pvt Ltd) fitted with 0.8 mm die roll at medium speed (25 ± 5 rpm)

Step 3: Load the collected extrudes of Step No. 2 into spheronizer (Make: Umang Pharmateck Pvt Ltd) fitted with 1.5 mm chequered plate for spheroinization into pellets by using Rotating speed 200 to 600 rpm, Rotation time 4-9 minutes.

Step 4: Drying was performed by Rapid dryer (Make: Retsch ; Type : TG 100) having Inlet air temperature 60°C and dried up LOD of pellets (at 105°C by auto mode using IR moisture analyzer) is 0.5% to 1.5%

Step 5: Sift the dried core pellets of Step No. 4 through mesh #25 and collect the passed pellets and Sift the passed pellets through mesh #30 and collect retentions Collect the #25 / #30 pellets of Step No. 4 and discard the remaining pellets

Preparation tolterodine tartrate drug loaded pellets.

Tolterodine tartrate drug loaded pellets was prepared by using hydroxypropyl methyl cellulose as binder in water and ethanol mixture.

Table 3: Composition of Drug Loading

S.no	Ingredient	Function	Qty mg/unit				
			DC1	DC2	DC3	DC4	DC5
Drug loading:							
1	Core pellets		140.0	150.0	160.0	150.0	150.0
2	Tolterodine tartrate	Active	4.0	4.0	4.0	4.0	4.0
3	Hypromellose USP 2910 5CPS (Methocel E5 LV Premium)	Binder	2.0	2.0	2.0	1.5	2.5
4	Dehydrated alcohol, USP (Ethanol)	Solvent	200.0	200.0	200.0	200.0	200.0
5	Purified water, HIS/USP/Ph.Eur	Solvent	25.0	25.0	25.0	25.0	25.0

Dissolved the drug and hypromellose USP 2910 5 cps in ethanol and purified water co solvent mixture and sprayed the drug solution on the core pellets by using fluid bed processor with below process parameters.

Table 4: Fluid Bed Processor Process Parameters for Drug loading

Formulation Development	Lab Scale
Equipment model	Glatt GPCG-1.1
Batch size	1 kg
Fluid bed insert	6″ Wurster
Partition height	15 mm
Distribution plate	Plate-B
Nozzle tip diameter	1.0 mm
Nozzle tip/air cap position	Flush
Product temperature	28-32 ºC
Spray rate	5-9 g/min
Atomization air pressure	0.90 bar
Air volume	Approx. 50% of flap setting

After completion of drug loading reduced the fluidization air flow to suitable level and dry the drug loaded pellets at the product temperature of 45 ± 5°C till to get LOD in less than 1% at 105°C by auto mode using suitable moisture analyzer. Sifted the dried drug loaded pellets through mesh #25 and #30 meshes and collected desired fraction of pellets #25/30 for control release coating.

Table 5: Composition of Controlled release coating layer

S.no	Ingredient	Function	Qty mg/unit				
			EC1	**EC2**	**EC3**	**EC4**	**EC5**
Controlled Release Coating:							
1	Aqueous Ethylcellulose Dispersion E-7-19010, IH (Surelease)	Control release polymer	Drug to polymer ratio - 1:0.10 and % wt build up 10%	Drug to polymer ratio - 1:0.15 and % wt build up 10%	Drug to polymer ratio - 1:0.20 and % wt build up 10%	Drug to polymer ratio - 1:0.15 and % wt build up 12%	Drug to polymer ratio -1:0.15 and % wt build up 15%
2	Hypromellose USP 2910 5CPS (Methocel E5LVPremium)	Pore former					
3	Purified water, HIS/USP/Ph.Eur		18.00	18.00	18.00	18.00	18.00

Tolterodine tartrate control release coating was done by using Aqueous ethyl cellulose dispersion (Surelease) used as control release polymer and hydroxyl propylmethyl cellulose used as pore former.

Prepared the aqueous suspension of control release coating by using Aqueous Ethylcellulose Dispersion E-7-19010,purified water and Hypromellose USP 2910 5CPS and coated on the Tolterodine Tartrate drug loaded pellets by using Fluid bed dryer with below parameters.

Table 6: Fluid bed dryer parameters for Controlled Release Coating

Formulation Development	Lab Scale
Equipment model	Glatt GPCG-1.1
Batch size	1 kg
Fluid bed insert	6″ Wurster
Partition height	15 mm
Distribution plate	Plate-B
Nozzle tip diameter	1.0 mm
Nozzle tip/air cap position	Flush
Product temperature	40-45 ºC
Spray rate	6-8 g/min
Atomization air pressure	1.20 bar
Air volume	Approx. 50% of flap setting

After completion of control release coating, dried the pellets at the product temperature of 50 ± 5°C till to get LOD in less than 1% at 105°C by auto mode using suitable moisture analyzer. Sifted the dried drug loaded pellets through mesh #25 and #30 meshes and collected desired fraction of pellets #25/30 for control release coating.

Preparation Protective Plasticizer coating layer on tolterodine tartrate control release pellets.

Protective plasticized coating is important for MUPS tablets, as this layer provide elastic nature to pellets and protect the pellets during compression. Protective plasticized coating coating was done by using excipients having plasticizer in nature Hydroxypropyl cellulose (Klucel LF) and Polyethylene glycol-6000.

Table 7: Composition of Plasticizer coating

S.no	Ingredient	Function	Qty mg/unit		
			FC1 10%	FC2 12%	FC3 15%
Plasticizer coating: (10% weight build up)					
1	Hydroxypropyl cellulose (Klucel LF)	Binder cum plasticizer	12.25	14.70	18.38
2	Polyethylene glycol-6000	plasticizer	5.25	6.30	7.88
3	Isopropyl Alcohol, USP	solvent	266	320	400
4	Methylene Chloride, USP/NF	solvent	133	160	200
5	Purified Water, IHS/USP/Ph.Eur	solvent	63	75	94

Dissolved the Hydroxypropyl cellulose (Klucel LF) and Polyethylene glycol-6000 in Isopropyl Alcohol, Methylene Chloride & Purified water and the prepared coating solution was sprayed on control release pellets by using below parameters.

Table 8: Fluid Bed Processor Process Parameters for Plasticizer coating

Formulation Development	Lab Scale
Equipment model	Glatt GPCG-1.1
Batch size	1 kg
Fluid bed insert	6″ Wurster
Partition height	15 mm
Distribution plate	Plate-B
Nozzle tip diameter	1.0 mm
Nozzle tip/air cap position	Flush
Product temperature	28-32 ºC
Spray rate	6-8 g/min
Atomization air pressure	1.3 bar
Air volume	Approx. 50% of flap setting

After completion of Protective Plasticizer coating, dried the pellets at the product temperature of 50 ± 5°C till to get LOD in less than 1% at 105°C by auto mode using suitable moisture analyzer. Sifted the dried drug loaded pellets through mesh #25 and #30 meshes and collected desired fraction of pellets #20/30 for control release coating.

Compression and Film coating of Protective plasticized control release tolterodine tartrate pellets:

Compression was done by using Compression machine (Mini press-II MT; Make: Karnavati Model: 12 station "Multi" tooling (D, B&BB)), 11.30 mm**,** round shaped, bevel concave punches embossed with **'**J' on the lower punch and '77' on upper punch separating 7 & 7 with score line (Parle Elizabeth Tools Pvt. Ltd) and finally film coating was done by using Coater (Make: Gansons; Model: GAC 275; Capacity: 500 g). The final formula is

Table- 9: Tolterodine tartrate controlled release MUPS Tablets Final Formula

S.no	Ingredient	Function	Qty mg/unit			
			T1	T2	T3	T4
Drug loading:						
1	Core pellets		150.00	150.00	150.00	150.00
2	*Tolterodine tartrate, IH*$^{\Theta}$	Active	4.000	4.000	4.000	4.000
3	*Hypromellose USP 2910 5CPS (Methocel E5 LV Premium)*	Binder	2.00	2.00	2.00	2.00
4	Dehydrated alcohol, USP (Ethanol) $^{@}$	solvent	100.000	100.000	100.000	100.000
5	Purified water, HIS/USP/Ph.Eur $^{@}$	solvent	50.000	50.000	50.000	50.000
			156.00	156.00	156.00	156.00

Extended Release Coating:						
6	*Aqueous Ethylcellulose Dispersion E-7-19010, IH (Surelease)* $^{\mu}$	Extended release polymer	15.00	15.00	15.00	15.00
9	*Hypromellose USP 2910 5CPS (Methocel E5LVPremium)*	Pore former	2.00	2.00	2.00	2.00
10	*Purified water*		52.192	52.192	52.192	52.192
			175.00	175.00	175.00	175.00
Protective plasticizer coating :						
			0%	10%	12%	15%
11	Hydroxypropyl cellulose (Klucel LF)	Binder	0.00	12.25	14.70	18.38
12	Polyethylene glycol-6000	Plasticizer	0.00	5.25	6.30	7.88
13	Isopropyl alcohol	solvent	0.00	266	320	400
14	Methylene chloride	solvent	0.00	133	160	200
15	Purified water	solvent	0.00	63	75	94
			0.00	17.50	21.00	26.25
			175.00	192.5	196.00	201.25
Pre-Lubrication:						
16	Micro crystalline cellulose (Ceolus Kg-1000)	Diluent	227.81	210.31	206.81	201.56
17	Polyethylene glycol-6000	Plasticizer	67.19	67.19	67.19	67.19
18	Crospovidone (Kollidon-CL)	Disintegrate	25.00	25.00	25.00	25.00
Lubrication:						
19	Magnesium stearate	Lubricant	5.00	5.00	5.00	5.00
			500.00	500.00	500.00	500.00
Film coating:						
20	Opadry white	Film coating	15.00	15.00	15.00	15.00
	Total weight of tablet		515.00	515.00	515.00	515.00

Characterization of inert core pellets:

Inert core is a water insoluble seed core. It is used as a seed core of controlled release and taste masked pellets. It has various superior characteristics as a seed core for drug layering and control release coating. It has composition of insoluble materials Microcrystalline Cellulose, Dibasic calcium phosphate and Ethyl Acrylate and Methyl Methacrylate Copolymer dispersion, these inert cores having good friability, spherical and narrow particle size. Bulk density and tapped density is measured by using Tap density tester Make: Electrolab;Model: ETD-1020.

Flow properties, Bulk and tapped density, Hausner Ratio of inert core:

Bulk density is the ratio of the weight of pellets to the volume it occupies. It is expressed as gm/ml. Volume occupied by pellets includes volume of the solid portion of the pellets voids between the particles.

$$\textbf{Bulk density} = \frac{\textbf{Weight of the powder}}{\textbf{Volume of the powder}}$$

Tapped density = Weight of the powder

Volume of the powder after tapping

Compressibility index is indirectly related to the relative flow rate, cohesiveness and particle size of a powder. The compressibility of a material can be estimated from the tap and bulk density measurements.

Compressibility index = Tapped density - Bulk density X 100

Tapped density

Hausner's ratio = Tapped density

Bulk density

Based on bulk density, tapped density, compressibility index and Hausner's ratio data, the API was characterized as good flow.

Particle size distribution of inert core:

Inert core pellets was having narrow particle size distribution was selected for drug loading and control release, the manufacturing process yields more than 95% desired fraction. final fraction was used for further studies is 90% pellets should pass through #25 mesh and 90% should retains on #30 mesh. PSD analysis is performed by using Sieve shaker Make: Retsch ; Type : AS 200 digit

Friability (mechanical strength) of inert core:

Test method – friability test

Method – B (Ph. Eur. Method 2.9.41)

Apparatus (Oscillating apparatus):

The apparatus granule friability tester (Model –EGF-1) consist of a 105 ml glass container, containing the granules to be examined, which is subjected to horizontal oscillations. The frequency and the duration of the oscillations can be varied continuously. The frequency can be adjusted, using a scale, time value 0 – 400 oscillations/min. The duration can be set to a value in the range 0 – 9999.

Calculation:

$$F = \frac{m1 - m2}{m\,1} \times 100$$

F : Friability

m 1 : mass of the granules before the test in grams

m 2 : mass of the granules after the test in grams

ASPECT RATIO

It is defined as the ratio of the length of a pellet divided by the width, with pellets being considered spherical (round) if the aspect ratio lies between 1.00 to1.20

ROUNDNESS

It is a measurement of the length/width relationship, with values in the range of 0 - 1. A perfect circle has roundness 1.0.

Roundness is determined using the equation:

Roundness = (4 * π * A) / P2

Where,

A is the measured area of the pellet

P is the perimeter of the pellet

EVALUATION FINAL TOLTERODINE TARTRATE CONTROL RELEASE MUPS TABLETS:

Assay (By HPLC) Tolterodine tartrate ($C_{22}H_{31}NO.C_4H_6O_6$)

Accuratly weigh and transfer pellets equivalent about 20 mg of tolterodine tartrate in to 100 ml volumetric flask. Add about 60 ml of diluents (water and acetonitril in the ration of 40:60) and sonicate for not less than 30 minutes with occasional shaking (Maintain the sonicator bath temperature between 20-25°C).Dilute to volume with diluents and mix. Centrifuge a portion of the solution at about 5000 ppm for 10 minutes.

Transfer 5.0 ml of the clear supernatant solution into a 25 ml volumetric flask. Dilute to volume with diluents and mix. Filter a portion of the solution through 0.45 micron membrane filter and discard first few of filtrate.

Chromatographic conditions:

Column: Purospher star RP-18,150 x 4.6 mm, 5 micron

Flow rate: 1.0 ml/minute

Injection volume: 10 µl

Column Temperature: 30^0C

Run Time: 10 minutes

Detection: UV, 210 nm

The retention time of tolterodine tartrate peak is about 6 minutes.

The column efficiency as determined for tolterodine peak from standard solution is not less than 2000 theoretical plates and tailing factor for the same peak is not more than 2.0

Calculation:

% of Tolterodine tartrate

$$\frac{A_T}{A_S} = \frac{W_S}{50} \times \frac{2}{50} \times \frac{100}{W_T} \times \frac{25}{5} \times \frac{P}{100} \times 100$$

Where,

A_T = Area of Tolterodine peak in sample solution

A_S = Area of Tolterodine peak in standard solution

W_S =Weight of Tolterodine tartrate working standard taken, in mg

W_T =Weight of sample taken, in mg

P = % Purity of Tolterodine tartrate working standard used (on as is basis)

In vitro drug release studies:

The in vitro drug release profile for pellets as well as tablets was performed using USP type I dissolution apparatus. The conditions maintained were shown in the table as follows:

The samples were drawn at specified time intervals and the obtained samples were analyzed by using HPLC method. The cumulative percentage release was calculated.

Table 10: Dissolution Method

Instrument	**Electro lab- USP type 1 dissolution test apparatus.**
Dissolution medium	Ph 6.8 Phosphate buffer
Apparatus	USP apparatus – I (Basket type)
Temperature	37±0.50C
RPM	100
Volume of medium	900 ml
Sampling intervals	1,2,3,4,5,7
Sample volume	5 ml withdrawn and replaced with 5 ml of dissolution medium

DSC analysis :

DSC analysis of pure drug and tablets was performed.

RESULTS AND DISCUSSION:

Table 11: Core pellets evaluation:

Sample Name / Batch No.	**Particle Size (As per A.S.T.M)**	**%Yield**	**Bulk Density**	**Friability**	**Aspect Ratio**	**Roundness**
Tolterodine Tartrate (B.no: CP1)	% retain on 20 mesh – 15 % passes through 25 mesh - 7	95%	0.90 g/ml	0.014 %	1.06	0.8473
Tolterodine Tartrate (B.no:CP2)	% retain on 20 mesh – 5 % passes through 25 mesh - 3	89%	0.90 g/ml	0.028 %	1.04	0.9267
Tolterodine Tartrate (B.no :CP3)	% retain on 20 mesh – 15 % passes through 25 mesh - 7	92%	0.90 g/ml	0.015 %	1.09	0.8419

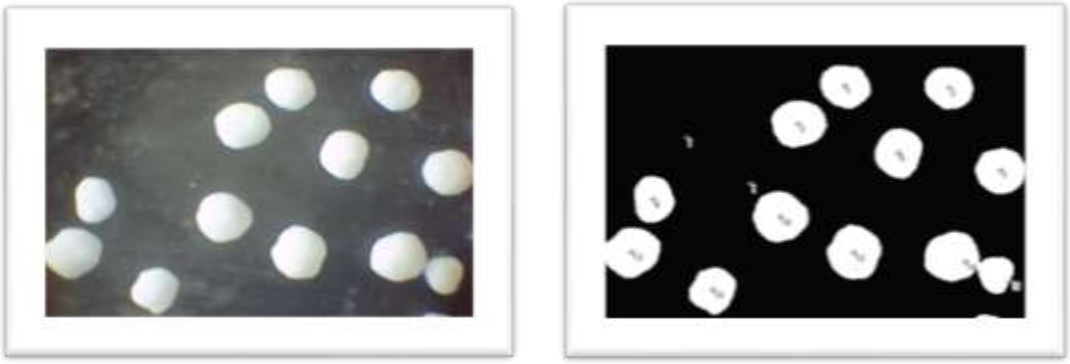

Figure 2: Inert core pellets, Batch No: CP1

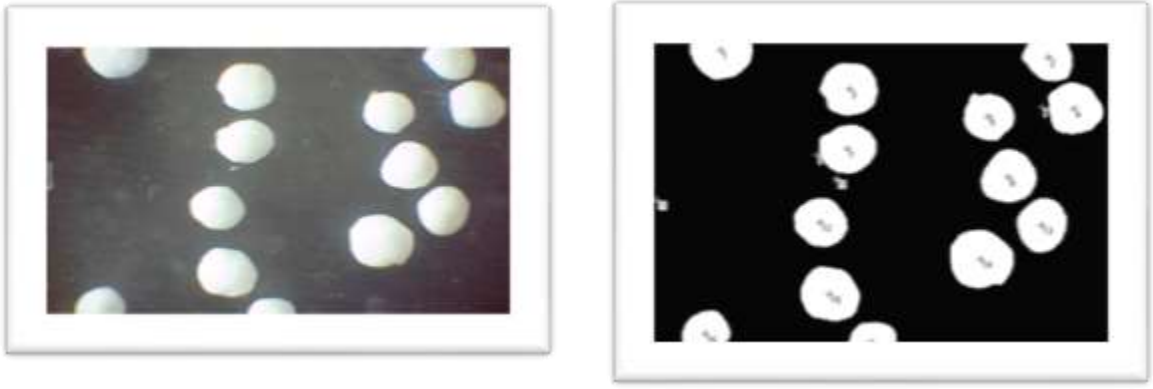

Figure 3: Inert core pellets, Batch No: CP2

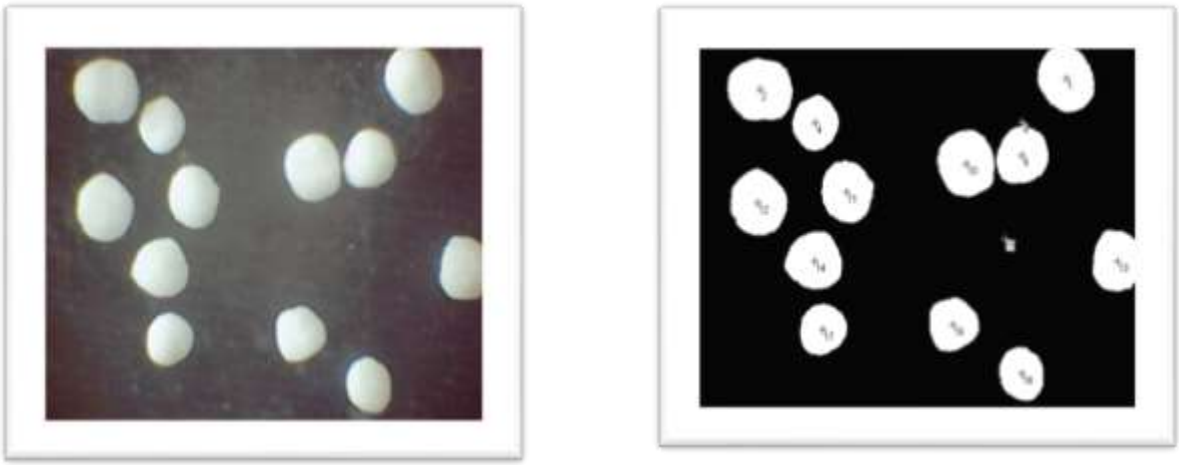

Figure 4: Inert core pellets, Batch No: CP3

Core Pellets Yield:

From above batches the trail CP1 got 95% of yield only, where as CP2 and CP3 got 89%, 92% yield respectively and selected CP1 for further trails.

Table 12: Drug loaded pellets

S.no	DC1	DC2	DC3	DC4	DC5
Assay	98	101	100	95	101

All the batches were showed there is no significant difference in assay values, hence from the above batches DC2 was selected for further trails.

Extended release coating:

Table 13: In-vitro dissolution profiles of tolterodine tartrate control release pellets

Time in hours	% Cumulative drug released					
	Reference (Detrol LA)	EC1	EC2	EC3	EC4	EC5
1	10	7	27	45	15	9
2	28	20	36	68	32	28
3	49	31	54	78	45	43
5	80	62	89	90	75	68
7	88	78	93	90	92	87

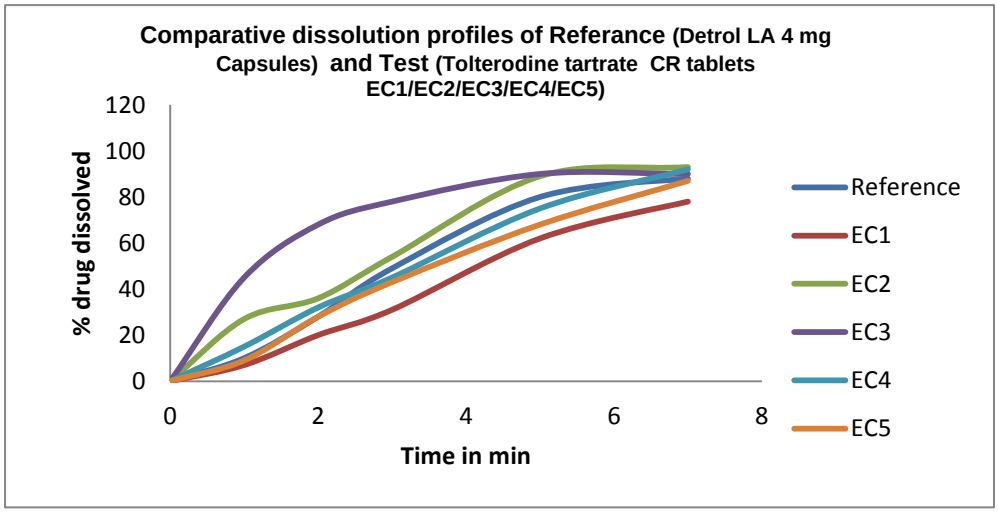

Figure-5 Comparative dissolution profiles of Reference (Detrol LA 4 mg Capsules) and Test (Tolterodine Tartrate CR tablets)

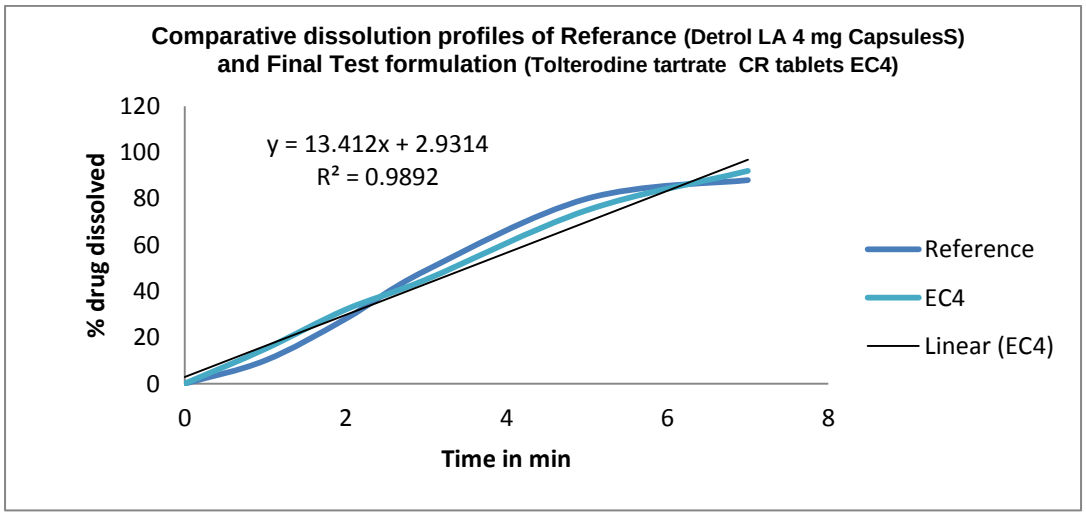

Figure 6: Comparative dissolution profiles of Reference (Detrol LA 4 mg Capsules) and Final test formulation (Tolterodine Tartrate CR tablets EC4)

From the screening trails EC1, EC2 and EC3 we observed that EC2 formulation was near to reference hence we selected EC2 formulation and selected 1:0.15 polymer to pore former ratio was selected for further trails. From trails EC4 and EC5 we selected EC4 formulation.

Protective plasticizer coating:

To optimize Protective plasticizer coating we given different percentage of weight bulid up to protect extended release layer from cracking during compression.

Table 14: Drug Dissolution

Time in hours	% Cumulative drug released			
	Reference (Detrol LA)	FC1	FC2	FC3
1	10	12	14	14
2	28	31	30	31
3	49	46	44	48
5	80	74	77	76
7	88	90	92	91

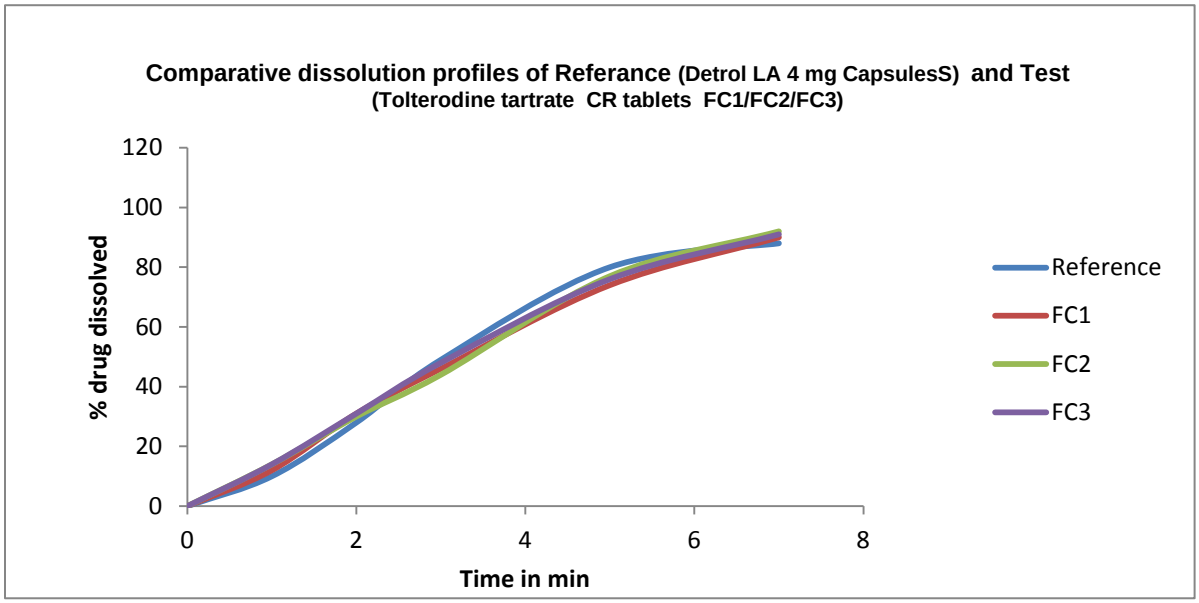

Figure 7 Comparative dissolution profiles of Reference (Detrol LA 4 mg Capsules) and Test (Tolterodine Tartrate CR tablets FC1/FC2/FC3)

From above results indicates that from 10 % coating to 15% coating, there is no significant difference between dissolution profiles.

Table 15: Comparative dissolution profile between Tolterodine tartrate control release tablets contain with and without protective plasticizer coating control release pellets.

Time in hours	% Cumulative drug released					
	Reference Detrol LA 4 mg capsules	EC4	T1	T2	T3	T4
1	10	15	20	12	11	14
2	28	32	39	29	30	31

3	49	45	56	46	45	48
5	80	75	85	75	77	77
7	88	92	90	92	92	92

From the above data it indicates with out Protective plasticizer coating tolterodine tartrate control release tablets formulation T1 showing higher dissolution profiles compared to extended release pellets hence it indicates that the formulation without Protective plasticizer layer extended release pellets are breaking, where as the formulation which contains Protective plasticizer layer all MUPS tablets showing similar dissolution profiles compared to pellets.

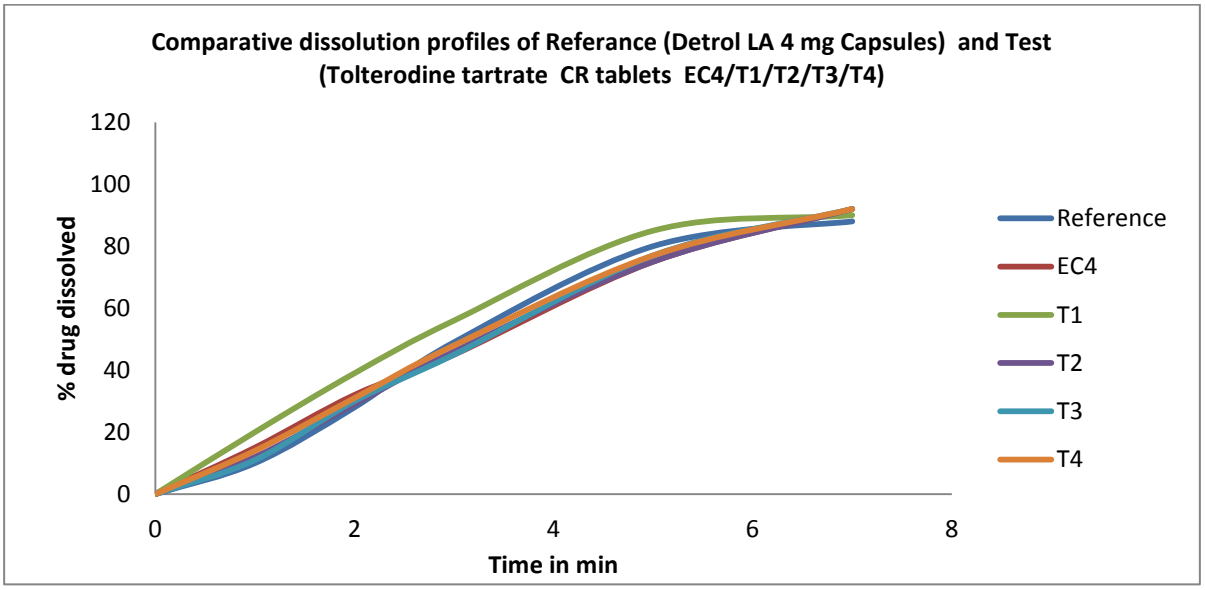

Figure-8 Comparative dissolution profiles of Reference (Detrol LA 4 mg Capsules) and Test (Tolterodine Tartrate CR tablets EC4/T1/T2/T3/T4)

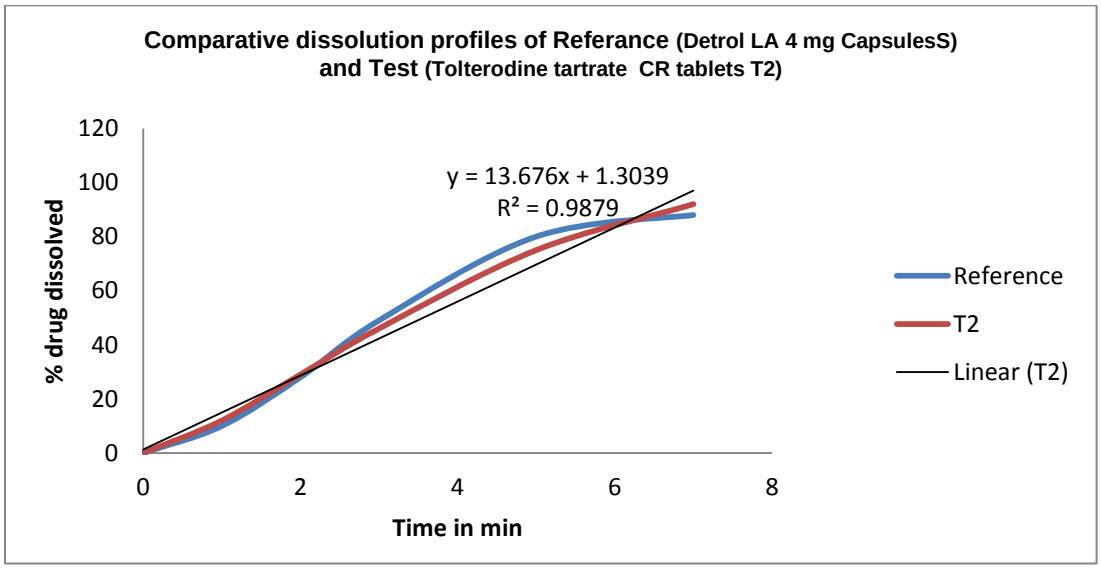

Figure-9 Comparative dissolution profiles of Reference (Detrol LA 4 mg Capsules) and Test (Tolterodine Tartrate CR tablets T2)

Table- 16: Evaluation final tolterodine tartrate control release MUPS Tablets

Batch No→ Parameters↓	**Reference Detrol LA 4mg B.no: # C100378**	**T1**	**T2**	**T3**	**T4**
Description	Blue color with symbol and 4 printed in white ink.	White to off white pellets	White to off white, round, bevel edged, biconvex, speckled tablets debossed with 'J' on one side and '77' on other side separating 7 & 7 with score line.		
Strength (Label claim)	Each extended release capsule contains 4 mg of Tolterodine tartrate	Each 175 mg of Control release pellets contains 4 mg of Tolterodine tartrate	Each Control release film coated tablets contains 4 mg of Tolterodine tartrate		
Weight of Capsule or Tablets (mg) byusing. Analytical Balance Make :Sartorius ; Model :LA 120S	237.25	175 mg	515 mg	515 mg	515 mg
Thickness (mm) by using Vernier calipers Make: Mitutoyo ; Model : CD-6" CSX	NA	NA	5.4 0 mm – 5.70 mm	5.4 0 mm – 5.70 mm	5.4 0 mm – 5.70 mm
Hardness (kp) by using Hardness tester Make: Pharmatest ; Type: PTB – 311E	NA	NA	12 to15 kp	12 to15 kp	12 to15 kp
Lock length (mm) Vernier calipers Make: Mitutoyo ; Model : CD-6" CSX	15.67	NA	NA	NA	NA
% Friability	NA	0.09	0.1	0.09	0.1
Assay, % w/w of labeled amount by using HPLC method.	98.80	99.0	100	101	99

NA : Not applicable

DSC analysis:

From the DSC analysis it is concluded that, there is no significant interaction was observed between the drug and excipients.

CONCLUSION:

In present study new core was Successfully prepared by using extrusion and spheronization technique, evaluated it properties like Particle Size, Bulk Density, Friability, Aspect Ratio, Roundness, and Successfully used it for preparation of tolterodine tartrate control release mups tablets. We does not find any breakages of pellets during various types of coating. Based on comparative dissolution profiles of with Protective plasticizer coated pellets and without Protective plasticizer coating pellets, it was concluded that this Protective plasticizer layer protects the pellets from breakage or cracking during the compression. Finally we developed tolterodine tartrate control release tablet and compared these mups tablets with marketed tolterodine tartrate extended release capsules, both having similar dissolution profiles. Results of XRD, residual solvents, relative substance indicates that product is compatible with the materials which are used in development of tolterodine tartrate control release MUPS tablets.

ACKNOWLEDGMENTS:

The authors are grateful for support from the Hetero Labs Ltd, Hyderabad.

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