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Design and Evaluation of Rectal Suppositories of Antihypertensive Drug

Mohammed Younus Ali*[a], Sadath Ali[b], PV Swamy[c], Y Anand Kumar[d], Najamuddin[e] and N Srinivasulu[d]

[a]JJT University Rajasthan.
[b]Director, Himalayan Institute of Pharmacy and Research, Dehradun.
[c]Shri Vishnu College of Pharmacy, Vishnupur, Bhimavaran-534202, W.G. Dist, A.P-India
[d]V.L College of Pharmacy, Raichur, Karnataka, India
[e]RME's College of Pharmacy, Gulbarga

ABSTRACT

In the present study an attempt has been made to design and evaluate rectal suppositories of atenolol an antihypertensive drug. suppositories were formulated utilizing different hydrophilic and hydrophobic polymeric bases like gelatin, PEG-400 and hydrogenated vegetable oil in combination with propylene glycol as plasticizer and beeswax as hardening agent by fusion method. The statistical evaluation of *in-vitro* release data depicted that the mechanism of drug release from all the formulations was found to be diffusion controlled (r=0.9427 to 0.9894). All the formulations has showed zero order release kinetics except those prepared by employing 10% beeswax w/w and gelatin suppositories without PEG-400. The formulation containing 30% of PEG-400 w/w of gelatin has displayed zero order release kinetics (r=0.9936) and released 99.10 % of atenolol within 150 min. The DSC and FT-IR studies reveal that there is mild to no interaction between polymer and the drug. The stability studies data suggested that there was no significant change in the drug content after a period of 6 months ($p<0.005$). The SEM images showed the uniform dispersion of the drug within the polymer with a minimum air entrapment. The overall results conclude that atenolol rectal suppositories can be conveniently formulated by fusion method utilizing hydrogenated vegetable oil and gelatin-PEG 400 bases.

Keywords: Atenolol, diffusion, zero order release, DSC, SEM, FT-IR, stability studies

Corresponding author

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INTRODUCTION

Suppositories are medicated solid /semisolid drug delivery systems generally intended for use in the rectum [1]. An ideal suppository would be easy to administer with good patient compliance and remain at the administered site avoiding the first pass effect in the liver and gastrointestinal tract conventional suppositories is solid/semisolid dosage form that melts or softens in the rectum [2]. Oral administration is the route of choice in the daily practice of pharmacotherapy, however oral route becomes impractical in certain cases such nausea, vomiting or convulsions; in such situations the rectal route may provide a practical alternative. The human rectum represents a body cavity in which drugs can be easily inserted and retained well. Rectal route is also good for drug that irritates gastrointestinal mucosa, other reasons for preferring the rectal route over the oral route is when the drug is extensively metabolized or deactivated by liver enzymes. The superior rectal vein perusing the upper part of the rectum drains into the portal vein and subsequently into the liver, on the other hand, the middle and inferior rectal vein drains the lower part of the rectum and venous blood is returned to inferior venacava. Hence the drug absorbed in the latter system will be delivered preferentially to the systemic circulation by passing first pass metabolism [3]. The rectal route is much preferred in pediatric and geriatric patients with difficulties in swallowing solid oral dosage forms. These are also the dosage forms of choice for unconscious and semiconscious patients. Major factors affecting the absorption of drugs from suppositories are anorectal physiology, suppository vehicle and physicochemical properties of drug [4]. Considering the above facts suppositories can be stated as having greatest potential as convenient dosage form in the treatment of chronic health disorders such as rheumatism and cardiovascular diseases especially among the elderly patients.

Atenolol [5] is an antihypertensive drug used in the management of hypertension, angina pectoris and emergency treatment of cardiac arrhythmias, but its oral bioavailability is only 50% because of its poor absorption from gastrointestinal tract, on the other hand the drug has a few gastro intestinal side effects such as nausea, vomiting and diarrhea. These side effects of the drug can be overcome by administering it as suppositories for rectal use. In the present study the rectal suppositories of Atenolol were formulated by using different hydrophilic and hydrophobic polymeric bases like gelatin, PEG-400 and hydrogenated vegetable oil using propylene glycol as plasticizer and beeswax as hardening agents. Fat like bases are used for water-soluble drugs and a hydrophilic base for an insoluble drug in water [6].

MATERIALS AND METHODS

AT was a generous gift from Glenmark Pharmaceuticals, Nasik, Maharashtra, India. propylene glycol, polyethylene glycol 400 (PEG 400) was procured from Sd Fine Chem Ltd, Mumbai. Gelatin, propyl paraben were purchased from Qualigens Fine Chemicals, Loba Chemie Pvt Ltd and Merck Specialities Pvt Ltd, Mumbai respectively. All other chemicals were of analytical reagent grade.

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Mould Calibration [7]

To avoid the variation in the mould capacity the moulds were calibrated before preparing the suppositories and were standardized. The melted base was poured into the mould and freeze dried, after freezing the suppositories were removed from the mould and weighed individually and the mean weight was taken as true capacity of the mould. The procedure was repeated for different bases. The calibrated mould capacities ranged from 1.02 to 1.21 g for gelatin-PEG 400 base and 1.02 to 1.12 g for vegetable oil beeswax suppositories.

Suppository Preparation

The displacement value for fatty base was calculated and was found that approximately 1.232 g Atenolol displaces 1 g of hydrogenated vegetable oil. Suppositories were prepared using fusion (pour moulding) method [8]. a) Hydrogenated vegetable oil was taken in a china dish and melted. The drug was dispersed in the melted oil with stirring for complete dispersion of the drug; after complete dispersion the melted base along with drug was poured into the pre-calibrated mould (rapid cooling should be avoided as it results in holing of the suppositories). b) Gelatin was taken in a beaker and small amount of water is added to it and heated on a magnetic stirrer after complete melting of the gelatin, the mixture of propylene glycol and PEG 400 along with accurately weighed amounts of drug and preservative (propyl-paraben) were added to this solution and was stirred until complete dispersion of the drug in the base, the beaker is removed from the magnetic stirrer and initially cooled for few seconds to remove the air entrapment and the solution was transferred into the precalibrated mould and cooled immediately which is very essential for gelatin suppositories. The drug loaded in each suppository is 50 mg. The prepared suppositories were wrapped in aluminium foil and store under refrigeration the composition of suppository formulation are tabulated in table-1.

Table-1: Composition of 30 suppositories

Sl.No	Ingredients	$ATVS_0$	$ATVS_1$	$ATVS_2$	$ATVS_3$	$ATPGS_0$	$ATPGS_1$	$ATPGS_2$	$ATPGS_3$
1	Hydrogenated vegetable oil (g)	28.5	27.33	26.61	25.89	---	----	----	----
2	Beeswax (g)	--	1.44	2.16	2.88	---	---	---	---
3	Gelatin	**---**	---	---		7.5	7.5	7.5	7.5
4	PEG 400 (g)	**---**	---	---		---	3.00	4.5	6.00
5	Propylene glycol (g)	---	---	---		18.00	15.00	12.00	9.00
6	Propyl paraben (g)	---	----	----		0.3	0.3	0.3	0.3
7	Distilled Water (ml)	---	---	---		3.0	3.0	3.0	3.0
8	Drug (mg)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Evaluation of Suppositories

The prepared suppositories were evaluated for physical appearance by visual examination, weight uniformity, drug content uniformity, liquefaction time and temperature, micromelting range test, stability studies, DSC was performed to study the thermal properties of the drug and to evaluate dispersion of the drug with polymer SEM studies was performed.

The physical examination was carried as per USP-30/NF-25. For determining the weight uniformity twenty suppositories were weighed individually and the average weight was determined. The individual weights were compared with the average weight for determination of weight variation and were found that no suppository deviate from average weight by more than 5%, and thus prepared suppositories comply with IP specifications [9]. The determination of drug content was carried out by slicing 10 suppositories into small pieces, suppository pieces equivalent to 100 mg Atenolol were accurately weighed and transferred into 100 ml volumetric flask and dissolved in 50 ml methanol by shaking for 90 min on a gyratory shaker and the volume was made upto mark with methanol. The absorbance of the solution was measured at 226 nm against the solvent blank. The drug content was calculated from the calibration curve. Average of five determinations was taken as mean drug content of the suppositories. For determination of liquefaction time and temperature [10], a simple apparatus with modification, fabricated in the laboratory has been used. A centrifuge tube with broken bottom was taken and cut suitably so that it is having a narrow opening at the bottom. The centrifuge tube was in hot water maintained at 37º C so that narrow end faces towards hot water. The suppository was introduced from the top of the tube through broad end and carefully pushed down its length until it reaches narrow end. A glass rod weighing 30 g was then inserted so that it rests over the suppository. The temperature at which the glass rod just comes down was noted which represents the liquefaction temperature. The time at which glass rod reaches to narrow end after complete melting of suppository represents the liquefaction time. For micro melting range test [11], the formulation was filled to about 1 cm height in capillary tubes of 10 cm length and dipped in a beaker containing water. The temperature was raised slowly and the temperature at which the mass liquefies was recorded.

In vitro Dissolution Studies

In vitro dissolution studies of Atenolol suppositories were carried out in USP XIII tablet dissolution test apparatus (Electro lab TDT – 06N) employing a basket at 50 rpm and using 900 ml of pH 7.4 phosphate buffer as dissolution medium at 37±0.5º C. One suppository was used in each test. At predetermined time intervals, 5 ml samples were withdrawn by means of a syringe fitted with a prefilter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5º C. The samples were analyzed for drug release by measuring the absorbance at 224.5 nm using UV-visible spectrophotometer after suitable dilution. Cumulative percent of Atenolol released was calculated and plotted against time. All the studies were run in triplicate (n=3).

Stability Studies

Stability studies were performed at a temperature of 25º ±3ºC/ 60± 5% RH over a period of 6 months on the promising suppository formulation (ATPGS3) Sufficient number of suppositories (15) were individually wrapped in aluminium foil and packed in card-board boxes. Samples are taken at monthly intervals for drug content estimation.

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RESULTS AND DISCUSSION

Rectal suppositories of Atenolol an antihypertensive drug, were formulated by fusion method using hydrogenated vegetable oil ($ATVS_0$ to $ATVS_3$), gelatin-PEG 400 ($ATPGS_0$ to $ATPGS_3$) as base, beeswax for increasing the melting point of hydrogenated vegetable oil and propylene glycol as plasticizer. The formulated suppositories were evaluated for appearance, weight variation, drug content uniformity, liquefaction time and temperature, micro-melting range, *in vitro* dissolution and short-term stability.

The moulds (1 g capacity) were calibrated for different bases used. The calibrated mould capacities ranged from 1.02 to 1.21 g for gelatin-PEG 400 base and 1.02 to 1.12 g for vegetable oil beeswax suppositories. All the suppositories were free from pits, fissures and cracks. The longitudinal section of the suppositories was opaque and uniform in appearance, indicating complete and even distribution of drug in the base.

The prepared suppositories were evaluated for uniformity of weight and the results are given in table-2. The percent deviation from the mean weights of all batches was found to be within the prescribed limits as per Indian Pharmacopoeia. The drug content was found to be in the range of 97.3% to 99.5%, which is within the acceptable limits. The low standard deviation values indicate drug content was uniform in the suppositories prepared. Melting/ softening time is the time at which the suppositories withstand body temperature of 37º C, which is helpful in convenient handling and release of the drug after administration in the rectum.

Table-2: Evaluation of suppositories

Formulation code	Weight Variation* (mean±SD)	Drug content* (mean±SD)	Liquefaction time/ temperature		Micro melting range (ºC)
			Time (min)	Temp (ºC)	
$ATVS_0$	1.12±0.008	99.23±0.00318	3.0±1.16	36.73±2.00	37.0±0.002
$ATVS_1$	1.015±0.00707	99.10±0.002516	5.45±2.645	37.66±0.58	37.66±0.577
$ATVS_2$	1.02±0.0107	97.91±0.001527	5.83±1.153	36.66±0.58	37.33±0.577
$ATVS_3$	1.03±0.0164	97.3±0.002516	6.51±1.00	37.0±0.00	38.0±1.00
$ATPGS_0$	1.212±0.0139	99.5±0.00353	3.3±0.0131	36.6±0.577	37.5±0.7071
$ATPGS_1$	1.21±0.0116	99.07±0.002	4.9±0.5773	38.00±0.00	37.3±0.5773
$ATPGS_2$	1.021±0.00737	99.25±0.00305	5.11±1.527	36.33±0.58	37.33±0.002
$ATPGS_3$	1.04±0.0117	98.20±0.00316	4.00±0.023	37.00±0.58	38.00±1.89

The suppositories prepared with hydrogenated vegetable oils alone were soft with low melting below 37^o C, to increase the hardness and melting beeswax was added in the formulation. In case of hydrogenated vegetable oil-beeswax suppositories the liquefaction time and temperature were found to be in the range of 03 to 06.51 min at 37±1^o, while with gelatin-PEG 400 suppositories the liquefaction time was found to be in the range of 03.3 to 5.11 min at 37±1^o C**.** The temperature for micro melting (Fig-1) of hydrogenated vegetable oil suppositories was between 37^o to 38^o C and for gelatin-PEG 400 suppositories it was found to be in between 37.5^o to 38º C in all the batches.

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In vitro dissolution studies on the formulated hydrogenated vegetable oil- beeswax suppositories ($ATVS_0$ to $ATVS_3$) and the gelatin-PEG 400 base suppositories ($ATPGS_0$ to $ATPGS_3$) were carried out in pH 7.4 phosphate buffer and the various dissolution parameters, viz., percent drug dissolved, $t_{50\%}$ and $t_{70\%}$ are shown in table-3 and dissolution profile are depicted in Fig-2 and 3. This data shows that hydrogenated vegetable oil-beeswax suppositories have released upto 99.20% ($ATVS_2$ containing 7.5% bees wax) of the drug in 150 min while gelatin-PEG 400 suppositories has released upto 99.10% ($ATPGS_3$ containing 30% of PEG-400) of the drug in 150 min. In case of the formulations $ATVS_0$ to $ATVS_3$ consist of hydrogenated vegetable oil- beeswax suppository base the release rate decrease as the concentration of the beeswax increases this might be due to the increase in melting time.

Fig 1: Micro melting Test Apparatus

Table 3: *In-vitro* drug release data

Sl.No	Formulation Code	$t_{50\%\ (min)}$	$t_{70\%\ (min)}$	Cumulative % drug release*
1	$ATVS_0$	99.0	118.5	99.04±0.557
2	$ATVS_1$	76.5	100.5	98.19±0.981
3	$ATVS_2$	78.0	106.5	99.20±0.997
4	$ATVS_3$	27	39	98.34±0.577
5	$ATPGS_0$	94.5	114.0	97.4±1.009
6	$ATPGS_1$	109.5	135.0	97.00±1.230
7	$ATPGS_2$	94.5	108.0	98.99±0.987
8	$ATPGS_3$	63.0	94.5	99.10±0.124

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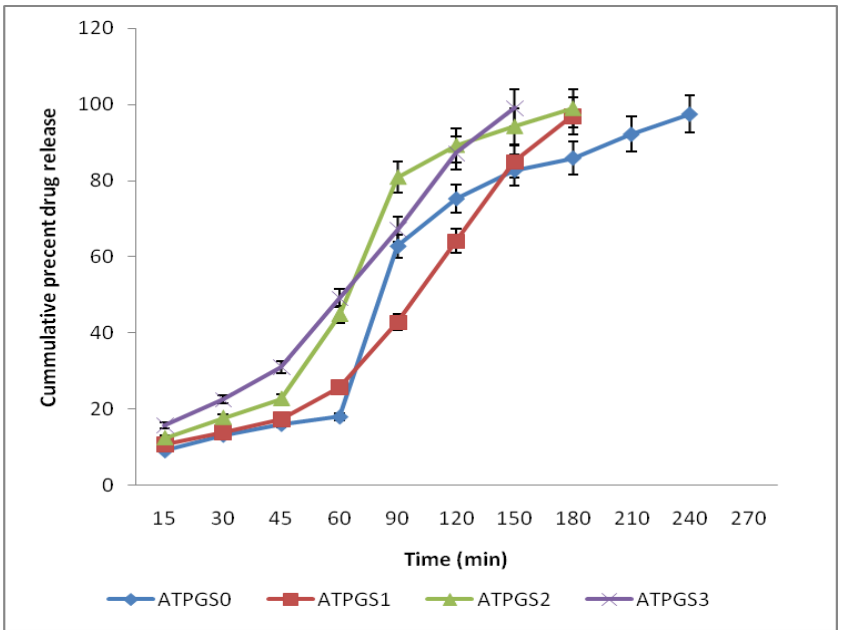

Fig 2: Cumulative percent drug release vs. time plots of Gelatin-PEG-400 suppositories of Atenolol

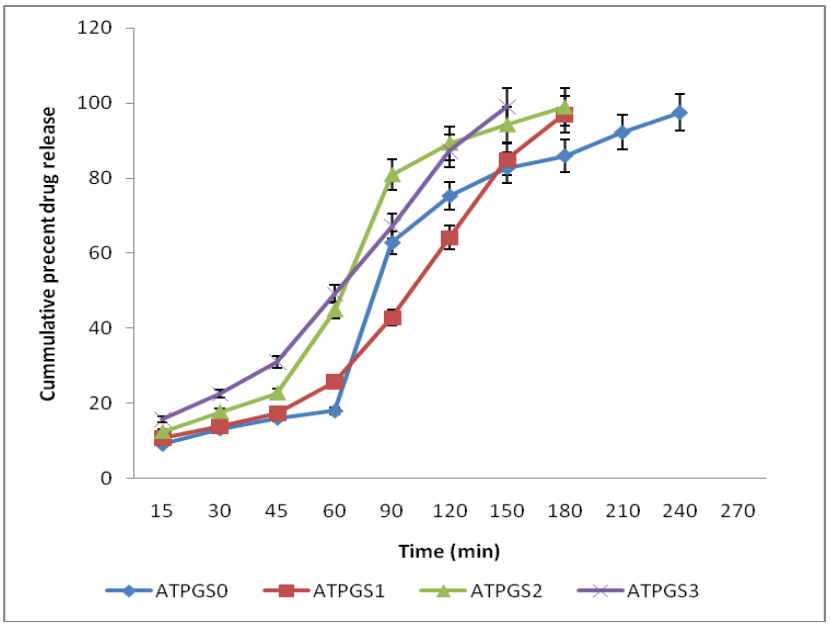

Fig 3: Cumulative percent drug release vs. time plots of Hydrogenated Vegetable oil beeswax suppositories of Atenolol

Drug Release Kinetics

The *in vitro* drug release data was subjected to goodness of fit test by linear regression analysis, according to first-order kinetic equations, zero order, Higuchi and Peppas models to determine the mechanism of drug release. The regression coefficient 'r' values for Higuchi's equation range from 0.9427 to 0.9894 indicating that the drug release is by diffusion

mechanism, and those of 'n' values of Peppas equation range from 0.5536to 1.51. As per the 'n' values of Peppa's equation the prepared suppositories have shown non-Fickian ($ATVS_1$, $ATVS_2$, $ATVS_3$, $ATPGS_0$, $ATPGS_1$, $ATPGS_2$ and $ATPGS_3$ n>0.45), and super case-II transport (ATVS0 n>1.0) release mechanism. The super case-II transport release mechanism may attributed to burst effect displayed by these formulations, The formulation $ATPGS_3$ containing 30% PEG-400 has displayed zero order release rate (r=0.9936) hence this formulation can be considered as promising formulation and it has released 99.10 % AT within 150 min. All the formulations except $ATPGS_0$ and $ATVS_3$ have shown zero order drug release kinetics.

Stability Studies

Stability studies of the above formulation indicated that there are no significant changes in drug content during a period of 6 months (p=0.005) Table-4.

Table 4: Stability study data (Drug content)

Trial	A(1^{st} Day)	B(180^{th} Day)	A-B
01	98.20	98.0	0.20
02	99.11	98.91	0.20
03	98.21	98.00	0.21
04	98.35	97.91	0.44
05	99.21	98.78	0.43
Mean SD	98.616 0.5014		0.296 0.1270

p=0.005

FT-IR

FT-IR was done to evaluate interactions between the drug and polymer. IR spectra for pure drug, gelatin and formulation of drug with gelatin are shown in Fig 4-6 were analyzed. The IR spectra of Atenolol had shown characteristic peaks at 889 cm^{-1}, ($C=CH_2$ stretch), 1612 cm^{-1} (Conjugated C=C (aromatic) stretch), 1637 cm^{-1} ($O=C-NH_2$ stretch), 1705 cm^{-1} (C=O stretch) and 2868 cm^{-1} (C-H stretch) 2923 cm^{-1} (CH_2 stretch), 2965 cm^{-1} (ester $C-CH_3$ stretch) respectively. Whereas the prominent peak of secondary amine was appeared at 3240-3277 cm^{-1} and of hydroxyl group appeared at 3355 cm^{-1}. The IR spectra of Atenolol formulation $ATPGS_3$ had exhibited similar characteristic peaks of pure drug which confirmed that there was mild to no interaction between the drug and the polymer.

Differential Scanning Colorimetry

The DSC thermogram of atenolol has exhibited a sharp endothermic peak at 153.29^{o}C with an onset of 152.49^{o}C corresponding to its melting point with ΔH -161.86 J/g. The thermogram of ATPGS3 formulation has shown endothermic peak at 124.69ºc with less intense peaks of drug indicating decrease in crystallinity due to mixing[12] or may be due to change in the heat capacity of atenolol: polymer, Finally the DSC result suggest that there is a lowering in the atenolol

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endothermic peak corresponding to the melting point of the atenolol indicating a possible mild interaction at molecular level between the drug and the polymer without affecting the integrity the drug Fig 8 and 9.

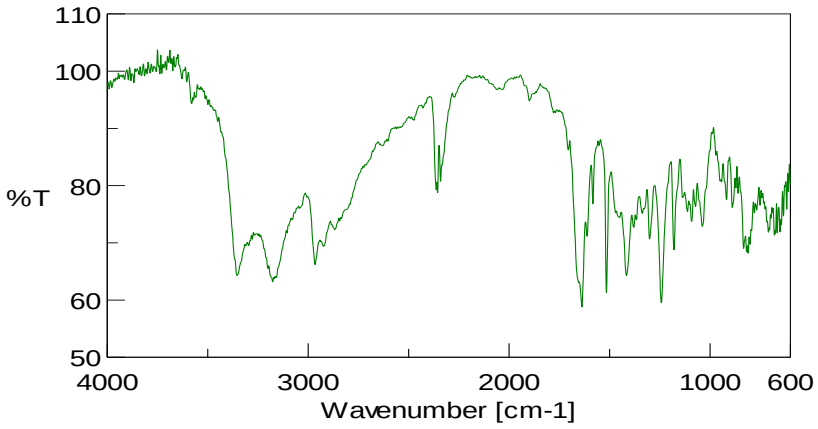

Fig 4: IR Spectra of Atenolol

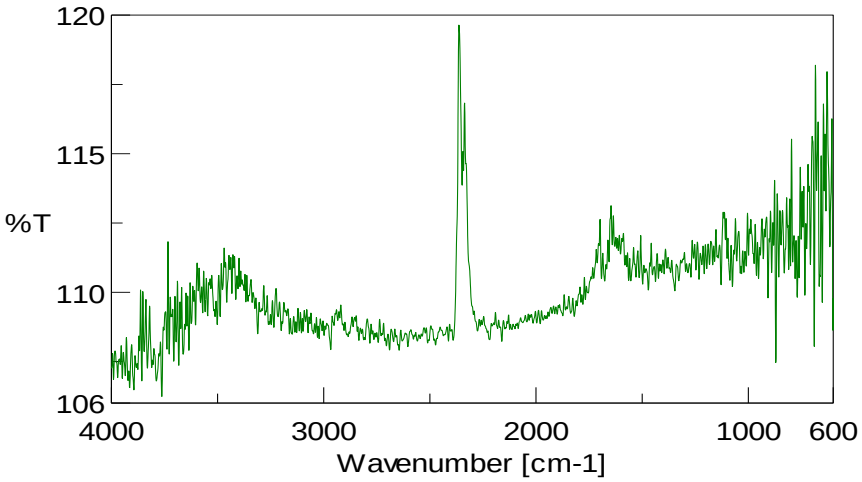

Fig 5: IR Spectra of Gelatin

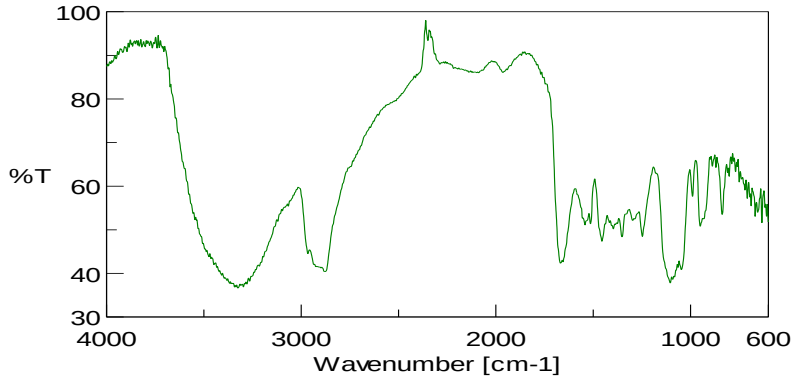

Fig 6: IR Spectra of ATPGS3

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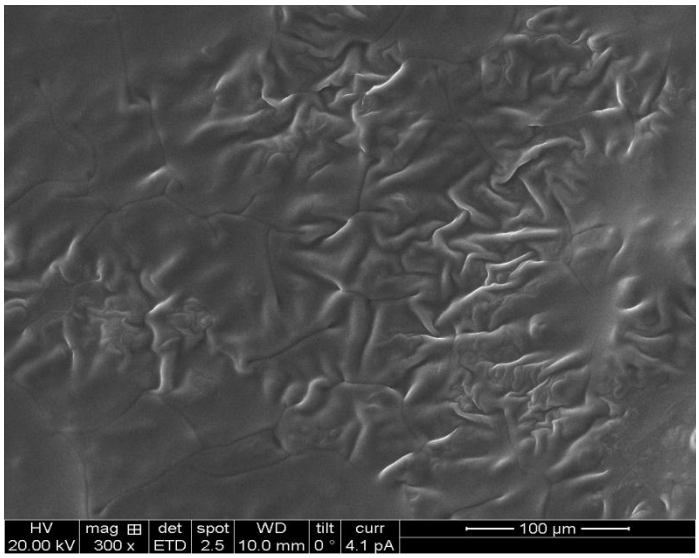

Fig 7: SEM Micrographs of ATPGS3

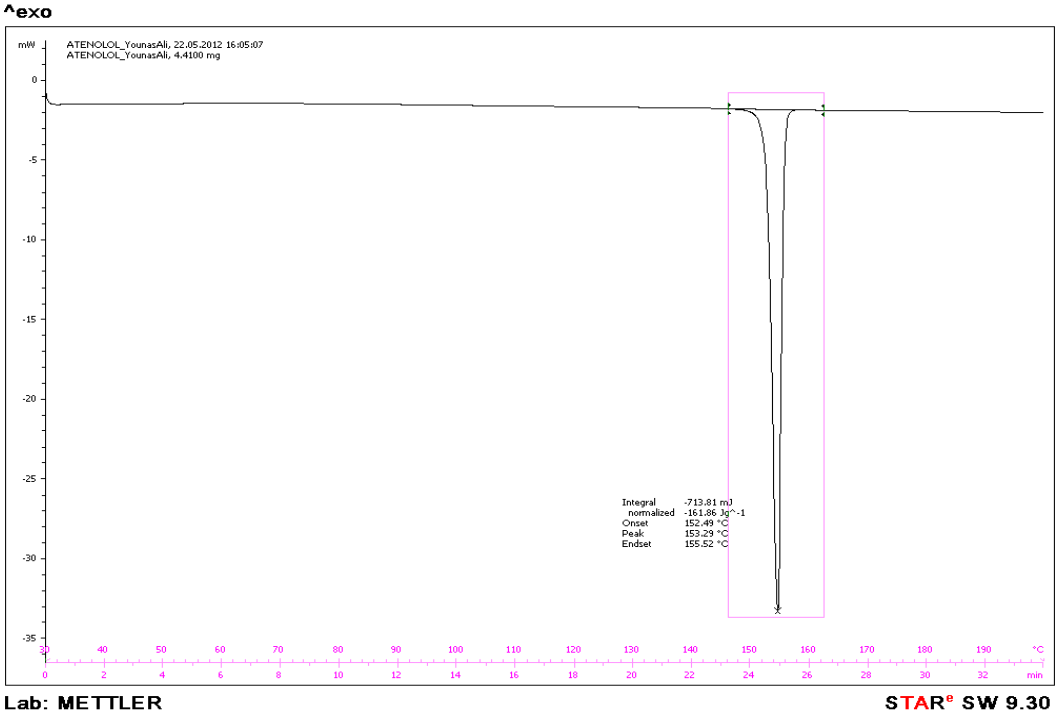

Fig 8: DSC thermogram of Atenolol

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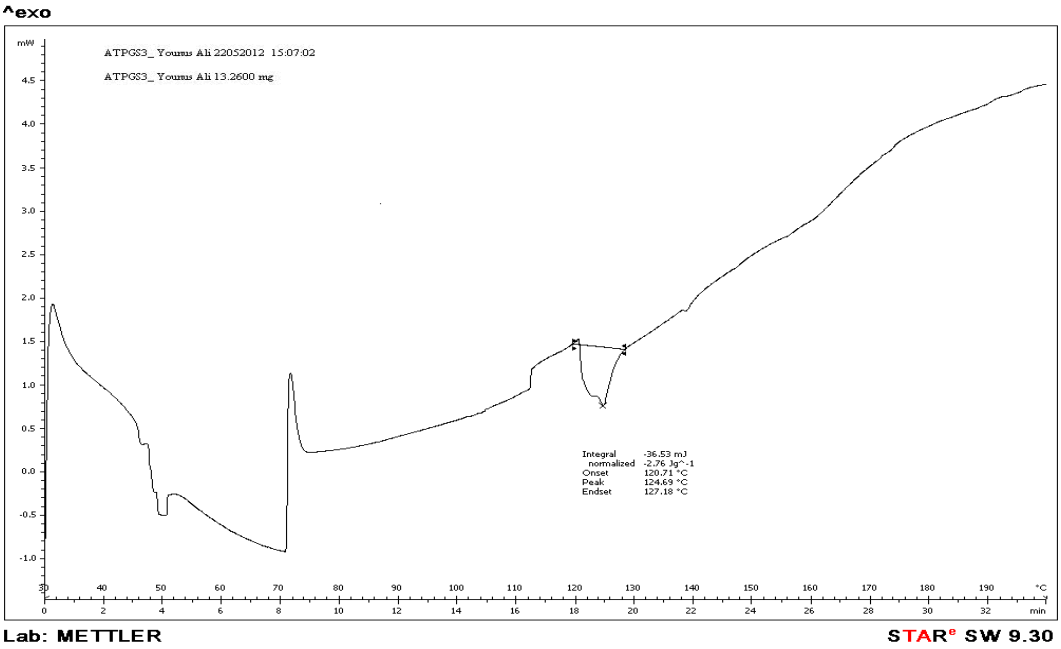

Fig 9: DSC thermogram of Formulation ATPGS3

Scanning Electron Microscopy (SEM)

The images of SEM suggest that uniform dispersion of the drug was found within the polymer with a minimum air entrapment. The SEM images further indicate that there is no crystallization of the drug Fig 7.

CONCLUSION

The overall evaluation results suggest that atenolol rectal suppositories can be conveniently formulated by fusion method utilizing hydrogenated vegetable oil and gelatin-PEG 400 bases.

REFERENCES

[1] Larry JC and Herbert AL. Suppositories. In: Lachman L, Liberman HA and Kanig JC. (eds.) The Theory and Practice of Industrial Pharmacy. 3rd ed. Varghese Publishing House, Mumbai 1987; pp.564-587.

[2] Young JP, Chul SY, Hak MK, Jong DR, Yu KO, Chong KK and Han GC. Int J Pharm 2003; 263: 105–111.

[3] Taha EI, Zaghloul AA, Samyb AM, Al-Saidan S, Kassem AA and Khan MA. Int J Pharm 2004; 279: 3-7.

[4] Lawrence HB. Remington. The Science and Practice of Pharmacy. 19th ed. Mack Publishing House, New York 1995; pp. 1577.

[5] Sweetman SC. Martindale. The Complete Drug Reference. 34th ed. Pharmaceutical Press. London (UK) 2005; pp.865.

[6] Hermann TW. Int J Pharm 1995; 123: 1-11.
[7] Carter SJ. Cooper and Gun's Dispensing for Pharmaceutical Students. 12th ed. CBS Publishers, New Delhi 2008; pp. 232-52.
[8] Coben LJ and Liberman HA. In: Lachman L, Libermann HA and Kanig JL. (eds.) 3rd ed. Varghese Publishing House, Mumbai 1989; pp.580.
[9] Indian Pharmacopoeia. 4th ed. Controller of Publications, Ministry of Health and Family Welfare, Govt of India, New Delhi 1996; pp. 572.
[10] Basvaraj BV and Nanjundaswamy NG. Indian Drugs 2005; 42(5): 305-8.
[11] Gowthamrajan K, Giriraj KT, Venkateswaran G, Samanta MK and Suresh B. Indian J Pharm Sci 2002; 64(6): 525-28.
[12] Niharika A, Sundaramoorthy K and Vetrichelvan T**.** Res J Pharm Biol Chem Sci 2010; 1(4): 655- 671.