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Formulation Development and Invitro Evaluation of Tamsulosin Hcl Extended Release Pellets

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Abstract: The purpose of this study was to develop and optimize oral extended release formulation for tamsulosin hydrochloride using a combination of ethyl cellulose N-50 and Eudragit L-100 as a coating material. Initially trials were done to optimize the drug loading on to sugar pellets for its uniformity of size and Assay, varying the concentration of HPMC E-5 as binder, Aerosil as lubricant and sodium starch glycollate as disintegrant.The drug release percentages at 2, 3, 5, and 8 hours were the target responses and were restricted to **13-34%,47-68%, NLT 70%, NLT 80%** respectively. The optimal coating formulation was achieved with Eudragit L-100 9% of the weight of the drug loaded pellets and ethyl cellulose N-50 with 25% of the Eudragit L-100 content.
The drug release from the optimized pellets was compared with the Innovator product FLOMAX ® capsule. It showed the similarity factor (F2) of **76.43**
Keywords: Tamsulosin HCl, Eudragit L-100, Ethyl cellulose N-50, pellets.

1. Introduction:

In the last two decades, pellets have established their position for many reasons [1, 2]. Pellets offer a great flexibility in pharmaceutical solid dosage form design and development. Pellets can be prepared by many methods, the compaction and drug-layering techniques being the most widely used today. They flow freely and pack easily without significant difficulties, resulting in uniform and reproducible fill weight of capsules and tablets [3, 4, 5]. Successful film coating can be applied onto pellets due to their ideal spherical shape and a low surface area-to-volume ratio[6]. Even pellets with different release rates of the same drug can be supplied in a single dosage form[7].The pelletized products can improve the safety and efficacy of the active agent. The pelletized product can freely disperse in the gastrointestinal tract as a subunit, thus maximizing drug absorption and reducing peak plasma fluctuation. Consequently, potential side effects can be minimized without impairing drug bioavailability. Local irritation derived from high local concentrations of a drug from a single-unit dose, can be avoided. The most important reason for the wide acceptance of multiple-unit products is the rapid increase in popularity of oral controlled-release dosage forms. Controlled-release oral solid dosage forms are usually intended either for delivery of the drug at a specific site within the gastrointestinal tract or to sustain the action of drugs over an extended period of time. With pellets, the above mentioned goals can be obtained through the application of coating materials (mainly different polymers), providing the desired function [8, 9, 10, 11, 12, 13, 14] or through the formulation of matrix pellets to provide the desired effect [15, 16].

Tamsulosin hydrochloride is a highly selective alpha 1A-adrenoreceptor antagonist that has been used for treatment of lower urinary tract symptoms suggestive

of benign prostatic hyperplasia (LUTS/BPH) [17]. Moreover, following oral administration of 0.4mg tamsulosin hydrochloride, the drugs absorbed from the intestine and is almost completely bioavailable[18]. However, many LUTS/BPH patients are elderly subjects with impaired cardiovascular regulation. They are particularly at risk for cardiovascular adverse events, which are not only unpleasant, but can also lead to serious morbidity, such as falls and fractures, potentially resulting in hospitalization, nursing home placement and/or death[19]. Therefore, the preferred formulation of tamsulosin hydrochloride provides a controlled-release that can modulate both the release rate of the drug and the absorption of the drug in the intestinal tract[20]. Prior to these Polymeric film coatings are frequently used to control drug release from solid pharmaceutical dosage forms. To obtain a particular, desired release profile which is adapted to the pharmacokinetic /pharmacodynamic characteristics of the drug and type of pharmacotreatment, different formulation and processing parameters can be varied, such as the coating level, type of polymer and type and amount of added plasticizer. However, the variation of these parameters is generally restricted and it is sometimes difficult to adjust optimized release kinetics. For instance, too low and too high coating levels must be avoided to prevent accidental film rupturing (and subsequent dose dumping) and too long processing times. The type of polymer used should be known to be non-toxic; otherwise time-and cost intensive toxicity studies are required. Too high amounts of added plasticizers lead to intense sticking of the coated dosage forms, whereas too low amounts result in too brittle films. Here we are using blend of polymer to control the release as per specifications and A blend of Eudragit L-100 and ethyl cellulose N-50 are used to control the drug release. The objective of this study is to develop a novel controlled release tamsulosin hydrochloride using Eudragit L-100 and ethyl cellulose N-50.where as earlier studies have been done on tamsulosin hydrochloride using different coating agents [21, 22, 23, 24, 25.]

2. Materials and Method:

Tamsulosin hydrochloride is obtained from RA chem. Pharma Pvt Ltd. Hydroxymethylpropylcellulose (HPMC were obtained from SHIN-ETSU, Japan). Methacrylic acid copolymer-A (Eudragit L100 from Evonik Degussa India Pvt Ltd).Ethylcellulose N-50 USP grade from Feicheng chemicals Ltd,China, Aerosil,PEG-6000, Talc and Isopropyl alcohol (IPA from Ranchem laboratories), Flomax® (Tamsulosin HCl) Capsules 0.4 mg for comparison All organic solvents were of high performance liquid chromatography (HPLC) grade. All other chemicals were of reagent grade.

3. Compatibility Studies

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The compatibility studies were carried out at 25^0C/60% RH and 40^0C/75% RH for 0, 2 and 4 weeks. With respect to physical and chemical aspects, they were tested for incompatibilities between Tamsulosin Hydrochloride and the excipients; sugar pellets (basic core pellets),HPMC-E5 (Binder), ethyl cellulose , Eudragit L 100, poly ethylene glycol (plasticizer), Aerosil, sodium starch glycollate, and talc.

4. Preparation of Drug Loaded Pellets.

A slurry of Tamsulosin hydrochloride is prepared in a solution of HPMC in isopropyl alcohol along with it Aerosil and sodium starch glycollate was added into the slurry. The sugar spheres (#20-#22) are preheated to about 35° C with gentle movement. In a fluid bed coater, and then sprayed with the coating solution prepared above while more drying air is introduced and fluidization intensified. Spray rate, inlet air temperature are adjusted in such a way that the core bed reaches a temperature of about 35° C. Over wetting of the cores is to be avoided as it may cause agglomeration. After complete quantity of the coating solution is consumed, the fluidization is reduced for a brief post-drying period. The pellets are then dried in a tray drier at about 45° C to moisture content of <2%. The dried pellets are sized on a sifter to remove agglomerates, broken pellets and fine powder. The pellets are now ready for coating.

5. Coating of Drug Loaded Pellets:

A solution of ethyl cellulose, methacrylic acid copolymers A and poly ethylene glycol is prepared in adequate quantity of isopropyl alcohol and water. Talc is suspended in this solution. The drug pellets are preheated to about 35° C with gentle movement in a fluid bed coater, and then sprayed with the coating solution prepared above while more drying air is introduced and fluidization intensified. Spray rate, inlet air temperature are adjusted in such away that the core bed reaches a temperature of about 35° C. Over wetting of the cores is to be avoided as it may cause agglomeration. The pellets are then dried in a tray drier at about 45° C to a moisture content of <2%. The dried pellets are sized on a sifter to remove agglomerates, broken pellets and fine powder. After checking the weight of the pellets and noting down the yield they are packed.

Fig.1: Tamsulosin Hydrochloride API

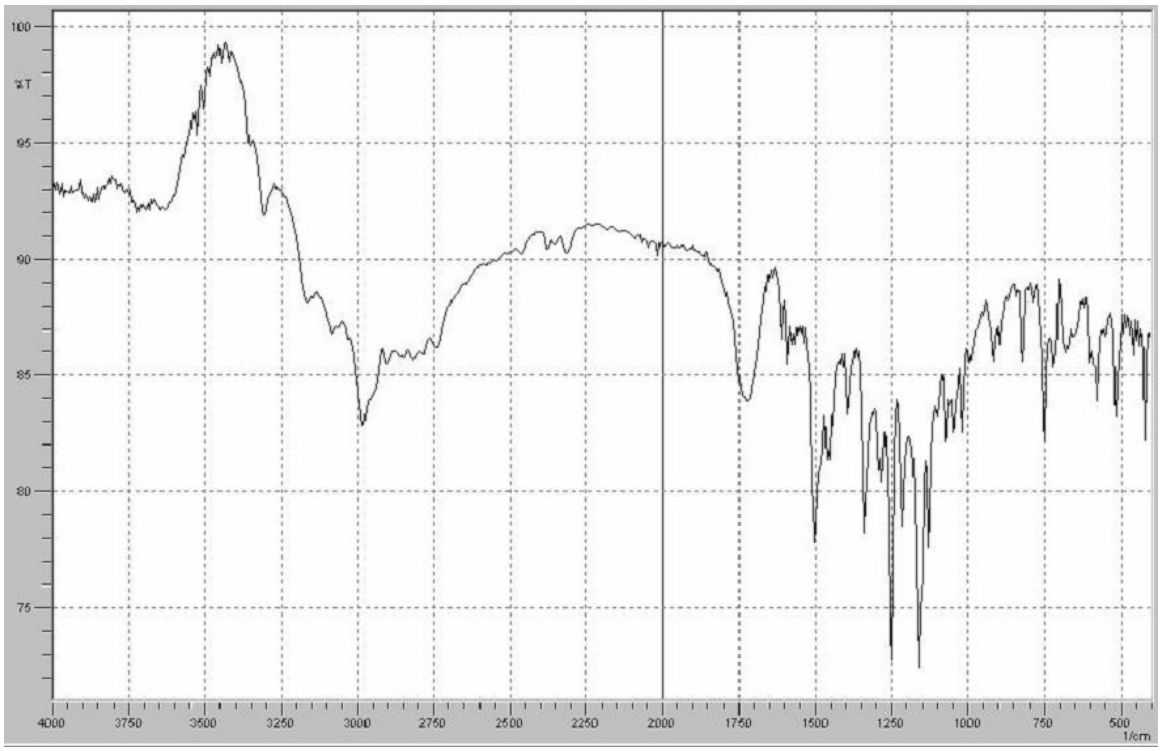


Fig.2: Tamsulosin Hydrochloride-Physical Mixture

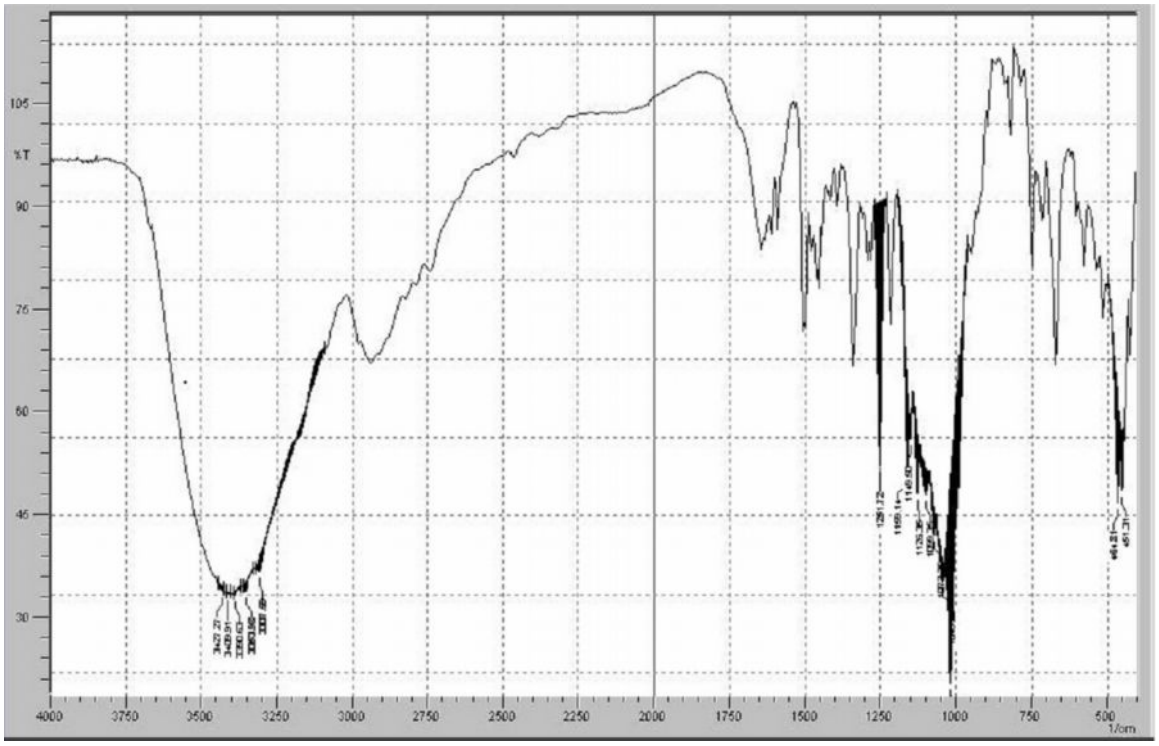


Fig .3: Tamsulosin Hydrochloride –Pellets

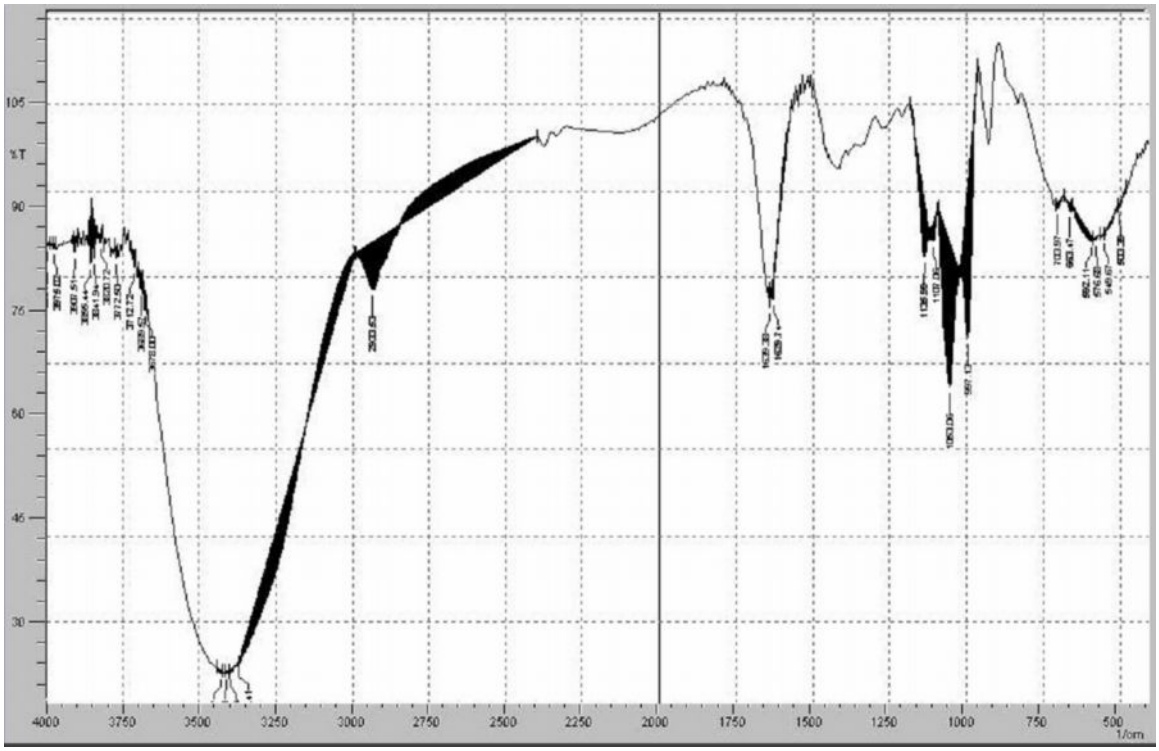


Table no.1:

S. No.	Excipients	Initial Physical Description	25°C / 60% RH & 40°C / 75% RH (Closed)		
			1st Week	2nd Week	4th Week
1	Tamsulosin	White crystalline powder	*	*	*
2	Tamsulosin + Sugar spheres	Off-white powder	*	*	*
3	Tamsulosin + Hydroxy propyl methyl cellulose	Off-white powder	*	*	*
4	Tamsulosin + Colloidal silicon dioxide	Off-white powder	*	*	*
5	Tamsulosin + Ethyl cellulose	Off-white powder	*	*	*
6	Tamsulosin + Methacrylic acid copolymer Type A	Off-white powder	*	*	*
7	Tamsulosin + Starch	White powder	*	*	*
8	Tamsulosin + Poly ethylene glycol	Off-white powder	*	*	*
9	Tamsulosin + Sugar spheres + HPMC + Ethyl cellulose + Starch+ methacrylic acid copolymerType A, + sodium starch glycolate+talc+ Sugar + Colloidal silicon dioxide + Poly ethylenglycol.	Off-white powder	*	*	*

Table No.2: Coating equipment parameters

Parameter	Stage
Fluidized air Volume	80-100m^3/hr
Product bed temperature	37-42^{0}c
Spray rate	30-40g/min
Atomizing air temperature	1.5barr
Inlet air temperature	45-55^{0}c

Table no. 3: Optimization of Drug loading onto pellets

Ingredients	Tam1	Tam2	Tam3	Tam4	Tam5	Tam6	Tam7	Tam8	Tam9	Tam10
Tamsulosin HCl	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sugar Pellets(#20-#22)	99.79	99.75	99.70	99.60	99.59	99.58	99.4	99.19	98.99	98.9
HPMC E-5	0.01	0.05	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Colloidal silicon dioxide	-	-	-	-	0.001	0.002	0.002	0.002	0.002	0.002
Sodium Starch Glycolate	-	-	-	-	-	-	0.2	0.4	0.6	0.8
IPA(mL)	100	100	100	100	100	100	100	100	100	100

Table No.4: Optimized Drug loaded Pellet

Ingredients	OPTIMIZED FORMULA
Tamsulosin HCL	0.2
Sugar pellets(#20-#22)	98.7
HPMC E-5	0.2
Colloidal silicon dioxide	0.002
Sodium Starch glycolate	0.8
Isopropyl alcohol(ml)	100

Optimization of Coating Solution

Table no.5: Effect of Coating Levels of Methacrylic Acid Copolymer on Drug-Release in 0.1 N Hydrochloric Acid(pH 1.2)

INGREDIENTS	TAM 11	TAM 12	TAM 13	TAM 14
Tamsulosin HCL	0.2	0.2	0.2	0.2
Sugar pellets(#20-#22)	98.7	98.7	98.7	98.7
HPMC E-5	0.2	0.2	0.2	0.2
Colloidal silicon dioxide	0.002	0.002	0.002	0.002
Sodium Starch glycolate	0.8	0.8	0.8	0.8
Isopropyl alcohol(ml)	100	100	100	100
Eudragit L-100 as percentage weight of the drug loaded pellets	3	6	9	12
PEG – 6000	8.33	8.33	8.33	8.33
Talc	10	10	10	10
Purified Water (ml)	10	10	10	10
Isopropyl alcohol (ml)	350	350	350	350

6. Formulation Trials:

Initial formulation trials were done on optimization of Drug loaded pellets (TAM1-TAM10) and then trials are done on the Coating solution composition for extending the drug release and the compilation of the trials are given in the table: 2, 4, 5

7. Dissolution:

The release of tamsulosin hydrochloride from coated pellets was performed according to the USP XXV paddle method using a dissolution apparatus (Electrolab).

The coated pellets containing 0.2 mg of drug were filled into hard gelatin capsules. The capsules were added into 500 mL of simulated gastric fluid without pepsin (adjusted to pH 1.2 with HCl) containing polysorbate 80 (0.003%, w/w) at 37 ± 0.1°C and with a paddle speed of 100 rev/min. A sinker was used to avoid capsule flotation. Each sample (5mL) was withdrawn at defined time intervals, and the same volume of simulated gastric fluid was compensated. After 2 h, 500 mL of simulated intestinal fluids without pancreatin (pH 7.2, phosphate buffer according to the USP without enzyme) was

replaced to adjust pH of dissolution medium from pH 1.2 to 7.2. The samples were analyzed using HPLC (LC-20AD). Dissolution tests were repeated six times for all formulations and then the % drug released from the controlled release pellets was calculated.

Chromatographic conditions

Column : Intersil ODS 3V, 250mm x 4.6mm x 5µm or its equivalent
Flow Rate : 1.0 ml/min
Wavelength : 220nm
Column Temperature : 25^0C
Injection volume : 10µL
Run Time : 10 mins

8. Loading of the Optimized Pellets into Capsules.

The pellets which are optimized after the trials were checked for the bulk density and were loaded into capsules No.2 with automatic capsule filling machine (Rimek formulations).

9. Evaluation of Loaded Capsules:

Weight variation test

Ten capsules were individually weighed and the contents were contents removed. The emptied capsules were individually weighed and the net weight of the contents was calculated by subtraction and the percent weight variation was calculated by using the following formula.

Weight variation

$$= \frac{\text{(Wt of capsule-Average Wt)}}{\text{Average Wt of capsules}} \times 100$$

Weight variation should not be more than 7.5 %.

Lock length

Ten individual capsules were taken from formulation trial batch and lock length was measured manually by using vernier calipers and average of ten capsules was noted.

Table no.6: Effect of Coating Levels of Ethyl cellulose-N50 on Drug-Release in 0.1N HCl & pH 7.2 Phosphate buffer

INGREDIENTS	TAM 15	TAM 16	TAM 17	TAM 18	TAM 19	TAM 20
Tamsulosin HCL	0.2	0.2	0.2	0.2	0.2	0.2
Sugar pellets(#20-#22)	98.7	98.7	98.7	98.7	98.7	98.7
HPMC E-5	0.2	0.2	0.2	0.2	0.2	0.2
Colloidal silicon dioxide	0.002	0.002	0.002	0.002	0.002	0.002
Sodium Starch glycollate	0.8	0.8	0.8	0.8	0.8	0.8
Isopropyl alcohol(ml)	100	100	100	100	100	100
Eudragit L-100 as percentage weight of the drug loaded pellets	9	9	9	9	9	9
Ratio of Ethyl cellulose to Eudragit L-100 as % of the Eudragit L-100 content	15	30	45	60	27.7	25
PEG – 6000	10	10	10	10	10	10
Talc	8.33	8.33	8.3	8.33	8.33	8.33
Purified Water (ml)	10	10	10	10	10	10
Isopropyl alcohol (ml)	350	350	350	350	350	350

Disintegration
The capsules are placed in the basket rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37ºC and observed over the time described in the individual monograph. To fully satisfy the test the capsules disintegrate completely into a soft mass having no palpably firm core, and only some fragments of the gelatin shell.

Assay
Preparation of Standard solution:
Accurately weigh and transfer 25mg of Tamsulosin HCl into a 50 mL of volumetric flask, add 30mL of methanol and sonicate dissolve dilute to volume with methanol. Transfer 2mL of the solution to a 100mL volumetric flask; dilute the volume with mobile phase. Filter the solution through 0.45µ nylon filter paper.

Preparation of Sample solution:
Accurately weigh and transfer the twenty capsules containing pellets of Tamsulosin HCl pellets crushed in to powder and transfer equivalent to about 2.0 mg of Tamsulosin HCl into a 200mL volumetric flask, add 60mL of methanol, shake for 2 minutes and add 60mL of mobile phase and sonicate for 15 minutes and dilute to volume with mobile phase. Filter the solution through 0.45µ nylon membrane filter.

Content uniformity
The amount of active ingredient determined by assay is with in the range of 85% to 115% of the label claim for 9 of 10 dosage units assayed with no unit outside the range of 70% to 125% of label claim.

Invitro Dissolution and Data Analysis:
There are many methods for the comparison of dissolution profiles. Here we Studied the similarity factor.

$$f_2 = 50 \times \log\left\{\left[1+\frac{1}{n}\sum_{i=1}^{n}(R_t - T_t)^2\right]^{-\frac{1}{2}} \times 100\right\}$$

Similarity factor is the Logarithmic transformation of the sum-squared error of differences between the test and reference product over all time points (Moore &Flanner, 1996). Where Log denotes logarithm based on 10.The scale up and post approval changes for immediate and modified release dosage forms guidance suggest that an f2 value between 50 and 100 be required to conclude similarity of two dissolution profiles. Only one time point after reaching 85% of dissolution was used to calculate f2 to avoid bias.

SEM Studies: Photographs of optimized pellets were taken in order to determine external morphology of pellets.

Stability Studies:
The optimized pellets were evaluated for its stability at different temperature conditions and compared with that of the commercial product. This includes storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated.
Storage conditions
Stability samples are stored at
Accelerated : 40±2°C/75±5% RH
Intermediate: 30±2°C/65±5% RH
Long term : 25±2°C/60±5% RH
Testing Intervals for
Accelerated: Initial, 1, 2, 3 & 6 months
Long term: Initial, 3, 6, 9, 12, 18, 24 & 36 months.
Intermediate: Initial, 3, 6, 9 & 12 months.

Comparative Dissolution Profiles.

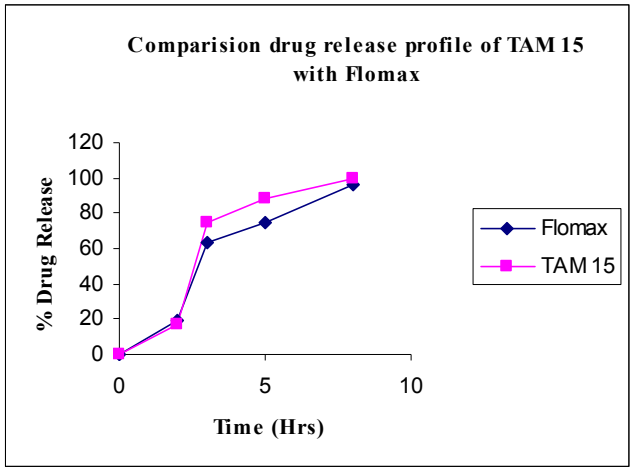


Fig. 4: TAM 15 Vs Flomax

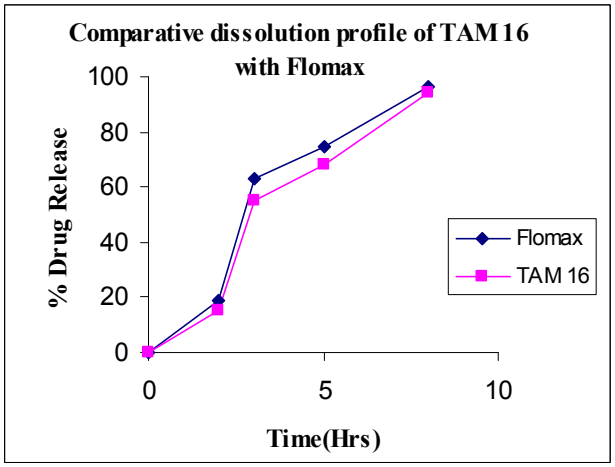


Fig. 5: TAM 16 Vs Flomax

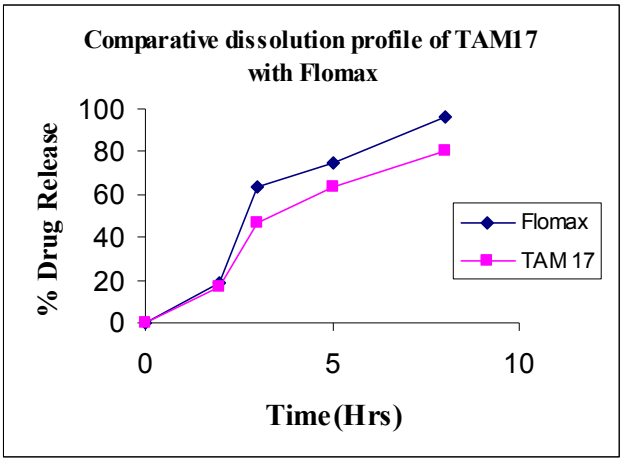


Fig. 6: TAM 17 Vs Flomax

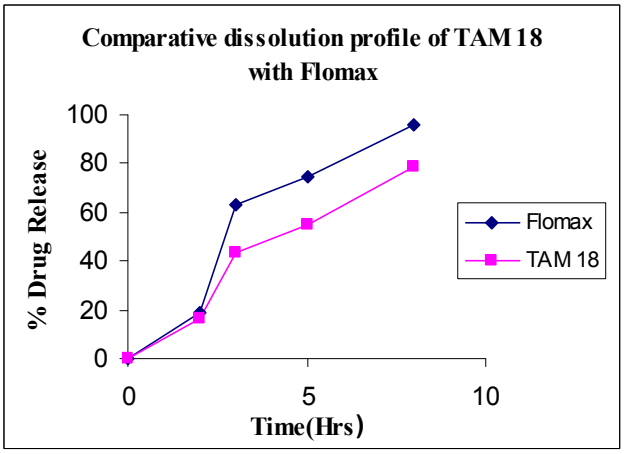


Fig. 7: TAM 18 Vs Flomax

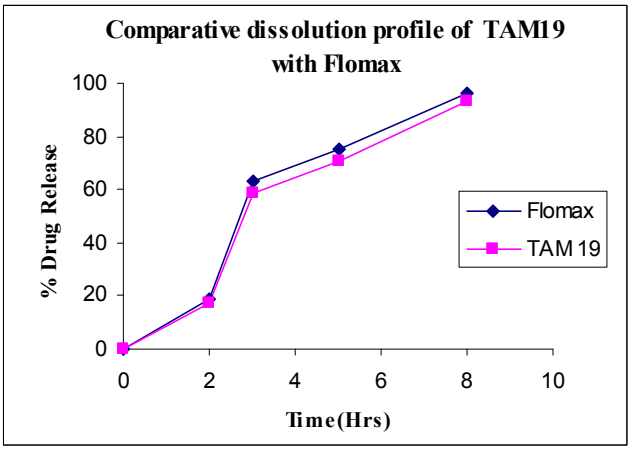


Fig.8 : TAM 19 Vs Flomax

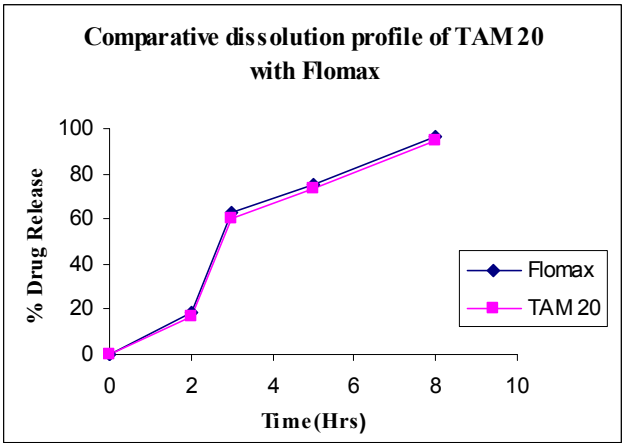


Fig. 9: TAM 20 Vs Flomax

Table no.7: Invitro Release Studies of Trial Batch TAM 15 –TAM20

S.NO	TIME (Hrs)	SECOTEX	TAM 15	TAM 16	TAM 17	TAM 18	TAM 19	TAM 20
1	0	0	0	0	0	0	0	0
2	2 (13-34%)	18.82	16.8	15.4	17.1	16.35	17.10	16.82
3	3 (47-68%)	63.26	74.2	55.3	46.81	43.75	58.66	53.10
4	5 (NLT-70%)	74.83	88.5	68.40	63.21	54.98	70.42	74.04
5	8 (NLT-80%)	96.08	99.7	94.34	80.56	78.62	93.21	95.42

Table no.8: Characteristics of Optimized Pellet Formulation

Yield (Limit-NLT 96%)	99%
Sieve analysis for 100 gm	
#16 passed	98 g
#20 retained	98 g
# 16 passed and 20 retained	98 g
Bulk density	0.829 g/ml
Tapped density	0.842 g/ml
Compressibility index	1.54
Angle of repose	25.76^0
Hausner's ratio	1.01

Table no.9: Evaluation of loaded capsules:

S.NO	Parameters	Observed Value	Limits
1	Assay	97.9%-102.01%	95%-105%
2	Avg Weight Variation	201.7	186.6-216.8
3	Disintegration time	3.2 minutes	NMT 30 minutes

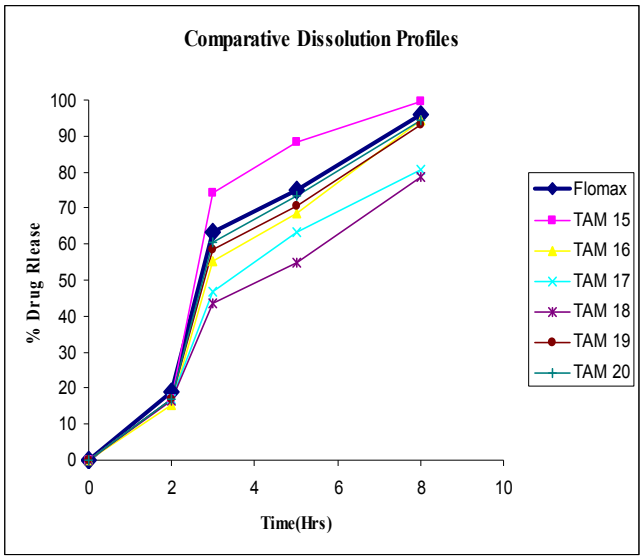
Table No.10: Evaluation parameter values at different temperature condition

S.No	Parameter	Stability conditions at		
		25°C	30°C	40°C
1	Assay	101.13%	99.35%	100.10%
2	Moisture content	1.74 %	1.78%	1.75 %
3	Disintegration time in minutes	3.30	3.25	3.20

Table No.11: In-vitro dissolution profile of optimized batch TAM 20 at 25^0 C/60% RH, 30^0 C/65 % RH and 40^0 C/75 % RH

Time (Hrs)	Percentage of Drug release					
	25°C±2°C/60% ± 5% RH		30°C±2°C/65% ± 5% RH		40°C±2°C/ 75% ± 5% RH	
	Flomax	TAM 20	Flomax	TAM 20	Flomax	TAM 20
0	0	0	0	0	0	0
2	15.03	16.25	15.81	17.03	15.43	16.33
3	63.68	58.53	62.36	59.48	62.12	60.46
5	74.93	73.69	73.46	72.39	73.08	74.01
8	95.80	95.54	94.92	94.56	94.16	93.82

Fig . 10: Comparative dissolution profile of formulations TAM 15-TAM 20



Comparative Dissolution Profile of Stability Studies:

Fig.11: Comparative dissolution profile of formulation TAM 20 and Flomax at 25^0 C/60% RH

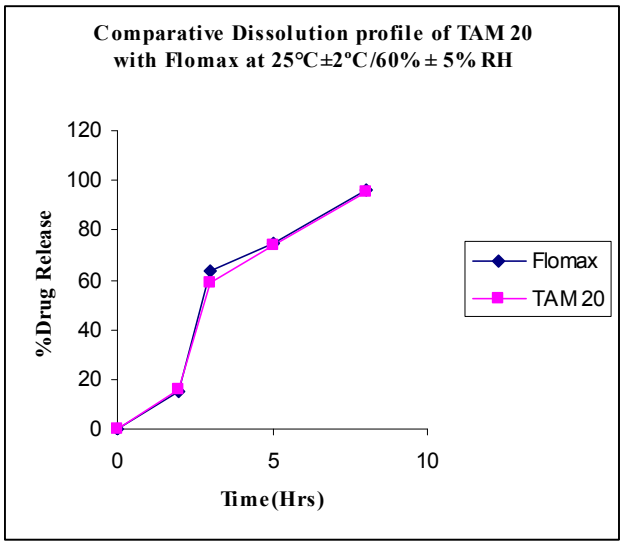


Fig.12: Comparative dissolution profile of formulation TAM 20 and Flomax at 30^0 C/65 % RH

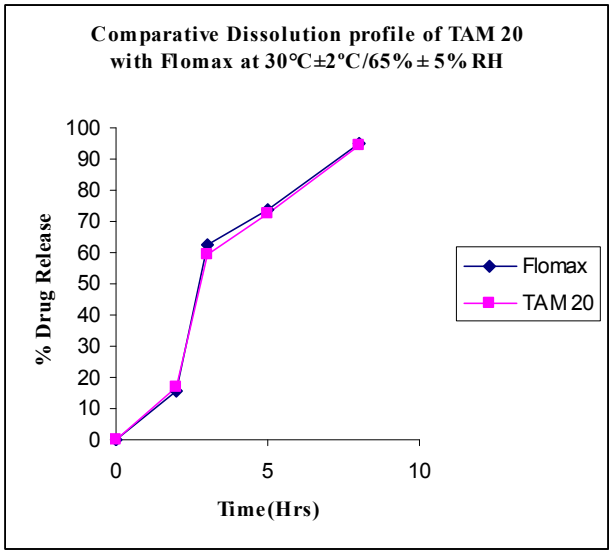


Fig.13: Comparative dissolution profile of formulation TAM 20 and Flomax at 40^0 C/75 % RH

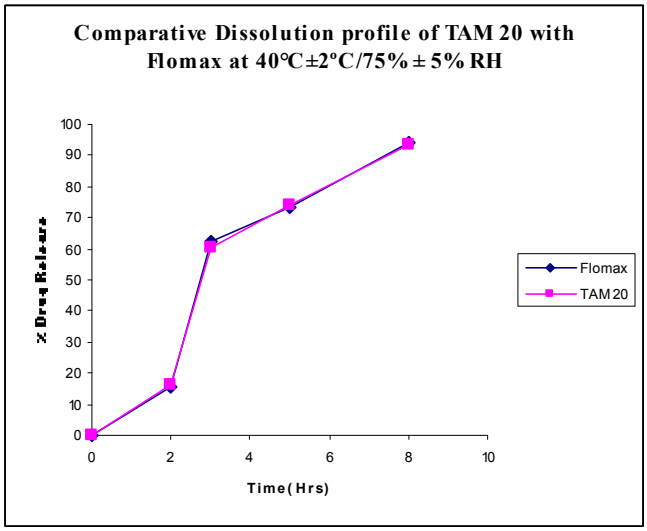
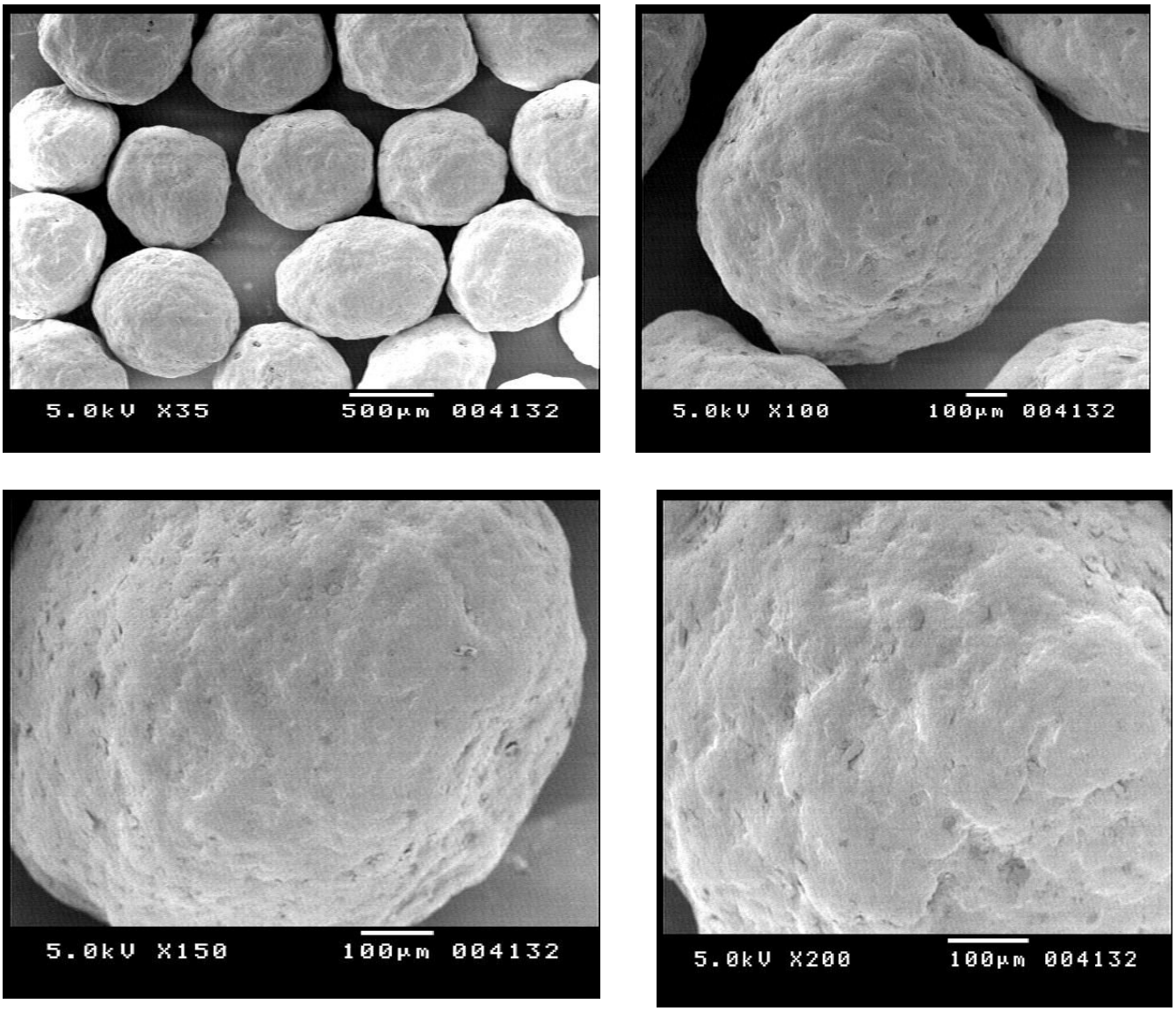


Fig.14: SEM photographs of optimized pellets



Results and Discussion:

Various batches of pellet formulation TAM 1- TAM 14 for the drug Tamsulosin HCl were developed using HPMC as binder , Colloidal silicon dioxide as lubricant , Sodium starch glycolate as disintegrant and TAM15-TAM20 were developed using ethyl cellulose N50 and Eudragit L100 as coating solutions in various ratios. All the pellets were developed by drug solution layering onto sugar pellets. As indicated in table:3 formulations TAM 1 – TAM4 were formulated using HPMC E-5 as binder and the concentration of binder was varied from 5 to 100% of the drug concentration. It was noted that the binder concentration in the range of 25% (TAM2) of the drug was optimum with smooth finish, uniform in size and without agglomeration but with slight breakage of pellets and the binder concentration in the range of 100 % of the drug was also very smooth finish but with some agglomeration, so we tried to include lubricant to avoid agglomeration.

In the next formulation in order to optimize the lubricant concentration we took the formulation of TAM 4 and varied the colloidal silicon dioxide as lubricant (TAM5-TAM6) and it was observed that pellets with 0.002% of lubricant to that of drug concentration produced smooth pellets without agglomeration, but they was slight decrease in the drug release than the other pellets. In next trial formulation in order to increase the release rate as that of other pellets processed to study the effect of super disintegrant sodium starch glycolate. Varying the percentage of super disintegrant from 100 to 400 % of that drug in concentration (TAM7-TAM10). It was found that super disintegrant in the range of 400% of the drug was optimum and produced the pellets with smooth finish and prompt release (TAM 10). From the formulation TAM1 to TAM10 we optimized the excipients for the drug loading onto sugar pellets, after optimizing the drug loaded pellets formulation we studied the effect of coating levels. In the formulation of trial batch TAM11-TAM14 we studied the effect of Eudragit L100 concentration and the drug release in pH 1.2,shown in table:5.The % of the Eudragit L100 were varied from 3% to 12% (TAM11-TAM14) of the weight of drug loaded pellets. It was found that TAM 13 with 9% was optimized as it controlled the release rate in acid buffer. As the release of drug in the acid media is controlled with Eudragit L100 the next trial was to control the release rate of drug in the in 7.2 phosphate buffer. For this we had a formulation of the trial batches TAM 14-TAM18 by varying the concentration of ethyl cellulose N50 in the range of 15 to 60 % of that of Eudragit L100 in the formulation. The drug release from all the above formulations (TAM14-18) were studied in the both acid media for 0-2hours and 3-8 hours in the 7.2 phosphate buffer medium. It was found that TAM 15 was almost giving the release rate as specified but it failed in the 5^{th} hour in phosphate buffer. So in order to increase the release rate in 5^{th} hour we reduced the concentration of ethyl cellulose to 27.7% (TAM19) here in this formulation the drug release was near to specification, and in the next formulation (TAM20) we still reduced the % ethyl cellulose to 25% which gave the release specifications. After optimizing the pellets formulation we had gone to characterize the pellets for its particle size, assay, moisture content, bulk density, tapped density, angle of repose.

Based on the observed bulk density we had selected capsule no.2 for loading of pellets, later evaluated the filled capsules and the results was shown in table no: 9, the lock length was found to be 17.7, and the capsules were passing the weight variation and content uniformity test.

SEM photographs of optimized pellets were shown in fig. 14 and it was observed that coating was even on the pellets and it was also observed that pellets appeared smooth.

The optimized pellets were compared with the Innovator product for their in-vitro drug release and the similarity factor (f2) was found to be 73.45.
Finally the pellets were studied for its stability at different temperatures and evaluated for the parameters as shown in the table no:10 and it was found to be stable at all temperature where drug release comparing with the commercial product was shown in table no:11 .

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