Sustained Release Rectal Suppositories as Drug Delivery Systems for Atenolol

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Abstract: Atenolol suppositories were prepared using either hydrophilic bases of polyethylene glycol (PEG), or hydrophobic emulsifying bases such as witepsol H15 (WH15). Interestingly, Atenolol showed high release rates from both bases (about 100% at 4 hours) due to its low partition coefficients and high hydrophilic properties. Sustained release (SR) suppositories are promising when oral route is inaccessible. SR suppositories were formulated in this study using different strategies. The first was to use HPMC as viscosity modifier and bioadhesive agent. The second one was to use nonionic surfactant span 60 (Sp 60) with or without cholesterol (CH) in combination with the base. Results showed that the PEG/Sp 60 bases formed niosomal vesicles upon hydration with water. On the other hand, the WH15/Sp 60 gave rise to emulsions when melted in phosphate buffer pH 7.4. Both types of new SR suppositories showed slow release rates for Atenolol when no CH added. Addition of CH to either WH15 or PEG bases resulted in increased Atenolol release rates. On the other hand, suppositories containing WH15/20%HPMC and PEG/30%HPMC also possess slow-release effect. W H15, W H15/ 20% HPMC, W H15/ Sp 60:CH(1:0), PEG, PEG/ 30% HPMC, and PEG/ Sp 60:CH (1:1) containing Atenolol in a dose of 20 mg/kg were selected to examine the *in vivo* antihypertensive effects of the drug via rectal administration into hypertensive rats and compare the results with that obtained from oral solution of the drug in distilled water (20mg/kg). Atenolol by the rectal route of administration has decreased the mean arterial blood pressure more readily when compared to the oral route in the first 2 hours after administration. The arterial blood pressure lowering was diminished in six hours with oral or fast release suppository bases (PEG or WH15) where it was lowered slowly along six hours for the sustained release formulations and persists at normal levels throughout the six hours.
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1. Introduction:

Rectal administration of drugs offers several advantages over other routes due to reduction of side effects namely gastrointestinal irritation and the avoidance of both disagreeable taste and first pass effect (**1-4**). It represents also an alternative route when oral route is not possible in nausea, vomiting, and unconscious conditions (**5,6**). Conventional suppositories are solids at room temperature and melt, soften or even dissolve at rectal temperature (**7,8**). Cacao butter and witepsols are commonly used as fatty bases that melt at 37 ˚C. However, glycerinated gelatin and PEGs are used as water soluble bases (**9,10**). The drug release from suppositories could differ depending on its physicochemical properties and the nature of the base used. If the drug is highly released from the selected base and multiple drug administration is required to maintain therapeutic effects, it is important to retard drug release and make it sustained for long period of time (**11,12**). The reported strategies to formulate sustained release (SR) solid suppositories were to add a viscosity modifier such as cellulose polymers to the base or to incorporate the drug in microspheres and disperse them into the base (**13-15**). Moreover, niosomes as vesicular bilayer drug carriers may offer good and convenient strategy for SR suppositories. They are self assembled when certain nonionic surfactants are hydrated with water (**16**). The addition of such kinds of nonionic surfactants to water soluble suppository bases could give rise to proniosomal structures that form niosomal vesicles upon hydration. In addition, it has been reported that proniosomes can increase drug stability and prolong its release time (**17**). On the other hand, this study has speculated that the incorporation of nonionic surfactants into a fatty base could form emulsions with buffers at 37 ˚C. The emulsions could form slowly as the base melts and mixes with water in the rectum which may retard drug release rates.

Atenolol, (RS)-4-(2hydroxy-3-isopropyl amino-propoxy) phenylacetamide, is a cardioselective β-blocker (**18**). It is reported to lack intrinsic sympathomimetic activity and membrane stabilizing properties (**19**). The drug is used to treat numerous cardiovascular disorders like hypertension, angina pectoris, cardiac arrhythmias, and myocardial infarction (**20**). Atenolol almost has no first pass

metabolism and excreted mainly through the kidney. The drug is slightly soluble in water (20 mg/ml) and has low partition coefficient. This may be responsible for its poor absorption and reduced bioavailability when taken orally (about 50% of the dose absorbed and the rest excreted in feces) (**21,22**). Administration of Atenolol tablets has been reported to exhibit fluctuations in plasma levels, resulting in side effects like bradycardia, dizziness, gastrointestinal upset and reduced concentration at receptor sites (**23**). This makes it of value to look for the possible ways to control the drug release, enhance its absorption and bioavailability. Rectal administration showed one of the best routes involved in increasing drug absorption and bioavailability. It is considered a convenient route of drug administration especially in cardiovascular emergencies where the patient is unconscious and oral route and sometimes the parentral route are not possible.

The aim of this study was to formulate and evaluate a modified release type suppositories for Atenolol. HPMC or Sp 60/CH was used as release modifiers for Atenolol from suppositories made from PEG or WH15 bases. The suppositories formulations containing Sp 60/CH as 50% of the base weight could be considered as new suppository formulae. The new suppositories can be defined as proniosomal type when in PEG bases or emulsifying type when in WH15 fatty base suppositories. The developed modified type suppositories could reduce drug dosing, enhance the bioavailability and lead to the convenient therapeutic effects.

2. Material and methods:

2.1. Materials:

Atenolol, HPMC (400 cP) and Witepsol H15 were kindly supplied as a gift by the Egyptian International Pharmaceutical Industries Co. (E.I.P.I.Co), Egypt. Polyethylene glycol (PEG) of molecular weights of 6000, 4000 and 400 were obtained from Memphis Co., Egypt. sorbitan monostearate (span 60), and cholesterol (CH; >99%) were purchased from Sigma Chemical Co., St. Louis, MO, USA. Spectrapore® nitrocellulose membranes (MWCO 2000–15,000) were obtained from Spectrapore Inc., NY, USA. All other chemicals and solvents were of Analar grade and obtained from El-Nasr Company for Pharmaceutical Chemicals, Cairo, Egypt.

2.2. Methods:

2.2.1. Preparation of Atenolol suppositories:

2.2.1.1 Conventional suppositories:

Suppositories containing 100 mg of Atenolol were prepared by the fusion method using a metal mould with six cavities. WH15 and PEG with different compositions mentioned in table 1 were used as suppository bases. Drug displacement values of the bases used were first determined and the amount of drug required was calculated.

2.2.1.2. Modified release suppositories:

i- HPMC containing suppositories:

HPMC in different concentrations 5%-30% wt/wt were incorporated into suppositories of WH15 or PEG bases by fusion technique.

ii- Span 60/Cholesterol containing suppositories:

Span 60 with or without cholesterol was melted with WH15 or PEG then the calculated amount of the drug was added slowly with continuous stirring. The ratio of amphiphilic mix/base was kept as 1:1. The homogenous melt was then poured into the mould and left to congeal at room temperature. The presence of amphiphile like Sp 60 in a fatty base could result in a form we called emulsifying type suppositories. On the other hand, PEG is a water soluble base and presence of amphiphile could result in niosomal vesicles upon hydration, hence this form could be named proniosomal suppositories.

2.2.2. Testing of the prepared suppositories:

2.2.2.1. Uniformity of the weight (B.P 1993) (24):

Weigh 20 suppositories individually then together and calculate the average weight according to the following equation:

Average weight = Total weight of the 20 suppositories/20

There must be not more than 2 suppositories differ from the average weight by more than 5% and no suppository differs from the average weight by more than 10%.

2.2.2.2. Melting point:

The time taken for the entire suppository to melt or disperse when immersed in a water bath maintained at 37 ± 1 ˚C (**25**).

2.2.2.3. Hardness of the suppositories (Breaking test):

The Erweka method is used to measure the weight in kilograms a suppository can bear without breaking. For satisfactory results, hardness should lay between 1.8 and 2 kg (**26**).

2.2.2.4. Determination of pH of suppositories:

The suppository was digested in warm water then filtered and the pH of the filtrate was measured by suitable pH meter.

2.2.3. Electron Microscopy:

The formation of niosomal vesicles was proved by electron microscopy (Joel Jim 1010, Japan). The hydrated suppository suspension was used for sampling. A drop of niosomal vesicles was taken on a carbon coated grid. The vesicles were stained using negative stain (uranyl acetate 2% w/v). The grids

were then visualized by transmission electron microscopy (TEM).

2.2.4. Determination of entrapment efficiency of Atenolol:

The percentage of Atenolol entrapped in niosomes formed after complete hydration of proniosomal suppositories was measured by dialysis method reported by **Mokhtar *et al.* (16)**.

The proniosomal suppository was dispersed in 5 ml phosphate buffer of pH 7.4 at 60 ˚C and the resultant niosomal dispersion is adjusted to 10 ml by phosphate buffer of pH 7.4 then cooled to room temperature. 1 ml of the niosomal dispersion was placed into dialysis cellophane bag mounted in 100 ml of phosphate buffer of pH 7.4 and dialyzing exhaustively for 24 hours at ambient room temperature and magnetic stirring. The entrapment efficiency percent (EE%) of atenolol was measured according to the following equation:

$$EE\% = \frac{Amount\ of\ drug\ entrapped}{Total\ amount\ of\ drug}\ X\ 100$$

2.3. *In vitro* release study:

In vitro release tests were carried out according to a modified USP XXII basket method. Each suppository was placed in a glass tube opened in one side and the other side was sealed by cellophane membrane via rubber band. About 2 ml of phosphate buffer pH 7.4 was added to donor side and the tube was hanged in place of the baskets in the dissolution apparatus. The glass tubes then lowered into a flask containing 100 ml of phosphate buffer (pH 7.4) maintained at 37 $\pm$ 0.5˚C and rotated at 50 rpm. About 2 ml samples were withdrawn at appropriate time intervals and replaced immediately by 2 ml of phosphate buffer pH 7.4 to maintain sink conditions. The amount of Atenolol released by time was assayed spectrophotometrically at 272 nm. The experiment was repeated three times and the results were calculated as the mean ± SD.

2.4. *In vivo* studies:

2.4.1. Induction of hypertension:

Hypertension was induced in adult albino male rats weighing 200~250 gm by complete left renal artery ligation according to method described by **Cangiano *et al.* (27)**. Rats were obtained from Faculty of Veterinary Medicine, Zagazig University, animal breeding center, Egypt and treated according to Ethical committee of animal handling in Zagazig University "ECAHZU"

This method can be summarized as follow:

1- Adult albino male rats weighing 200~250 gm each were anaesthetized with thiopental sodium (40 mg/ kg b.wt.) injected intraperitoneally (**28**).
2- After shaving of hair and sterilization of skin, 2 cm-long incision was made in the left side just below the ribs and 0.5 cm away from the vertebral column.
3- The left renal artery was identified then stretched by means of a retractor placed between the kidney and the muscle layer; the artery was separated from the vein with a hook and dissected from the surrounding connective tissue (**29**).
4- The exposed left renal artery was completely ligated with 4-0 sterile surgical silk as close as possible to the aorta. The incision was closed by careful continuous suturing of the muscle layer of 4-0 silk with a non cutting needle; then the skin is approximated and closed with interrupted sterile surgical 0-silk sutures (**27**).
5- Postoperatively, the rats were given penicillin G (100,000 units I.M) per rat for 3 successive days; and were allowed with free access to food and water for 28 days(**29**).

In- vivo studies were done on the selected Atenolol suppositories formulations to evaluate their efficiency in comparison to Atenolol solution that given orally. Freshly prepared suppositories containing Atenolol (10 mg/1 g) were used in the study. Each rat has received Atenolol in a dose of 20 mg/kg. Suppositories which are containing PEG base were moistened with water before insertion.

Animals were divided into 8 groups each consisting of 4 rats (n=4):

Group 1 : (-ve control): rats were subjected to operation but not received any drug.

Group 2: (+ve control) : rats were subjected to operation and received oral Atenolol dissolved in distilled water.

Group 3: rats were treated with (WH15) suppositories.

Group 4: rats were treated with (WH15/ 20 %HPMC) suppositories.

Group 5: rats were treated with (WH15/ Sp 60 : CH (1:0)) suppositories.

Group 6: rats were treated with (PEG III) suppositories.

Group 7: rats were treated with (PEG III/ 30 %HPMC) suppositories.

Group 8: rats were treated with (PEG III/ Sp 60: CH (1:1)) suppositories.

2.4.2. Blood pressure measurement:

2.4.2.1. Anaesthesia of the animals:

The rats were anaesthetized with urethane (ethyl carbamate) in a dose of 1.75- 2.0 gm/kg body weight (**30**).

2.4.2.2. Preparation of the animals:

Intra arterial cannulation was done and the systemic arterial blood pressure was recorded as follows:

1- The blood pressure of rats was determined employing the method of **Parasuraman and Raveendran (30)**.
2- After stabilization of anaesthesia, the animal was placed on a board in a supine position.
3- The four limbs were extended and fixed to the sides of the board.
4- A mid line longitudinal skin incision started just below the neck and extended to the sternum was done, the skin was removed and pretracheal muscles and fascia were separated away as shown in figure
5- The trachea was then exposed and dissected for a suitable distance. Lateral to trachea in the left side, the pulsation of the common carotid artery was located.
6- The artery was separated from accompanying nerves (vagus and cervical sympathetic nerves) and internal jugular vein was carefully freed from connective tissue for a distance as long as possible.
7- A tight ligature of the artery was applied at its distal end (cephalic end), while a loose ligature was applied around the artery at its proximal end (thoracic end)
8- A small snip across the artery was opened by a small sharp scissors and poly ethylene arterial cannula filled with heparinized saline solution was inserted gently towards the heart, the ligature was tied around the cannula and the bulldog clamp was then removed.

The mean arterial blood pressure was calculated according to the following equation: (31)

Mean arterial B.P = Diastolic B.P + (Systolic B.P – Diastolic B.P)/3

2.5. Test of irritation:

After finishing the *in vivo* experiment of hypertension measuring, rats were scarified using over dose of phenobarbitone (100 mg/kg) and the rectum mucosa was examined visually for any irritation produced due to the applied suppository. Animals were given scores for the degree of irritation according to the redness of the mucosa or even the presence of blood as following:

- If severe redness with bleeding will be given +ve symbol.
- If mild redness without bleeding will be given –ve symbol.
- If no irritation at all with normal mucosal membrane will be given 0 symbol.

2.6. Statistical analysis:

For comparisons a one way analysis of variance followed by the least significant difference (LSD) as a post-hoc test was applied, using SPSS program version 9 software. The difference was considered as significant when $P<0.05$.

3. Results and Discussion:

3.1. Physicochemical properties:

The produced suppositories were pale white or yellowish color and smooth with no surface cracks or fissures. The results of the fracture point (Hardness test), the softening time, the weight uniformity, the content uniformity and the drug distribution within each suppository was found satisfactory and listed in table 2. The fracture point of the prepared suppositories was between 0.6 to 4.5 Kg which proves sufficient mechanical strength to withstand abrasive forces during storage or transportation processes. The average suppository weight was ranged between 1 and 1.3 g with no statistical differences between them ($P>0.05$). The softening time was found to differ as the suppository base changed and also according to additive materials. It was found to be as low as 5 minutes in case of WH15 base and greater than 30 minutes for PEG bases. HPMC (10% to 30% w/w) has increased the softening time of WH15 to 25 minutes where this time was decreased to 20 min when HPMC was 5% w/w. Also, WH15/ Sp60/CH bases showed softening times lower than 30 minutes. All PEG suppository bases with HPMC of any concentration or with Sp 60/CH showed high softening times which was more than 30 min. The softening time is important for fatty suppositories as it could control the rate of drug release, where for suppositories of PEG bases, they already solubilized by water and drug release will be controlled by other additives such as HPMC or Sp60/CH.

3.2. Microscopic examination:

Transmission electron microscopy of the hydrated suppositories at 37 ˚C has proved the formation of niosomal vesicles in case of PEG/span suppositories or bigger emulsion droplets formed when WH15/Sp 60 melted in phosphate buffer (Figure 1). Interestingly, the formed niosomal vesicles were of the unilammelar type of sizes below 100 nm. This could be as a result of the dispersion of span surfactant in high amount of PEG matrix which dissolved in the buffer. This could give the surfactant molecules the chance to aggregate in small numbers and smaller vesicles were produced. Conversely, WH15/Sp 60 melt can`t form niosomal vesicles as

they are oily in nature and instead emulsion droplets could form which congealed upon cooling forming solid spheres as shown in figure 1. These emulsion droplets couldn`t form with WH15 where no Sp 60 added.

3.3. *In Vitro* Release properties:

The release of Atenolol from different suppository bases was shown in figure 2. It is clear that the drug is well released from both hydrophilic and hydrophobic bases. The percentage drug released after 4 hrs was 103.8%, 91.3%, 88.8%, and 85.1% from WH15, PEGIII, PEGII, and PEGI, respectively. The result might be due to the fact that Atenolol has low partition coefficient (log $P_{octanol/water}$=0.23) and so it is highly hydrophilic drug (**32**). Also, it is clear from the results that the differences in drug release were not high using PEG bases of varied composition. There are only 6% difference between the highest releasing base (PEG III) and lowest one (PEG I). Accordingly, PEG III base was chosen to prepare SR suppositories. The results revealed that both hydrophilic PEG bases and lipophilic witepsol bases were suitable for SR suppository formulations for Atenolol.

In order to control the release of Atenolol from a suppository base, HPMC and Sp 60/ CH were used and evaluated. Results are represented in figures 3 to 6. The addition of HPMC to a suppository base at 10% and 20% concentrations in PEG III base showed similar patterns with that obtained from pure PEG III formula. On the other hand, at 30% HPMC concentration, the release of Atenolol has decreased markedly to about 50% after 4 hours (Figure 3). The previous results could be due to the increased hydrophilicity of PEG base upon HPMC addition at lower concentrations, where at high HPMC concentrations the viscosity of the matrix might markedly increase forming network structure and hinder the drug diffusion. The addition of HPMC to WH15 base showed more precise pattern where the release of Atenolol was linearly decreased as the concentration of HPMC increased. Atenolol release was decreased from 94% to 22% as HPMC concentration increased from 5% to 30% in WH15 base, respectively (Figure 4). As previously discussed by **Abass *et al.* (33)**, the decreased release rates due to a viscosity modifier was attributed to the more gelling behavior exhibited by the gelling component. The mucoadhesion properties of HPMC also give the formulation more intensive promise as SR rectal formulation.

Sp 60 has the ability to self assemble in water forming bilayer vesicular structures called niosomes (**34**). As a drug delivery system, niosomes can retard drug release by entrapment either in the bilayer structure or within the aqueous compartment. The incorporation of Sp 60 into PEG III base resulted in good elegant suppositories with acceptable physicochemical properties listed in table 2. The produced suppositories could be a proniosome type where niosomal vesicles were evidently photographed after hydration and represented in figure 1. The complete dispersion of the suppository followed by hot buffer addition resulted in niosomes dispersions and the entrapment efficiency of Atenolol into niosomes was listed in table 3. From table 3 it is obvious that Atenolol entrapment efficiency decreased from 96.8% to 66% as cholesterol percentage (calculated as percent of total span molar concentration) increased from 0% to 50%. The high encapsulation of Atenolol may be attributed to the solubility of the drug in the lipid mixture before reconstitution in the buffer which embed the drug in the lipid bilayer. As Atenolol packed into the bilayer, it could compete with cholesterol for positions in the bilayer structure and this led to the decrease in drug entrapment efficiencies as cholesterol percentages increased (**16**). The release of Atenolol from proniosomal suppositories could be explained on the basis of the drug entrapment efficiency. Figure 5 indicates a great decrease in Atenolol release rate where Sp 60 incorporated into PEG suppositories in the absence of cholesterol (about 17% after 4 hours). The percentage Atenolol release increased to 38% after 4h when cholesterol increased to 50% of total lipid concentration (Figure 5). It is considerable that as the percentage of un-entrapped drug increased the rate of Atenolol release increased.

The incorporation of Sp 60 into WH15 fatty base could not form niosomes up on hydration due to the excess oily medium which inhibit the self assembly of the surfactant into bilayer structures (Figure 1). Emulsions instead could form and the release of Atenolol also affected. Figure 6 shows a decreased rate of release of Atenolol from 103% to 34% when Sp 60 added to WH15 base and in absence of CH. Again, the addition of cholesterol had increased the drug release rate from 34% at 0% CH to 96% at 50% CH, however this might be ascribed to the increase in the lipophilicity of the base as CH added (Figure 6). As mentioned above, the low partition coefficient of the drug led to the rapid release from fatty bases.

3.4. *In vivo* study of SR suppositories:

Figure 7 shows that both rapid release suppositories of PEG and WH15 have decreased the mean arterial blood pressure to normal values for short time intervals. Also, the oral solution of the drug containing the same dose of Atenolol (20 mg/kg) showed the mean arterial blood pressure lowering in hypertensive rats was continued for only

2 hours after administration. The mean arterial blood pressure has lowered to 100 mmHg after one hour of oral administration and raised in the second hour directly. The result reflects the poor drug absorption from the GIT. Comparing the results obtained after oral administration with those obtained after rectal administration using either PEG III or WH15 suppositories, the mean arterial blood pressure showed normal levels for more than 3 hours and elevated in the fourth hour using rapid release suppositories which is better than using drug solution. This confirmed the fact that the drug bioavailability after rectal administration is better than oral route due to several causes such as the elimination of first pass effect and bypassing the GIT secretions, pH, enzymes, motility and other factors (**35**). Interestingly, the SR suppositories of both base types gave slow and precise blood pressure lowering which persisted from the first hour to the end of the experiment at normal blood pressure measures. Statistical analysis revealed that the mean arterial blood pressure after 6 hours of administration of SR suppositories was significantly lowered when compared to that obtained after oral solution or rapid release rectal suppositories of both bases ($P<0.05$). On the other hand, there were no statistical differences when comparing PEGIII/30% HPMC with PEGIII/ Sp 60:CH(1:1), WH15/20% HPMC, or WH15/Sp 60 SR suppositories ($P>0.05$). Results could lead to the fact that both HPMC and Sp 60 with or without CH were useful additives for the control of hypertension resulting in SR formulations. It is well known that HPMC is a mucoadhesive polymer which adhered to mucosal membranes increasing the drug contact time to rectal mucosa (**36**). Also, it is evident that niosomal vesicles were formed after hydration of PEG suppositories containing Sp 60 surfactant, where the presence of Sp 60 in fatty bases led to the formation of emulsion droplets in presence of water. Both niosomal vesicles and emulsion droplets have the ability to increase the residence time of the drug with rectal mucosa through surfactant membrane interaction (**37**). The interaction of Sp 60 with rectal mucosal membrane could enhance the rate of drug diffusion and bioavailability. From the results it is clear that the SR suppository formulae have enhanced the drug effects due to the increased drug absorption and prolonged contact time of the drug to the rectal mucosa.

The irritation test (Table 4) indicated that even moist PEG III suppositories were highly irritant to rectal mucosa. The irritation become mild upon the addition of HPMC to PEG bases. Conversely, there were no irritation at all when Sp 60 with or without CH was added to PEG base. Also, WH15 bases with or without SP 60 or HPMC showed no irritation of the rectal mucosa.

Table 1: Composition of suppositories of different formulations:

Formulae	Composition of each suppository calculated as percentages of total weight.							
	WH15	PEG 4000	PEG 6000	PEG 400	HPMC	Sp 60	CH	Water
W H15	100	-	-	-	-	-	-	-
W H15/ 5%HPMC	95	-	-	-	5	-	-	-
W H15/ 10%HPMC	90	-	-	-	10	-	-	-
W H15/ 20%HPMC	80	-	-	-	20	-	-	-
W H15/ 30%HPMC	70	-	-	-	30	-	-	-
W H15/ SPAN: CH (1:0)	50	-	-	-	-	50	-	-
W H15/ SPAN: CH (9:1)	50	-	-	-	-	45	5	-
W H15/ SPAN: CH (7:3)	50	-	-	-	-	35	15	-
W H15/ SPAN: CH (1:1)	50	-	-	-	-	25	25	-
PEG I	-	33	47	-	-	-	-	20
PEG II	-	60	-	40	-	-	-	-
PEG III	-	-	40	60	-	-	-	-
PEG III/ 5% HPMC	-	-	38	57	5	-	-	-
PEG III/ 10% HPMC	-	-	36	54	10	-	-	-
PEG III/ 20% HPMC	-	-	32	48	20	-	-	-

*Atenolol was fixed as 100 mg in each suppository.

Table 1 (Continued): Composition of suppositories of different formulations:

Formulae	Composition of each suppository calculated as percentages of total weight.							
	WH15	PEG 4000	PEG 6000	PEG 400	HPMC	Sp 60	CH	Water
PEG III/ SPAN: CH (1:0)	-	-	20	30	-	50	-	-
PEG III/ SPAN:CH (9:1)	-	-	20	30	-	45	5	-
PEG III/ SPAN:CH (7:3)	-	-	20	30	-	35	15	-
PEG III/ SPAN:CH (1:1)	-	-	20	30	-	25	25	-

*Atenolol was fixed as 100 mg in each suppository.

Table 2: Physicochemical parameters of the prepared suppositories. Data represented as the mean ±SD

Formulae	Hardness (Kg)	Softening Time (mins)	Average wt (g)	pH
W H_{15}	4.5	5	1.2±0.3	10.7
W H_{15}/ 5%HPMC	4	20	1.3±0.4	11.7
W H_{15}/ 10%HPMC	4	25	1±0.2	11.7
W H_{15}/ 20%HPMC	4	25	0.99±0.1	11.7
W H_{15}/30%HPMC	4	25	1.2±0.1	11.7
W H_{15}/1 Sp: 0 CH	4	25	1.2±0.0	10
W H_{15}/ 9 Sp: 1 CH	4	25	0.9±0.3	10.8
W H_{15}/ 7 Sp: 3 CH	3.5	20	0.99±0.1	10.3
W H_{15}/ 1 Sp:1 CH	2.5	20	1.02±0.3	10.8
PEG I	2	>30	0.9±0.3	10
PEG II	2.4	>30	1.1±0.3	10
PEG III	2.5	>30	1.2±0.1	10.3
PEG III/ 5% HPMC	4	>30	0.9±0.2	10
PEG III/ 10% HPMC	4	>30	1.12±0.1	10
PEG III/ 20% HPMC	4	>30	1.05±0.2	10
PEG III/ 1 Sp: 0 CH	4	>30	1.2±0.2	11.2
PEG III/ 9 Sp: 1 CH	0.9	>30	1.1±0.1	10.8
PEG III/ 7 Sp: 3 CH	0.6	>30	1.2±0.1	10
PEG III/ 1 Sp: 1 CH	0.6	>30	1.02±0.2	10

Table 3: The entrapment efficiency percentage of Atenolol into niosomes prepared from proniosome suppositories PEG base was 50% of the total suppository weight: Data represented as the mean ±SD (n=3).

Sp 60/CH	Average un-entrapped Atenolol %	Atenolol Entrapment efficiency %
1/0	3.1 ± 0.1	96.9 ± 0.1
9/1	17.4 ± 0.2	82.6 ± 0.2
7/3	27.9 ± 1	72.1 ± 1
1/1	34 ± 1.9	66 ± 1.9

Table 4: Irritation scores for the applied suppositories.

Formulae	Irritation score	Formulae	Irritation score
WH15	0	PEG III	+ve
WH15/20% HPMC	0	PEG III/30% HPMC	-ve
WH15/ Sp 60	0	PEG III/ Sp 60:CH (1:1)	0

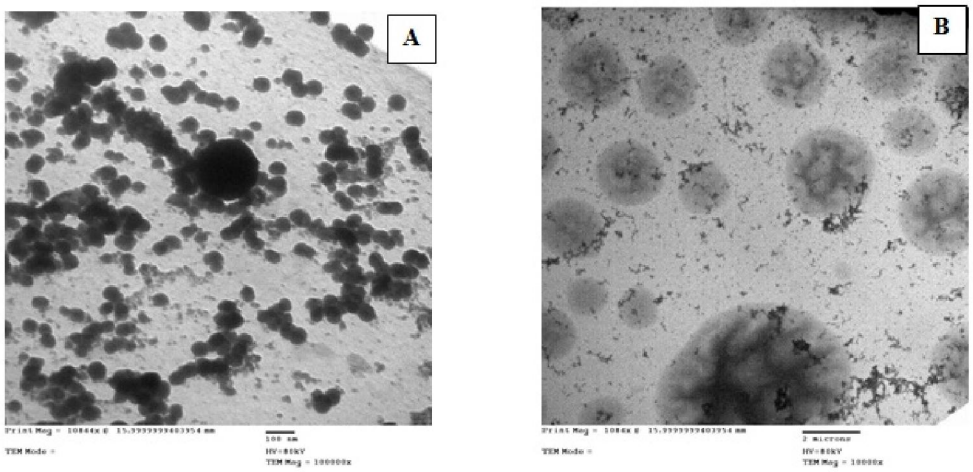

Figure 1: TEM photographs of niosomal vesicles (A) formed from hydrated proniosomal suppositories and congealed emulsion droplets (B) formed from emulsifying WH15/Sp 60 suppositories with the buffer.

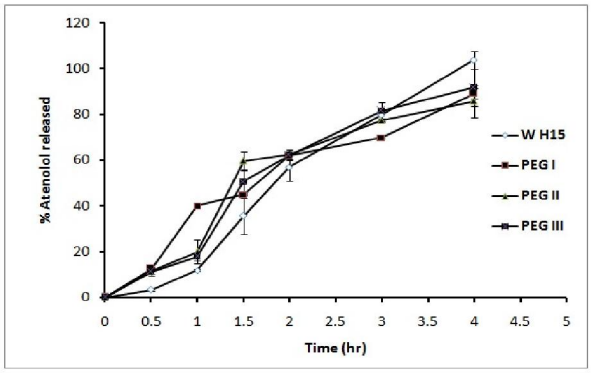

Figure 2: Release of Atenolol from Hydrophobic base WH15 versus hydrophilic PEG bases. Data represented as the mean ± SD (n=3).

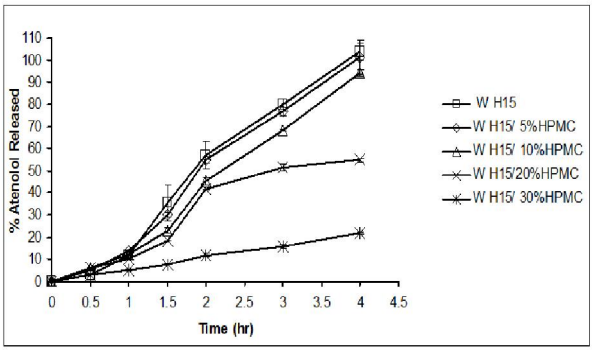

Figure 4: Release of Atenolol from WH15/HPMC suppositories. Data represented as the mean ± SD (n=3).

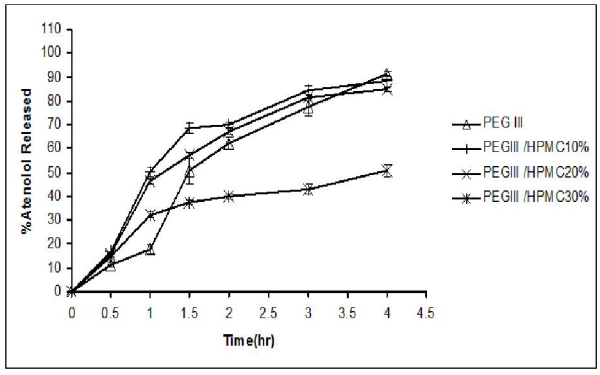

Figure 3: Release of Atenolol from PEG III/ HPMC suppositories. Data represented as the mean ± SD (n=3).

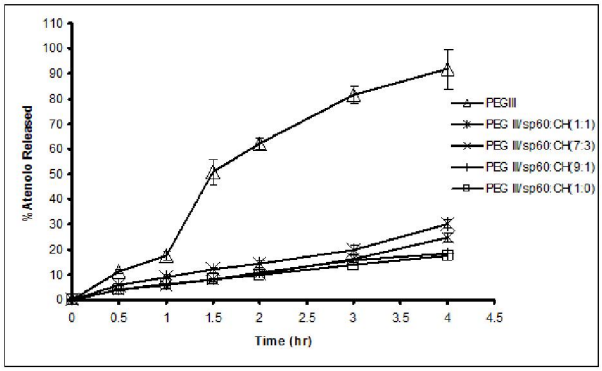

Figure 5: Release of Atenolol from PEG III/ Sp 60:CH suppositories. Data represented as the mean ± SD (n=3).

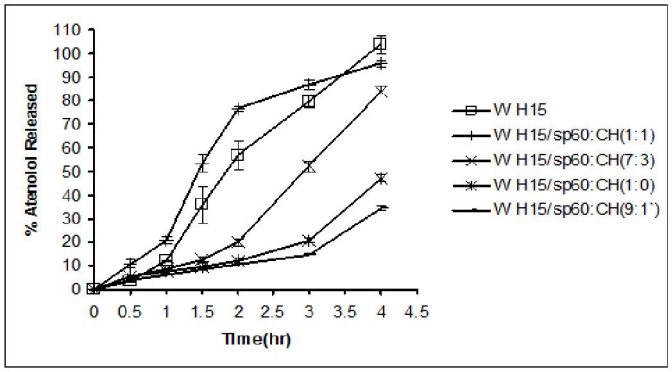

Figure 6: Release of Atenolol from WH15/Sp 60:CH suppositories. Data represented as the mean ± SD (n=3).

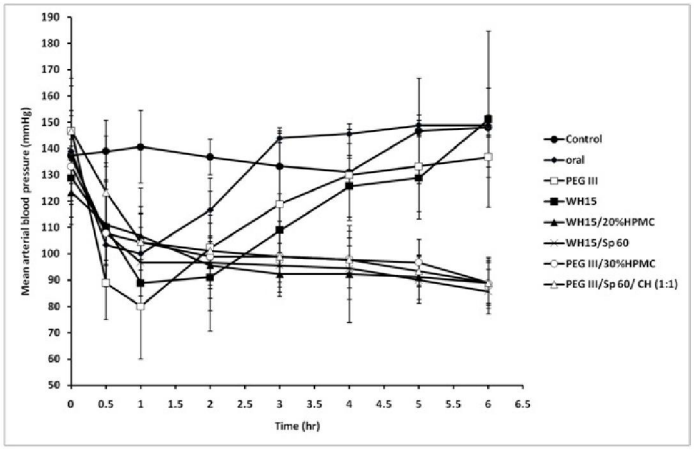

Figure 7: The mean arterial blood pressure after oral administration of Atenolol solution or rectal administration of Atenolol suppositories (20 mg/kg) using rats. Data represented as the mean ± SD (n=4).

4. Conclusion:

SR rectal suppositories of Atenolol were successfully formulated either by using HPMC as a mucoadhesive polymer, proniosomal technology in hydrophilic PEG or emulsification of WH15 base with Sp 60. The proniosomal type suppositories, the WH15/Sp 60 and WH15/ HPMC suppositories showed non irritant, slow release and prolonged antihypertensive effects of Atenolol which was better than both oral or rectal administration of rapid release formulae. Finally, this study suggested the formulation of Atenolol into SR rectal suppository dosage form to enhance the drug absorption and prolonged its pharmacologic effect.

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