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EVALUATION OF DIFFERENT SYNTHETIC AND NATURAL POLYMERS AS PROTECTIVE LAYER POLYMERS ON TOLTERODINE TARTRATE CONTROL RELEASE MUPS TABLETS

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Keywords:

Multi-unit pellet system (MUPS), Control release, Compression of pellets, Drug release, Natural and Synthetic Polymers

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ABSTRACT: Evaluation of different natural and synthetic polymers as protective layer polymers in the manufacturing of control release multi-unit pellet tablets, Tolterodine Tartrate was selected as a model drug with aqueous ethylcellulose suspension is used as control release polymer. Tolterodine Tartrate is highly soluble BCS Class- I molecule, hence selected aqueous solution layering method for drug loading in Fluid bed processor, Optimized formulation was manufactured by using seal coating on microcrystalline cellulose pellets followed by drug loading and control release coating applied by using solution and suspension layering method respectively in Fluid bed processor. Given coating on these functional coated pellets with different natural and synthetic polymers like Klucel, Polyethylene glycol 6000, Hypromellose 5 cps, Guar gum, and Xanthan gum. Evaluated these pellets for physical characterization, DSC, SEM and comparative *in-vitro* dissolution profiles. Drug release profiles of Control release MUPS tablets containing protective layer coating was compared to those control release pellets and f2 values observed was more than 50 with Klucel, Polyethylene glycol 6000, Hypromellose 5 cps, Guar gum, and Xanthan gum coated multi-unit pellet tablets respectively. whereas faster release profiles were observed with Polyethylene glycol 6000 protective layer MUPS tablets. Based on these dissolution profiles it was concluded that by applying low viscous natural or synthetic binders on functional coating pellets gives good protection to functional coating pellets from damage during compression and also provided similar dissolution profiles compared to control release pellets. It is a very effective and potential strategy for manufacturing of MUPS tablets.

INTRODUCTION: Tolterodine tartrate is chemically (R)-N,N-diisopropyl-3-(2-hydroxy-5-methyl phenyl)-3- phenylpropanolamine L-hydrogen tartrate. The molecular formula is $C_{26}H_{37}NO_7$ with a molecular weight of 473.58. Tolterodine is a competitive muscarinic receptor antagonist.

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Both urinary bladder contraction and salivation are mediated *via* cholinergic muscarinic receptors. After oral administration, Tolterodine is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite.

The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of Tolterodine, contributes significantly to the therapeutic effect. Both Tolterodine and the 5-hydroxymethyl metabolite exhibit a high specificity for muscarinic receptors, since either show negligible activity or affinity for other

neurotransmitter receptors and other potential cellular targets, such as calcium channels [1-4]. Tolterodine has a pronounced effect on bladder function. The main effects of Tolterodine are an increase in residual urine, reflecting an incomplete emptying of the bladder, and a decrease in detrusor pressure, consistent with an antimuscarinic action on the lower urinary tract [5].

Tolterodine and its active metabolite, 5-hydroxymethyl tolterodine, act as competitive antagonists at muscarinic receptors. Cmax and area under the concentration-time curve (AUC) determined after a dosage of tolterodine are dose-proportional over the range of 1 to 4 mg. Based on the sum of unbound serum concentrations of tolterodine and the 5- hydroxymethyl metabolite ("active moiety"), the AUC of tolterodine extended release 4 mg daily is equivalent to tolterodine immediate release 4 mg (2 mg bid). Cmax and Cmin levels of tolterodine release are about 75% and 150% of tolterodine immediate release, respectively. Maximum serum concentrations of tolterodine extended release are observed 2 to 6 hours after dose administration [6-9].

Pharmaceutical solid dosage forms are using a functional coating to modify the release. Due to the disadvantages of coated single-unit dosage forms, such as dose dumping, less predictable gastrointestinal (GI) transit times and may potentially lodge in restrictions within the GI tract, which could lead to variable drug absorption and cause damage to the gastric mucosa if the drug is irritant, and hence coated multi-particulates are preferred. Coated multi-particulates can eventually be filled into capsules or compressed into tablets. Tablet dosage form is more desirable as unit production costs of considerably lower and machinery is more easily available. However, some challenges are there in the manufacturing of multi-unit pellet tablets, compression forces can result in damage to the functional coating, its function segregation pellets during compression. Hence, it is important to understand the factors affecting coat damage during compression [10-12] and segregation of pellets during the manufacturing of tablets.

There are many relevant articles and literature available on the preparation of pellets and coating technology. However, only a few research articles discuss the issue of compaction of pellets into tablets [13]. A different techniques were used to prevent the damage of functional layers in past work, but remains an unmet need for drug delivery, some of the techniques are use of cushioning excipients and/or compressible excipients, novel granulation techniques to protect the coating layer against fracture during compaction [14-19], improved by thermal exposure [20], Layering the top surface of beads with compressible excipients, such as microcrystalline cellulose (MCC), to modify the mechanical properties of the beads was successful in addressing this issue. This approach, however, requires a huge amount of the layering excipients, but still with mixed results [21].

In this article we given protective layering on the functional coated pellets with different natural (Guar gum and Xanthan gum) and synthetic polymers (Klucel, Polyethylene glycol 6000, Hypromellose 5 cps) and studied the effect of compression on damage of function layer, for this study tolterodine tartrate is selected as model drug, it is freely soluble in water.

MATERIALS AND METHODS: 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), Ceolus KG-1000 was gifted by Asahi Kasei, USA. Calipharm A from Rhodia. Methocel E5 LV Premium from Dow chemical's. Aquos ethylcellulose dispersion from colorcon. Ethanol from Jiangya Huaxi International Trade Co.Ltd. Klucel LF from Aqualon Hercules. Polyglycol 6000 P from Clariant Chemicals (India) Ltd. Kollidon C from BASF and magnesium stearate from peter greven. All other Polymers and solvents used were of analytical grade. Tolterodine tartrate drug substance was gifted by Hetero Drugs Ltd., Hyderabad, India

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.

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.

Manufacturing of Inert Core by using Extrusion Spheronization:

Step 1: 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.

TABLE 1: 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. 1 through 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 spheronization into pellets by using Rotating speed 200 to 600 rpm, Rotation time 4-9 min.

Step 4: Drying was performed by the 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 were prepared by using hydroxypropylmethyl cellulose as a binder in water and ethanol mixture. 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 a fluid bed processor with below process parameters.

TABLE 2: 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 the drug, loading reduced the fluidization air flow to a 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 the desired fraction of pellets #25/30 for control release coating. Tolterodine tartrate control release coating was done by using aqua coat ECD 30d used as control release polymer and hydroxyl propyl methyl cellulose used as pore former.

Prepared the aqueous suspension of control release coating by using Aqueous Ethylcellulose Dispersion E-7-19040, 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 3: 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, drying 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 the desired fraction of pellets #25/30 for control release coating.

Preparation Protective Plasticizer Coating Layer on Tolterodine Tartrate Control Release Pellets: The protective plasticized coating is important for MUPS tablets, as this layer provide elastic nature to pellets and protect the pellets during compression. The protective plasticized coating was done by using excipients having plasticizer in nature Hydroxypropyl cellulose (Klucel LF) and Polyethylene glycol-6000.

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

TABLE 4: 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, drying 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 the 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 stations "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).

TABLE 5: TOLTERODINE TARTRATE CONTROLLED RELEASE MUPS TABLETS FINAL FORMULA

S. no.	Ingredient	Function	Qty mg/unit					
			T1	T5	T6	T7	T8	T9
	Core pellets							
1	Microcrystalline Cellulose, USP/NF (Avicel PH 101)	Diluent	70.00	70.00	70.00	70.00	70.00	70.00
2	Dibasic calcium phosphate Anhydrous USP(Calipharm A)	Diluent	70.00	70.00	70.00	70.00	70.00	70.00
3	Ethyl Acrylate and Methyl Methacrylate Copolymer dispersion, USP/NF (Eudragit NE 30D)	Binder	10.00	10.00	10.00	10.00	10.00	10.00
4	Purified water	Solvent	q.s	q.s	q.s	q.s	q.s	q.s
	Drug loading							
5	Core pellets		150.00	150.00	150.00	150.00	150.00	150.00
6	Tolterodine tartrate, IH$^{\Theta}$	Active	4.000	4.000	4.000	4.000	4.000	4.000
7	Hypromellose USP 2910 5CPS (Methocel E5 LV Premium)	Binder	2.00	2.00	2.00	2.00	2.00	2.00
8	Dehydrated alcohol, USP (Ethanol)	solvent	100.000	100.000	100.000	100.000	100.000	100.000
9	Purified water, HIS/USP/Ph.Eur	solvent	50.000	50.000	50.000	50.000	50.000	50.000
			156.00	156.00	156.00	156.00	156.00	156.00

	Extended release coating							
10	Aqueous Ethylcellulose Dispersion E-7-19040, IH (Surelease)	Extended-release polymer	15.00	15.00	15.00	15.00	15.00	15.00
11	Hypromellose USP 2910 5CPS (Methocel E5LVPremium)	Pore former	2.00	2.00	2.00	2.00	2.00	2.00
12	Purified water		52.192	52.192	52.192	52.192	52.192	52.192
			175.00	175.00	175.00	175.00	175.00	175.00
	Protective plasticizer coating:							
13	Hydroxypropyl cellulose (Klucel LF)	Binder	---	17.5	---	---	---	---
14	Polyethylene glycol-6000	Binder	---	---	17.5	---	---	---
15	Hypromellose 5 cps	Binder	---	---	---	17.5	---	---
16	Guar gum	Binder	---	---	---	---	17.5	---
17	Xanthan gum	Binder	---	---	---	---	---	17.5
18	Isopropyl alcohol	solvent	q.s	q.s	q.s	q.s	q.s	q.s
19	Methylene chloride	solvent	q.s	q.s	q.s	q.s	q.s	q.s
20	Purified water	solvent	q.s	q.s	q.s	q.s	q.s	q.s
			175.00	192.5	192.5	192.5	192.5	192.5
	Pre-lubrication							
21	Micro crystalline cellulose (Ceolus Kg-1000)	Diluent	227.81	210.31	210.31	210.31	210.31	210.31
22	Polyethylene glycol-6000	Plasticizer	67.19	67.19	67.19	67.19	67.19	67.19
23	Crospovidone (Kollidon-CL)	Disintegrate	25.00	25.00	25.00	25.00	25.00	25.00
		Lubrication:						
24	Magnesium stearate	Lubricant	5.00	5.00	5.00	5.00	5.00	5.00
	Core tablet weight		500.00	500.00	500.00	500.00	500.00	500.00
	Film coating							
25	Opadry white	Film coating	15.00	15.00	15.00	15.00	15.00	15.00
	Total weight of the tablet		515.00	515.00	515.00	515.00	515.00	515.00

Characterization of the Protective Layer Coated Pellets and Precompression Blend:

Apparent Bulk Density: The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the contribution of the interparticulate void volume. Hence, the bulk density depends on both the density of powder particles and the spatial arrangement of particles in the powder bed. The bulk density is expressed in grams per ml (g/ml).

The bulk density was determined by transferring the accurately weighted amount of the sample to the graduated measuring cylinder and noted initial volume. The bulk density of the sample was then calculated by using the below formula.

$$\text{Bulk density} = \text{Mass (M)} / \text{Bulk volume } (V_0)$$

Tapped Density (g/ml): The tapped density was determined by using tapped density apparatus make. Electro lab, Model ETD-1020 the procedure involves the weighed quantity of sample was taken in 250 ml a measuring cylinder and the cylinder was kept in cylinder holder and allowed to tap for 10, 500, and 1250 taps on the same powder sample and read the corresponding volumes V10, V500, and V1250 to the nearest graduated unit. If the difference between V500 and V1250 is less than or equal to 2 % V1250 is the tapped volume If the difference between V500 and V1250 exceeds 2% repeated in increments such as 1250 taps, until the difference between succeeding measurements is less than or equal to 2%. Fewer taps may be appropriate for some samples when validated. The tapped density was determined by using the following formula.

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

Compressibility Index or Carr's Index: The percentage Compressibility of the drug was determined by using the following formula. It is measured in percentage (%) and limits were presented in **Table 6**.

$$\text{Compressibility index (\%)} = [(\text{Tapped density} - \text{Bulk Density}) / \text{Tapped density}] \times 100$$

TABLE 6: LIMITS FOR CARR's INDEX

Carr's index (%)	Flow character
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very, very poor

Hausner's ratio: It related to the flow properties of powder samples and is measured by the ratio of tapped density to bulk density or ratio of bulk volume to tapped volume, it is related to interparticle friction. Limits of Hausner's ratio were presented in **Table 7**.

TABLE 7: LIMITS FOR HAUSNER's RATIO

Hausner's ratio	Flow character
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-.59	Very poor
>1.60	Very, very poor

Hausner's ratio = Tapped density / Bulk density = Bulk volume / Tapped volume

Angle of Repose: The angle of repose is a characteristic related to interparticle friction or resistance to movement between particles. It is the constant, three-dimensional angle (relative to horizontal base) assumed by a cone like a pile of material formed by any of several different methods. The limits of the angle of repose were presented in **Table 8**.

$$\text{Tan } Ø = (h/r)$$

Where' h' is the height of the cone; 'R' is the radius of the cone.

TABLE 8: LIMITS FOR THE ANGLE OF REPOSE (DEGREES)

Flow character	The angle of repose (degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, vibrate	46-55
Very poor	56-65
Very, very poor	>66

Evaluation of Compressed Tablets:

Thickness (mm): The thickness of the tablets was determined using vernier calipers. Three tablets were picked up randomly and thickness was measured individually using the formula.

$$\text{Thickness} = \text{MSR} + [\text{VSR} \times 0.01]$$

Where, MSR= Main scale reading; VSR= Vernier scale reading

Hardness (kp): The hardness of the tablets was determined using hardness tester Make: Pharmatest; Type: PTB – 311E. It was expressed in kp. Three tablets were randomly picked and the average value of hardness was determined.

Weight Variation Test: To study weight variation, 20 tablets of each formulation were weighed using an electronic balance, average weights were calculated, individual tablet weights were compared with the average weight. Not more than two individual weights deviate from the average weight by more than the percentage shown in the following Table and the results were shown in **Table 7**.

$$PD = [(W\ avg) - (W\ initial) / (W\ avg)] \times 100$$

Where, PD = Percentage deviation; W avg = Average weight of tablets; W initial = Individual weight of tablet.

Standard Weight Variation (IP):

TABLE 9: LIMITS FOR WEIGHT VARIATION

Average tablet weight (mg)	Percentage deviation (%)
Up to 80 mg	5
> 80mg,<250 mg	7.5
250mg or more	10

Friability test (%): Friability is the measure of tablet strength. It is expressed in Percentage (%), the friability of the tablet was determined by using Roche Friabilator. 10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated for 100 revolutions (25 rpm/min), and then tablets were taken out and dedusted. The percentage weight loss was calculated by reweighing the tablets. The percentage friability was then calculated by

$$\%\ \text{Friability} = (W1 - W2) / W1 \times 100$$

Where, W1 = initial weight of the tablets; W2 = Final weight of the tablets

Friability Limits: less than 1% is acceptable.

***In-vitro* Disintegration Test:** The test was carried out on 6 tablets using digital tablet disintegration tester make Electrolab in purified water at 37 ºC ± 2 ºC.

Drug release measurements and comparisons: 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 **Table 10**. The samples were drawn

at specified time intervals and the obtained samples were analyzed 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 ± 0.5 ºC
RPM	100
Volume of medium	900 ml
Sampling intervals	1, 2, 3, 5, 7
Sample volume	5 ml withdrawn and replaced with 5 ml of dissolution medium

Differential Scanning Calorimetry (DSC): Differential Scanning Calorimetry (DSC) studies were carried out using DSC TA Inotr, having TA Instrument. Accurately weighed samples were placed on an aluminum plate, sealed with aluminum lids and heated at a constant rate of 10 °C/min, over a temperature range of 0 °C to 350 °C.

Fourier Transform Infrared Spectroscopy (FTIR): FTIR spectra of Tolterodine Tartrate API, Tolterodine Tartrate MUPS tablets and Tolterodine Tartrate MUPS Tablets placebo formulations were recorded using a Fourier transform Infrared Spectrophotometer. The analysis was carried out in Shimadzu-IR affinity-1 Spectrophotometer. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at a pressure of 7 to 10 tons.

Scanning Electron Microscopy: The shape and surface morphology of the Tolterodine Tartrate over coated pellets and MUPS tablets were examined using a scanning electron microscope.

RESULTS AND DISCUSSION:

Micromeritic Properties of Protective Layer Pellets: The Protective layer pellets of all the batches (T1, T5, T6, T7, T8, and T9) were evaluated for bulk density, tapped density, Compressibility index, Hausner's ratio and presented in **Table 11**. Based on the results it indicated that the protective layer pellets possess satisfactory flow and compressibility index.

TABLE 11: EVALUATION OF PROTECTIVE LAYER PELLETS

S. no.	Formulation	Description	Bulk Density(g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio
1	T1	Off-white pellets	0.700	0.735	4.76	1.050
2	T5	Off-white pellets	0.699	0.745	6.17	1.066
3	T6	Off-white pellets	0.721	0.762	5.38	1.057
4	T7	Off-white pellets	0.702	0.761	7.75	1.084
5	T8	Off-white pellets	0.690	0.753	8.37	1.091
6	T9	Off-white pellets	0.702	0.761	7.75	1.084

Micromeritic Properties of the Lubricated Blend: The Lubricated blend of all the batches (T1, T5, T6, T7, T8, and T9) was evaluated for bulk density, tapped density, Compressibility index, Hausner's ratio and angle of repose and presented in **Table 12**. Based on the above results it indicated that the lubricated blends possess satisfactory flow and compressibility index.

TABLE 12: EVALUATION OF LUBRICATED BLEND

S. no.	Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio
1	T1	0.619	0.728	14.973	1.176
2	T5	0.598	0.725	17.517	1.212
3	T6	0.621	0.735	15.510	1.184
4	T7	0.615	0.730	15.753	1.187
5	T8	0.610	0.728	16.209	1.193
6	T9	0.621	0.735	15.510	1.184

Process Parameters for Tablet Compression:

TABLE 13: EVALUATION PARAMETERS OF FORMULATED TABLETS

Formulation	Description	Weight of Capsule or Tablets (mg)	Thickness (mm)	Hardness (kp)	% Friability
T1	White to off-white, round, bevel edged, biconvex, tablets	516 ± 2.000	5.66 ± 0.060	14.1 ± 0.513	0.09
T5		516 ± 1.732	5.56 ± 0.021	13.7 ± 0.802	0.08
T6		517 ± 1.528	5.57 ± 0.017	14.1 ± 0.252	0.07
T7		517 ± 2.646	5.55 ± 0.038	14.5 ± 0.252	0.05
T8		517 ± 1.155	5.56 ± 0.025	13.8 ± 0.306	0.07
T9		516 ± 1.528	5.56 ± 0.042	13.2 ± 0.436	0.04

Mean ± SD, n = 3

FTIR Spectral Analysis: FTIR spectral studies were performed on some selected optimized MUPS tablets of Tolterodine Tartrate to study any drug excipients interactions. FTIR spectral studies were performed on BRUKER FTIR spectrophotometer using potassium bromide pellets.

FTIR spectra of pure drugs of Tolterodine Tartrate was taken initially to check the basic functional groups present in them. The spectra of budesonide pure drugs MUPS tablet formulations and placebo of MUPS tablet were shown below.

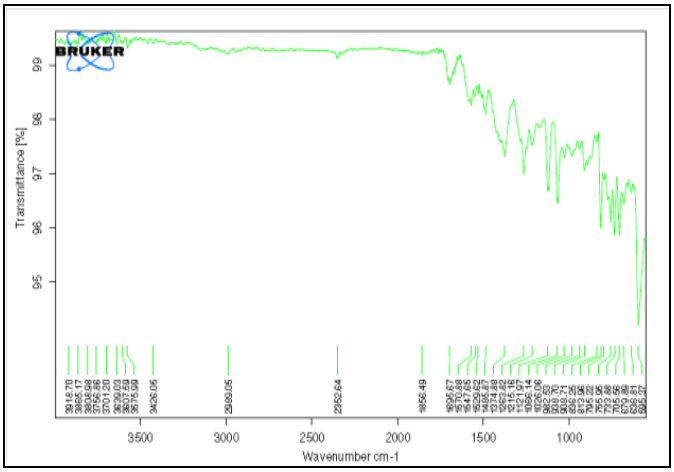

FIG. 1: TOLTERODINE TARTRATE API

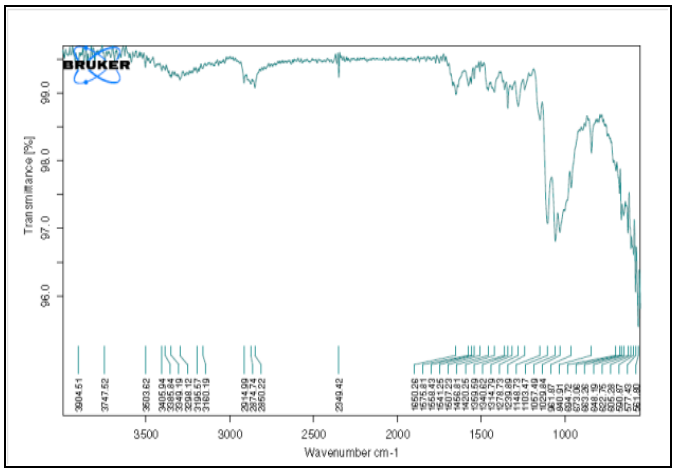

FIG. 2: TOLTERODINE TARTRATE MUPS TABLETS WITH GUAR GUM

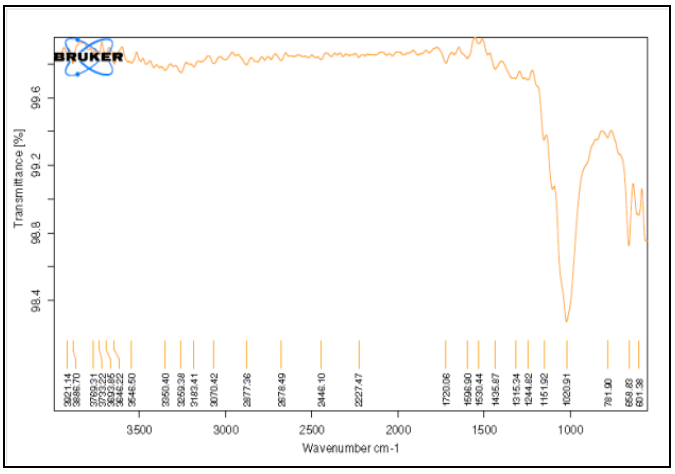

FIG. 3: TOLTERODINE TARTRATE MUPS TABLETS WITH GUAR GUM PLACEBO

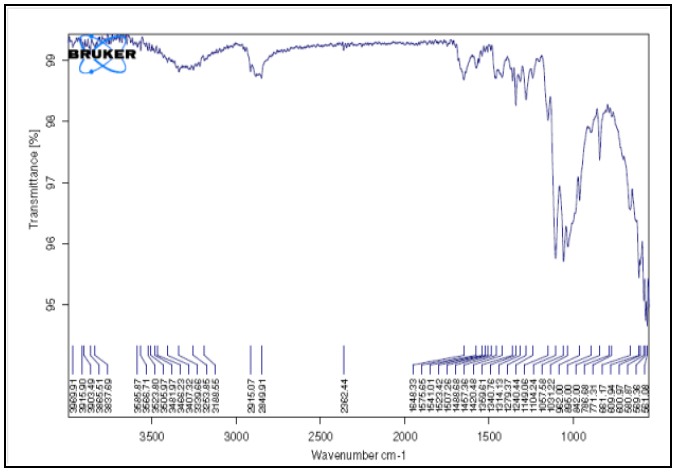

FIG. 4: TOLTERODINE TARTRATE MUPS TABLETS WITH HYPROMELLOSE 5 cps

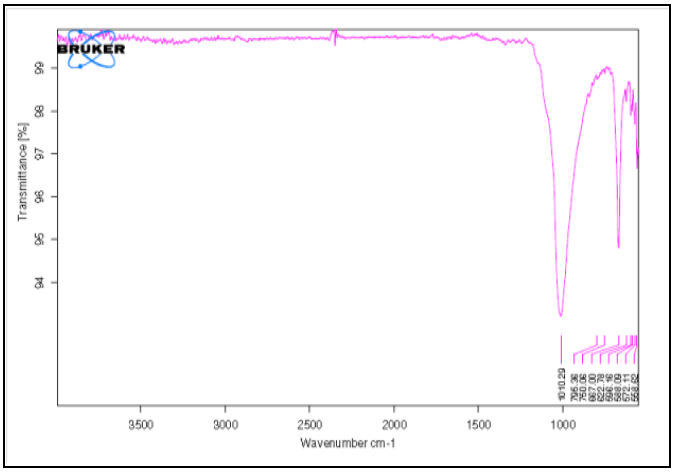

FIG. 5: TOLTERODINE TARTRATE MUPS TABLETS WITH HYPROMELLOSE 5 cps PLACEBO

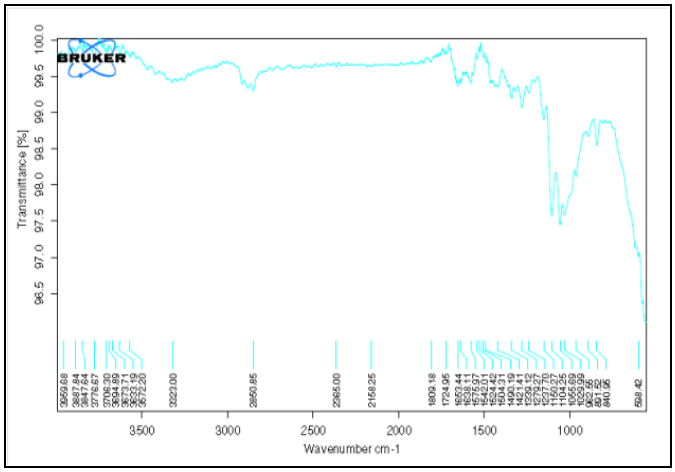

FIG. 6: TOLTERODINE TARTRATE MUPS TABLETS WITH KLUCEL-LF

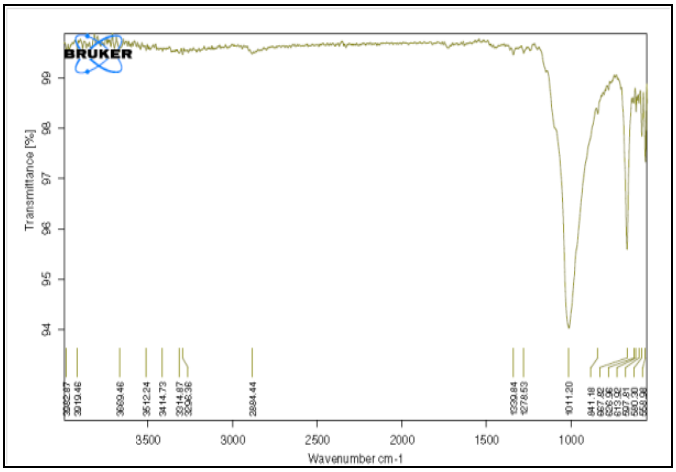

FIG. 7: TOLTERODINE TARTRATE MUPS TABLETS WITH KLUCEL-LF PLACEBO

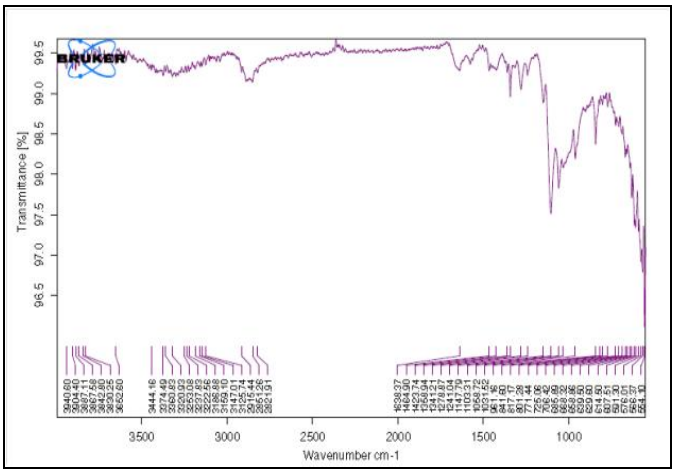

FIG. 8: TOLTERODINE TARTRATE MUPS TABLETS PLACEBO WITH PEG 6000

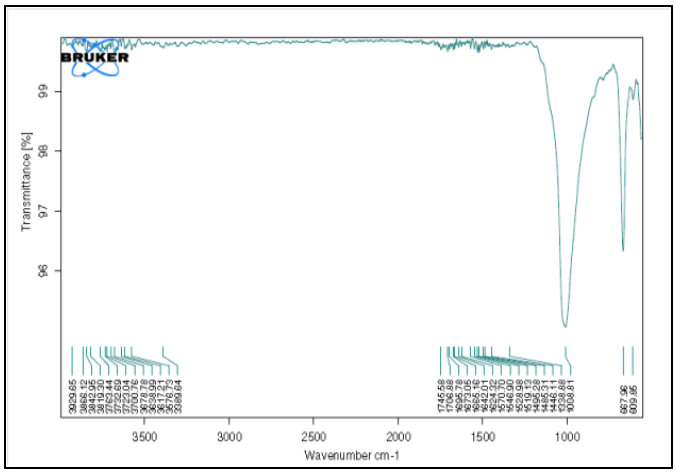

FIG. 9: TOLTERODINE TARTRATE MUPS TABLETS WITH PEG 6000 PLACEBO

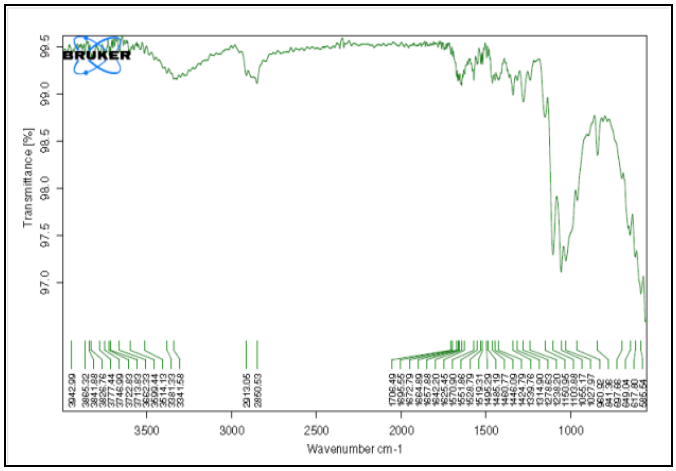

FIG. 10: TOLTERODINE TARTRATE MUPS TABLETS WITH XANTHAN GUM

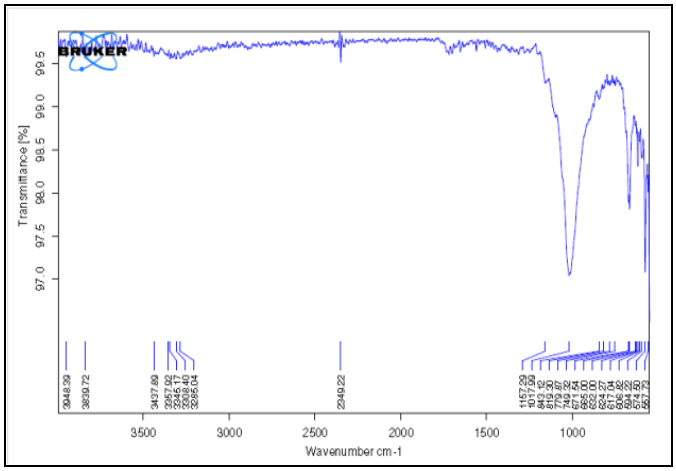

FIG. 11: TOLTERODINE TARTRATE MUPS TABLETS WITH XANTHAN GUM PLACEBO

The characteristic peaks of 3500-3650 (Hydroxyl free groups), 2850-3000 (Methyl (-CH3) Stretch), 350-1000 (Amine –C-N- Stretch), 900-690 (Mono-substituted benzenes) of Tolterodine Tartrate that are not shifted significantly in Tolterodine Tartrate MUPS tablets, that there is no interaction between drug and excipients present in formulation. The formulations with klucel-LF, PEG-6000, HPMC, xanthan gum, guar gum showed the characteristic peaks at wave numbers close to that of Tolterodine Tartrate API. There was no alteration in the characteristic peaks of in the Tolterodine Tartrate MUPS tablets, indicates that there was no chemical interaction between the drug and polymer.

Differential Scanning Calorimetry (DSC): The DSC measurements were performed for Tolterodine Tartrate API, Tolterodine Tartrate MUPS tablets and Tolterodine Tartrate MUPS placebo tablets tablet to study drug excipient interaction on a DSC with a thermal analyzer. The DSC thermogram is shown below.

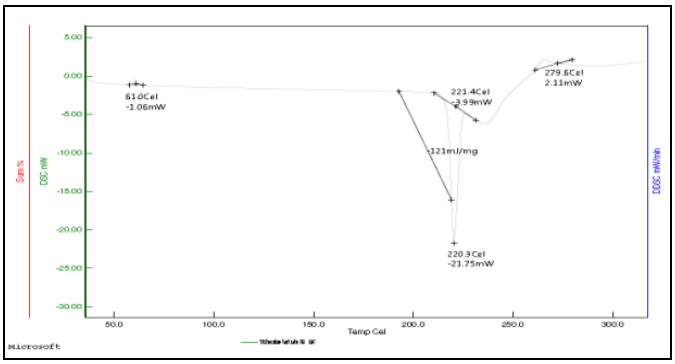

FIG. 12: TOLTERODINE TARTRATE API

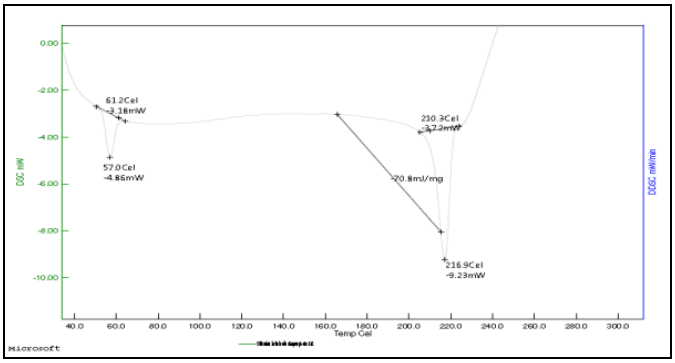

FIG. 13: TOLTERODINE TARTRATE MUPS TABLETS WITH GUAR GUM

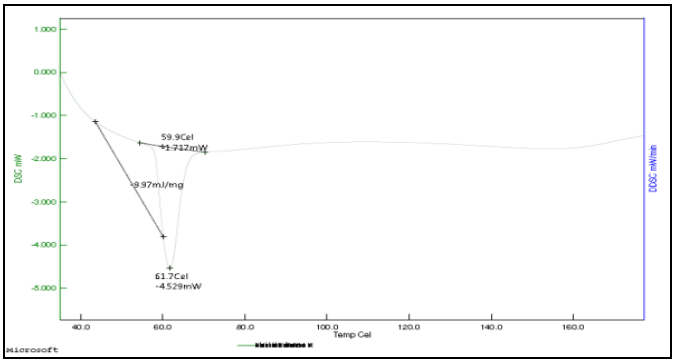

FIG. 14: TOLTERODINE TARTRATE MUPS TABLETS WITH GUAR GUM PLACEBO

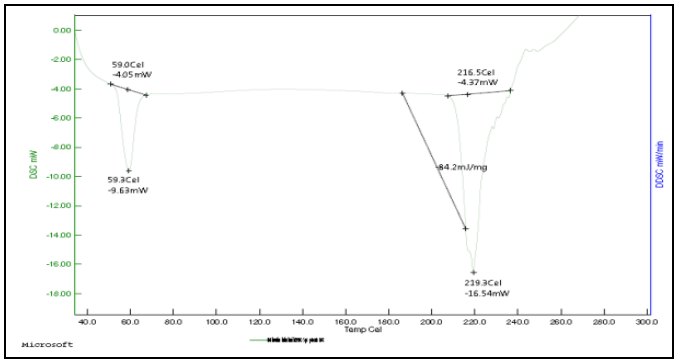

FIG. 15: TOLTERODINE TARTRATE MUPS TABLETS WITH HPMC 5cps

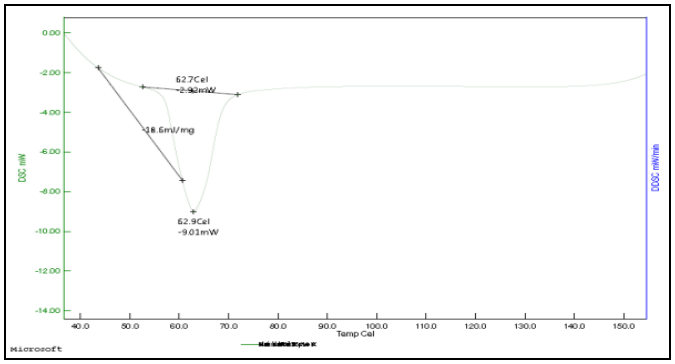

FIG. 16: TOLTERODINE TARTRATE MUPS TABLETS WITH HPMC 5cps PLACEBO

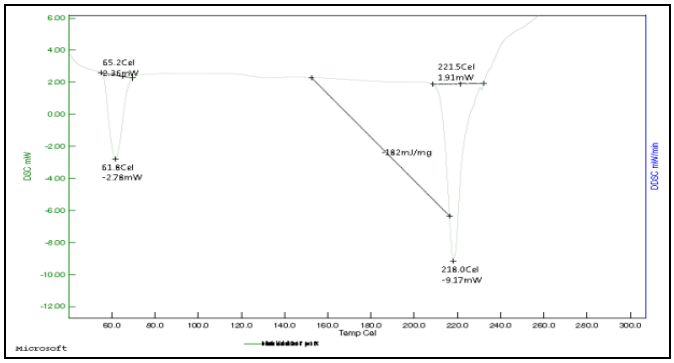

FIG. 17: TOLTERODINE TARTRATE MUPS TABLETS WITH KLUCEL LF

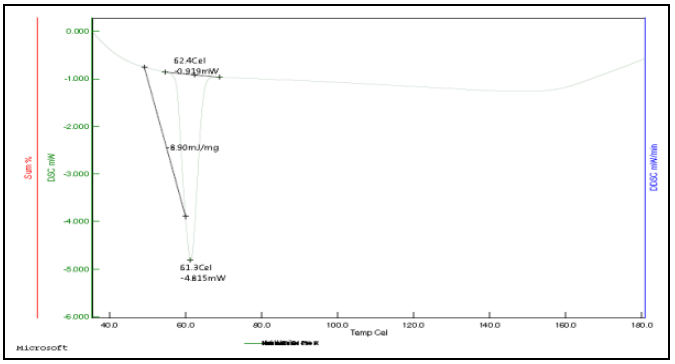

FIG. 18: TOLTERODINE TARTRATE MUPS TABLETS WITH KLUCEL LF PLACEBO

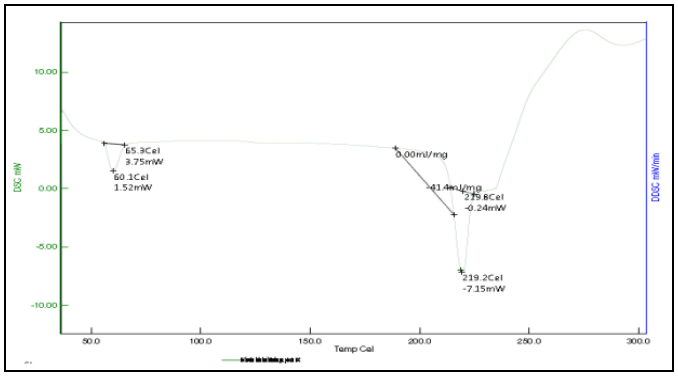

FIG. 19: TOLTERODINE TARTRATE MUPS TABLETS WITH XANTHAN GUM

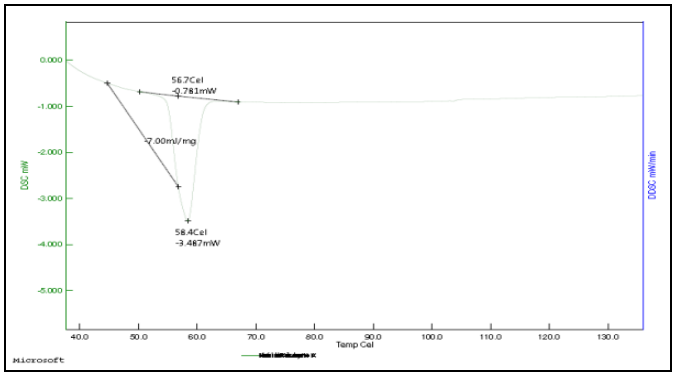

FIG. 20: TOLTERODINE TARTRATE MUPS TABLETS WITH XANTHAN GUM PLACEBO

The DSC of Tolterodine Tartrate API showed a sharp endothermic peak at 220 ºC which corresponding to the melting point of the drug, DSC thermogram of Tolterodine Tartrate MUPS tablets showed a sharp peak at near to 220 ºC, which indicates that there is no interaction between drug and selected excipients.

Scan Electron Microscopy:

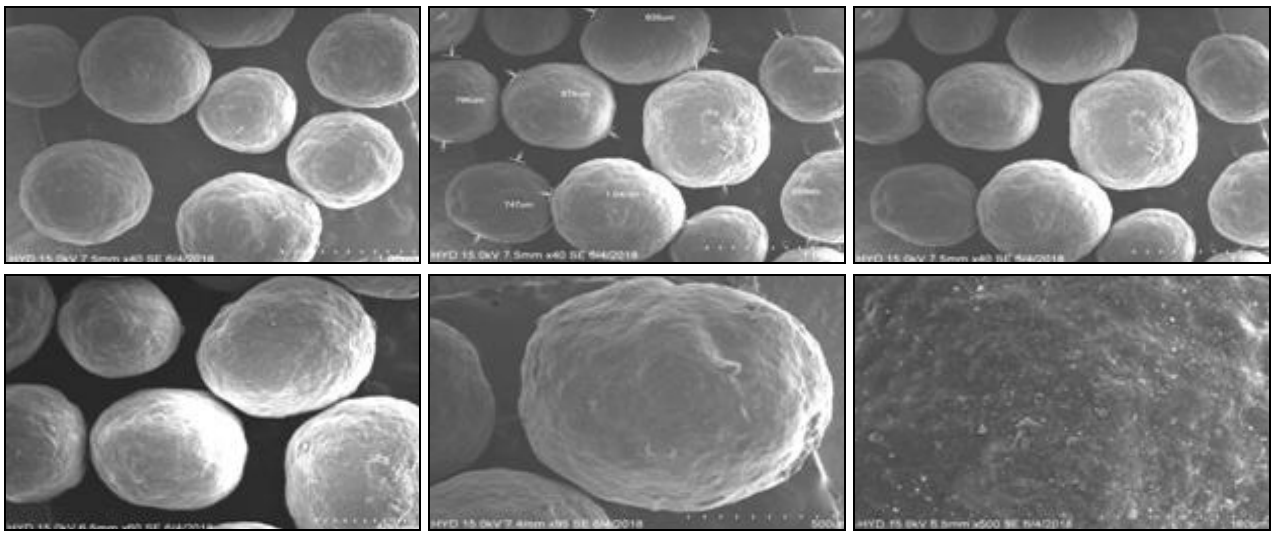

FIG. 21: SEM ANALYSIS OF TOLTERODINE TARTRATE OVER COATED PELLETS

SEM analysis of Tolterodine Tartrate MUPS Tablets:

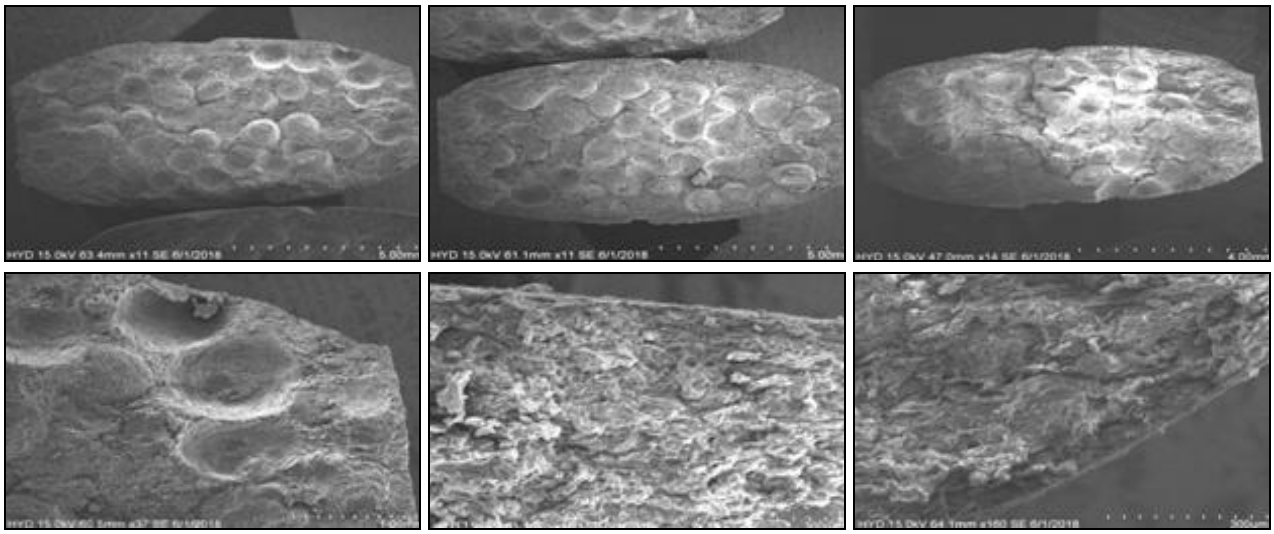

FIG. 22: SEM ANALYSIS OF TOLTERODINE TARTRATE MUPS TABLETS

Drug Release Measurements and Comparisons: The prepared controlled release pellets divided into six parts, one part is used for dissolution studies and other five parts were used for protective coating of five polymers Klucel, Polyethylene glycol 6000, Hypromellose 5 cps, Guar gum, and Xanthan gum. The prepared protective layer coated pellets of synthetic polymers Klucel, Polyethylene glycol 6000, Hypromellose 5 cps and natural polymers Guar gum, Xanthan gum was free-flowing, free from agglomerates. We taken controlled release common pellets, protective layer pellets of five different polymers and compressed into tablets and compared the dissolution profiles of controlled release pellets, protective layer pellets, MUPS tablets compressed with controlled release pellets and MUPS tablets compressed with protective layer pellets. The hardness was selected 8-10 kp where MUPS tablets made with the controlled release pellets are breaking and release the drug faster than controlled release pellets.

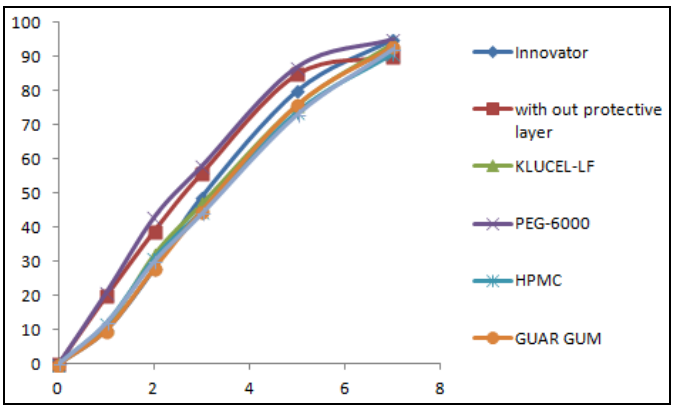

FIG. 23: COMPARATIVE DISSOLUTION PROFILE WITH THE INNOVATOR

CONCLUSION: Tolterodine Tartrate controlled-release tablets were prepared successfully by using ethyl cellulose and hypromellose used as release-modifying excipients and low viscous natural or synthetic binders like klucel, polyethylene glycol 6000, hypromellose 5 cps, guar gum, and xanthan gum as protective layer coating agents. The flow properties of the pellets and the lubricated blend were evaluated and found to be satisfactory. The process parameters of Tolterodine Tartrate MUPS tablets were found to be well within limits.

Based on comparative dissolution profiles of MUPS tablets, controlled release pellets, and protective layer coating pellets it was concluded that by applying low viscous natural or synthetic binders like klucel, hypromellose 5 cps, guar gum and xanthan gum on functional coating gives good protection to functional coating layers from damage during compression. Hence, it is concluded that this approach is a very effective and potential strategy for manufacturing of MUPS tablets. Whereas, very low viscous polymers polyethylene glycol 6000 not able to protect the functional coating layer of pellets from damage during compression.

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CONFLICT OF INTEREST: The authors have no conflicts of interest to declare that are directly relevant to the content of this manuscript.

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