Research Article

Design and Evaluation of Sustained Release Propranolol Hydrochloride Suppositories

Basappa Veerabhadraiah Basavaraj[*1], Sundaram Devi, Srinivasan Bharath[1], Rajamanickam Deveswaran[1], Varadharajan Madhavan[2]
*[1]Department of pharmaceutics, M.S.Ramaiah College of Pharmacy, M.S.R. Nagar, M.S.R.I.T. Post, Bangalore, India.
[2]Department of pharmacognosy, M.S.Ramaiah College of Pharmacy, M.S.R. Nagar, M.S.R.I.T. Post, Bangalore, India.
***Corresponding author's E-mail:** bvbasu@gmail.com

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ABSTRACT

The aim of the present study was to prepare a sustained release suppository of propranolol hydrochloride, an antihypertensive drug for rectal administration. Firstly, the microspheres of Propranolol hydrochloride were formulated using ethyl cellulose by non-aqueous solvent evaporation technique. The microspheres were evaluated for percentage yield, particle size, entrapment efficiency, scanning electron microscopy and *in vitro* drug release studies. The prepared microspheres exhibited prolonged drug release up to 8 h. The mean particle size increased with increase in polymer concentration and the drug release rate decreased at higher polymer concentration due to increase in the diffusional path length. The microsphere formulations showed *peppas* model with non-fickian drug release mechanism. Sustained release suppositories using PEG 4000 and PEG 6000 were formulated with the different ratios of microspheres by fusion method. The formulated suppositories was evaluated for its physical parameters, melting point studies, softening temperature, liquefaction temperature, liquefaction time, drug content, *in vitro* drug release and *in vitro* permeability studies. The results suggested that all the formulations were physically stable complying with the official specifications. The melting range suggested PR-3 base was not suitable when compared to PEG bases as stearic acid resulted in hard suppositories. The conventional suppositories without microspheres released the drug within 4 h compared to the sustained release suppositories releasing the drug up to 45 to 87 % till 8 h from the dispersed microspheres. Inverse relationship was observed between the permeability and drug releases studies with the permeability ranging from 40 to 70 %. The results of investigation clearly suggest that a rectal drug delivery system of Propranolol hydrochloride can be successfully designed to achieve a sustained delivery of drug for particular clinical conditions.

Keywords: Fusion molding, Microspheres, Propranolol hydrochloride, Solvent evaporation technique, Sustained release suppository.

INTRODUCTION

Suppositories are the unit solid dosage form of medicament meant for insertion into body cavity. Suppositories are the alternate dosage forms for drugs with less bioavailability when taken orally. The advantages of suppositories over other dosage forms are reduction of side effects namely gastrointestinal irritation and avoidance of both the unpleasant taste and first pass metabolism[1], as the rectal route can deliver 60 – 70% of the administered drug directly into the systemic circulation, thus avoiding loss of drug due to the first pass effect.[2] It is also highly recommended for treating unconscious patients and children.[3]

Besides the conventional form, sustained release suppositories can be prepared in order to achieve sustained–action mechanism by achieving and maintaining a desirable blood concentration of the drug at a roughly constant level for a suitable period of time.[4] A variety of approaches have been investigated for producing controlled release suppository formulations of different drugs. These include modification of the suppository base, use of additives and polymer-coated drug particles.[5]

Propranolol hydrochloride is a nonselective beta-blocker as it blocks the action of epinephrine and nor - epinephrine on both β_1- and β_2- adrenergic receptors. Beta-blockers reduce the work load on the heart and help it to beat more regularly. Propranolol hydrochloride is used to treat tremors, angina (chest pain), hypertension (high blood pressure), heart rhythm disorders, and other heart or circulatory conditions. It is also used to treat or prevent heart attack and to reduce the severity and frequency of migraine headaches.[6] Propranolol is a highly lipophilic drug, rapidly and completely absorbed after oral administration. It readily crosses the blood brain barrier and the plasma half-life is only about 2 to 3 hours. However, it undergoes an extensive hepatic metabolism and on an average only about 25% of Propranolol hydrochloride reaches the systemic circulation.[7]

The Propranolol hydrochloride microspheres were formulated with an appropriate release retarding polymer ethyl cellulose to achieve a sustained drug release. Microspheres have greater applications for targeting the therapeutic molecules, when the dose of the drug is less. The concept of microspheres can be utilized to provide a more reliable and long lasting release of the drug for local and systemic action. The microspheres beneficially alter the absorption of drug, and have been utilized to obtain prolonged and uniform release, afford the possibility of a longer lasting and more reliable release of the drug from dosage form and thereby enhancing the bioavailability.

The main purpose in designing, development and evaluation of sustained release suppositories was to obtain a desirable blood concentration of Propranolol

hydrochloride over an extended period. Furthermore, the formulation of sustained release suppositories of Propranolol hydrochloride obviously gives a new dimension in increasing the therapeutic possibilities.

MATERIALS AND METHODS

Materials

Propranolol hydrochloride (Medopharm, Malur); Ethyl cellulose (Central Drug House, New Delhi); Ethanol, Petroleum ether, Heavy liquid paraffin, PEG 4000, PEG 6000 (Rankem RFCL Limited, New Delhi); Stearic acid (Spectrum Reagents and chemicals private limited, Cochin). All other solvents and reagents used were of analytical grade.

Methods

Preformulation Studies

Compatibility studies of drug and excipients used for preparing microspheres and suppositories

FTIR Study

The drug and polymer interactions were studied by Fourier Transform Infrared Spectroscopy by KBr disc method. FTIR spectra help to confirm the identity of the drug and to detect the interaction of the drug with the carriers. The spectras were recorded for pure drug Propranolol hydrochloride, ethyl cellulose polymer and the physical mixture of drug and polymer in the ratio 1:1 at the scanning range of 400-4000 cm^{-1} using FTIR-8400S, Spectrophotometer (SHIMADZU, Japan). The IR spectrum of physical mixture was compared with the standard IR spectrum of the pure drug.

Similarly, the drug and bases used in preparing suppositories were also studied by FTIR. The spectra were recorded for pure drug Propranolol hydrochloride and polymers PEG 4000, PEG 6000, Stearic acid and the physical mixture of drug and bases in the ratio 1:1 at the scanning range of 400-4000 cm^{-1} using FTIR-8400S, Spectrophotometer (SHIMADZU, Japan). The IR spectra of drug with bases were compared with the standard IR spectrum of the pure drug.

Procedure: A small amount of drug was mixed with the Spectroscopic grade of KBr and triturated for uniform mixing. The thin and transparent palate is prepared by applying 2000 psi pressure. The prepared palate is exposed to the IR beam and spectra are recorded by using FTIR 8400 Shimadzu, Japan.

Differential Scanning Calorimetry

The DSC analysis of pure drug, polymer and the physical mixture of both drug and polymer were carried out to evaluate any possible interaction between drug and polymers using Mettler-7 DSC, Germany.

Method: Samples of about 5 mg were placed in 50 µl perforated aluminum pans and sealed. Heat runs for each sample were set from 5 to 300 °C, using nitrogen as purging gas. The apparatus was indium-cyclohexane calibrated.

Preparation of Propranolol hydrochloride – ethyl cellulose microspheres

Microspheres containing Propranolol hydrochloride as core material were prepared by non-aqueous solvent evaporation technique. Drug and ethyl cellulose in varying ratios (1:1 to 1:5) as shown in Table 1 were dissolved in 3:2 ratio of acetone: ethanol with continuous agitation to form uniform drug-polymer dispersion. This dispersion was slowly introduced into 100 ml heavy liquid paraffin while being stirred at 1000 rpm by a mechanical stirrer equipped with a three bladed propeller at 37 ± 0.5°C for 4 h, to allow the solvent to evaporate completely. Liquid paraffin was decanted and the microspheres were collected by filtration through buchner funnel. The microspheres were washed thrice with petroleum ether until free from oil and dried at room temperature overnight and stored in desiccator.

Table 1: Formulation of Propranolol hydrochloride-ethyl cellulose microspheres

Formulation Code	Ratio of drug to polymer	RPM
P-1	1:1	1000
P-2	1:2	1000
P-3	1:3	1000
P-4	1:4	1000
P-5	1:5	1000

Characterization of Microsphere Formulations

Yield of microspheres

The percentage yield of microspheres was calculated by using the following formula

$$\% \text{ yield} = \frac{\text{actual weight of product}}{\text{total weight of drug and excipient}} \text{ X } 100$$

Particle size and shape

The surface morphology and internal structure of the products were observed by

a. Optical microscopy: The microspheres were observed under 10 X magnification and average mean diameter of 50 particles was counted in an optical microscope (Olympus LITE Image).

b. Scanning electron microscopy: The surface morphology and internal structure of the products were observed by scanning electron microscopy using JEOL JSM-T scanning electron microscope (Japan).

Drug entrapment efficiency

Accurately weighed quantity of microspheres equivalent to 50 mg of Propranolol hydrochloride was dissolved in 0.1N HCl using sonication for 5 min and the volume was made up to 50 ml with 0.1N HCl. The resulting solution was diluted suitably with 0.1N HCl. The absorbance of the

resulting solution was measured at 290 nm, using 0.1N HCl as blank. The percentage drug entrapment was determined using the following equation,

$$\% \text{ Drug entrapment efficiency} = \frac{\text{Amount of drug acctually present}}{\text{Theoritical drug loaded expected}} \times 100$$

In vitro drug release studies

In vitro drug release was studied using dissolution test apparatus USP XXII type I (rotating basket method). The drug loaded microspheres equivalent to 50 mg of Propranolol hydrochloride were introduced into 900 ml pH 7.4 phosphate buffer, which was maintained at 37±0.5 ºC and stirred at 100 rpm. 2 ml of sample was withdrawn at regular intervals and sink conditions were maintained throughout the study by replacing equal volume of fresh dissolution medium. The samples were diluted to 25 ml with 0.1N HCl and analyzed spectrophotometrically at 290 nm using 0.1N HCl as blank. All the analysis was carried out in triplicate.

Drug release kinetics

Data obtained from *in vitro* drug release studies were fitted to various kinetic models like zero-order, 1st order, Higuchi, Korsemeyer peppas and Hixon crowell model using PCP Disso V3 to predict the drug release mechanism.

Formulation of Sustained Release Propranolol Hydrochloride Suppositories

Mold calibration

The bland suppositories were prepared using a clean, dried and lubricated mold of various bases which was weighed. In each case the average weight was taken as true capacity of that particular mold. The mold volume was recorded for the bases and its values are documented for calculation of displacement value and finalizing the formula

Procedure for preparation of suppositories

Base was melted in a pre-heated china dish with vigorous stirring. The drug Propranolol hydrochloride and microspheres containing Propranolol hydrochloride was added and mixed completely in the base. The resulting mixture was poured into the pre-lubricated mold until it over flows at a stretch and allowed to set by cooling on ice. The molds were chilled for 15 min and the excess was trimmed off. The mold was taken out, opened and suppositories were carefully removed from the molds and the formulated suppositories were packed in aluminum foil.

Table 2: Formulation of Propranolol hydrochloride suppositories

Formulation code	Drug (% w/w)	Microspheres ratio	PEG 4000	PEG 6000	Stearic acid
PR-1	5	-	100	-	-
PR-2	5	-	-	100	-
PR-3	5	-	-	-	100
PR-4	5	1:1	100	-	-
PR-5	5	1:2	100	-	-
PR-6	5	1:3	100	-	-
PR-7	5	1:4	100	-	-
PR-8	5	1:5	100	-	-
PR-9	5	1:1	-	100	-
PR-10	5	1:2	-	100	-
PR-11	5	1:3	-	100	-
PR-12	5	1:4	-	100	-
PR-13	5	1:5	-	100	-

Characterization of Propranolol Hydrochloride Suppositories

Surface, appearance, uniformity of mix

Suppositories were inspected for physical appearance on its outer surface for smoothness or gritty conditions. Formulated suppositories are inspected for uniformity of mix by slicing longitudinally. Checked for the uniformity of drug, microspheres and also base.

Weight variation (IP)

Weigh individually 20 suppositories taken at random, determine the average weight. The percentage deviation from the mean was subsequently determined. Not more than 2 of the individual weight should deviate from the average weight by > 5 % and none should deviate by > 10 %.

Mechanical strength/ hardness test

The hardness of suppository formulation was tested using a tablet crushing strength tester. It signifies the

mechanical force necessary to break a suppository and denotes whether it is brittle or elastic. The mechanical strength should not be less than 2 kg/cm^2.

Disintegration time

The disintegration times were recorded utilizing USP tablet disintegration apparatus. The suppository was completely immersed in a constant water bath (37 ºC) and the time taken for the suppository to melt or disperse in phosphate buffer pH 7.4 was recorded.

Drug content determination

It is determined by taking a suppository, weighed, powdered and dissolved in 0.1N HCl in 50 ml volumetric flask, using a sonicator. The sample was diluted suitably and the absorbance was measured at 290 nm using 0.1N HCl as blank.

Melting point test

It is a critical factor in the determination of the release rate of the active ingredient. Melting point is a measure of the time that it takes for the entire suppository to melt. The Figure 6 represents the melting range test.

Softening and liquefaction temperature

The softening and liquefaction temperature was determined by Setnikar and Fantelli method. The suppository is introduced in to the upper part of the glass tube. A glass rod is placed on the suppository. The outer jacket is filled with distilled water and heated on a water bath with rising the temperature. When the suppository collapses, the glass rod sinks by a distance of 5 mm, the temperature at which this occurs is the softening temperature. As the temperature of the water jacket rises, the suppository liquefies and it flows through the 3 mm constriction of the glass tube of the apparatus, the temperature at which this occurs is the liquefaction temperature. The time that it takes the weight resting on the suppository to reach the stricture is measured as liquefaction time.

In vitro release studies

The *in vitro* release studies were carried out in USP XXIII (type I). The suppositories were taken in 900 ml pH 7.4 phosphate buffer maintained at 37±0.5°C at 100 rpm. Samples of 2 ml was withdrawn at every 1 h interval and replaced with the same medium to maintain sink conditions. The withdrawn sample was diluted to 25 ml with 0.1N HCl and the extent of drug release was determined spectrophotometrically at 290 nm.

In vitro permeability studies

A simple assembly was used for the permeation studies. The suppository to be tested was placed in an open ended glass tube over one end of which cellophane membrane (pretreated with 0.1N HCl) was stretched and securely fastened with the rubber band. The tube was hung in a vertical position in to a 500 ml beaker containing 200 ml of pH 7.4 buffer, such that the lower end of the tube was 3 cm from the bottom of the beaker as shown in the Figure 6. The beaker was then placed on a magnetic stirrer agitated at 50 rpm and maintained the temperature at 37 °C. Samples of 2 ml was withdrawn at 1 h interval and replaced by fresh buffer. The samples withdrawn was made up to 25 ml with 0.1N HCl and analyzed spectrophotometrically at 290 nm.

Drug release kinetics

Data obtained from *in vitro* drug release studies were fitted to various kinetic models like zero-order, 1st order, Higuchi, Korsemeyer-Peppas and Hixon crowell using PCP Disso V3 to predict the drug release mechanism.

RESULTS AND DISCUSSION

Preformulation Studies

Compatibility studies of drug and excipients used for preparing microspheres and suppositories

FTIR Spectroscopy

The FTIR spectrum of pure drug Propranolol hydrochloride was found to be similar to the standard spectrum of Propranolol hydrochloride. IR spectrum of Propranolol hydrochloride is shown in Figure 1 and it showed characteristic absorption peaks at 1105.14 cm^{-1} denoting stretching vibrations of C—N. 1267.14 cm^{-1} and 1240.14 cm^{-1} denoting stretching vibrations of C=O. 769.54 cm^{-1} and 796.55 cm^{-1} indicating C-H(aromatic) stretch. 1577.66 cm^{-1} absorption peak indicates N-H bend.

IR spectrum of ethyl cellulose showed the characteristic absorption bands for C-O-C stretching vibration at 1122.49 cm^{-1} and C-H stretching bands at 2974cm^{-1} and 2968cm^{-1}. The absorption peaks at 1373.22 cm^{-1} corresponds to C-H bending.

IR spectrum of the bases PEG 4000, PEG 6000 and Stearic acid is shown in the Figure 2 with their corresponding groups of characteristic peaks.

The IR spectra of physical blend of drug and polymer (Figure 1,2) drug and bases with their physical blend showed that there was no shift or disappearance of the characteristic peaks of drug and polymer was very much in conformity with the standard reference spectra, substantiating the compatibility of the drug and the polymers used.

Differential Scanning Calorimetry

The DSC thermogram of pure drug Propranolol hydrochloride was clear showing a sharp endothermic peak at 164.38°C indicating to its melting point, such endothermic peak indicates that Propranolol hydrochloride was in crystalline nature. The DSC thermogram of ethyl cellulose showed a sharp peak at 95.54°C, represents its melting point and also indicates that it is crystalline in nature. As drug showed peak at 164.27°C, in the physical mixture of drug and polymer exhibited only one sharp characteristic peak at 164.27°C.

This represents the absence of chemical interaction between drug and the polymers used.

Percentage Yield

The percentage yield of formulations was calculated and the yield was found to in the range of 85 % - 99.66 % as shown in Table 3.

Particle size analysis

The mean particle size of ethyl cellulose microspheres was found to be in the range between 147.72 ± 1.82 to 279.34 ± 1.69 µm and is shown in Table 3. The mean particle size of microspheres significantly increased with increasing the polymer concentration. The viscosity of the medium increased at higher polymer concentration resulting in an enhanced interfacial tension leading to the formation of slightly oversize microspheres.

Surface morphology

The surface morphology of Propranolol hydrochloride-ethyl cellulose microspheres were captured by Scanning Electron Microscopy (SEM). SEM photographs of the samples revealed that the microspheres were rough, porous and almost spherical in shape. SEM photographs of microspheres were shown in Figure 1.

Table 3: Physical characteristics of the formulations of Propranolol hydrochloride-ethyl cellulose microspheres

Formulation Code	% Yield	Mean particle size (µm)	Drug Entrapment Efficiency (%)	Drug Release (%)
P-1	85.00	147.72 ± 1.82	101.80	100.10
P-2	94.66	193.77 ± 3.81	100.60	100.13
P-3	99.50	195.70 ± 1.36	99.37	86.50
P-4	99.20	208.63 ± 2.46	98.12	82.07
P-5	99.66	279.34± 1.69	97.50	72.64

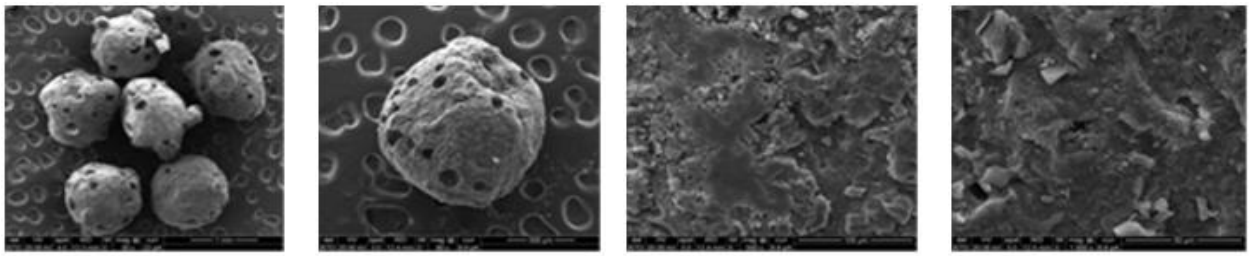

Figure 1: Scanning electron microphotographs of Propranolol hydrochloride-ethyl cellulose microspheres

Estimation of drug entrapment efficiency

The percentage drug entrapment of Propranolol microspheres in all the formulations were found to be in the range of 97.5 % -101.8 %. From the results it was seen that as the polymer concentration increased, viscosity of the dispersed phase increased and entrapment efficiency got decreased which is recorded in Table 3.

***In vitro* drug release studies**

The *in vitro* drug release data is showed in Table 3. The drug release ranged from 72 % to 100.13 %. With increase in the polymer concentration the drug release rate was found to be decreased. P- 2, 3, 4, 5 released 100, 86, 82, 72 % at the end of 8 h respectively except formulation P-1 which showed 100 % release at 7 h itself.

Drug release kinetics

The kinetics of the formulation of Propranolol hydrochloride-ethyl cellulose microspheres drug release was found to follow *peppas* model and the mechanism of drug release was by fickian diffusion as their 'n' value was less than 0.5. Diffusion is related to transport of drug from the dosage matrix into the *in vitro* study fluid depending up on the concentration. The formulation from P-1 to P-5 was best fitted to Korsmeyer peppas model, as their R value was found to be highest, almost approaching 1. P-5 best exhibited the matrix drug release pattern.

Characterization of formulated Propranolol hydrochloride suppositories

Surface and appearance

The physical evaluation parameters comprising of color, surface condition and homogeneity were found to be satisfactory. Almost all the formulations retained their unique physical features ranging from gritty to smooth with an elegant appearance. The colors were found to be white, cream and pale yellow.

The mold capacity or volume and displacement values were found to be in the range of 0.823-0.996g and 1.16 - 4.1 respectively.

Uniformity of mix

Almost all the suppositories were mixed uniformly hence homogeneity was almost similar except PR-12 formulation, which might be due to improper mixing.

Mechanical strength/ hardness test

The mechanical strength results indicated that all the formulations exhibited an acceptable degree of hardness ranging between 3.5 to 4.5 kg/cm^2, Sufficient enough to ensure the structural rigidity and easy rectal insertion at ambient temperature.

Disintegration time

The disintegration time data values clearly signifies the rapid melting, softening and de-aggregation within first 30 min. PR-3 showed a delayed disintegration because of its hard nature and disintegrated around 93 min., where as the other formulations disintegration time ranged from 8 to 14 min.

Weight variation (IP)

The results of weight variation suggested that the average weight for all the suppositories ranged from 0.847 to 1.024 g, very much within the specified limit.

Drug content determination

The percent drug content found in all the formulations was estimated and found to be in the range of 92 to 99 %, indicating the uniform distribution of Propranolol and Propranolol loaded microspheres in all the suppositories.

Melting point and range test

The melting point, melting time and melting range values are some of the important parameters to be determined as they play a major role in the disintegration and availability of the drug for absorption from the rectal route. The melting point of all the formulations ranged between 40 to 57 °C. The melting range was from 37 to 61 °C. The melting time was found in the range of 8 to 21 min. The formulations without microspheres showed faster melting point than those containing the microspheres. The melting time was found to be highest for PR-3 formulation owing to its high molecular weight and its hard nature. PR-1 exhibited a less melting time compared to all formulations at 8 min.

Softening and liquefaction temperature

The softening temperature, liquefaction temperature and liquefaction time of all the formulated suppositories showed softening temperature in the range of 37 to 65 °C. Liquefaction temperature of all the suppositories ranged between 44 to 79 °C and the liquefaction time ranged between 49 to 129 min. The sequence involved in the softening and liquefaction process is clearly depicted in the Figure 6. The formulations PR-1, PR-4, PR-5, PR-6, PR-7 combinations containing PEG 4000 base almost readily softened at body temperature. Whereas the formulations containing PEG 6000 base softened at an elevated temperature. The suppository containing stearic acid PR-3 showed softening temperature at 65 °C. The suppositories with low softening and low liquefaction temperature are desirable to facilitate drug release in to the rectum.

In vitro release studies

The authentic drug release profiles of formulation (PR-1 to PR-13) are recorded in Table no.6. On critical examination, the data revealed that drug release was more superior from water soluble bases. The formulations of conventional suppositories subjected to *in vitro* dissolution studies exhibited complete release of Propranolol within 4 h. PR-1, PR-2 released 106 % and 101 % at the end of 4 h. The suppositories made from using stearic acid was hard and stiff which released only 40% drug at the end of 8 h hence stearic acid is not used s a base for the formulation of suppositories. The Comparative *in vitro* drug release profile of the conventional Propranolol hydrochloride suppositories is shown in Figure 2. With increase in the polymer concentration there was a sustained drug release profile up to 8 h. The formulations which showed 100% release at the end of 8 h was the best candidates of choice for formulating in to suppositories.

Comparative *in vitro* drug release profiles of the conventional and sustained Propranolol hydrochloride suppositories using PEG 4000 base and PEG 6000(PR-4 to PR-8) is represented in Figure 3 and 4. The drug release data indicated that the formulations prepared using PEG 6000 showed delayed release than from PEG 4000.

It can be rightly concluded that release rate is significantly affected by the molecular weight and composition of the base.

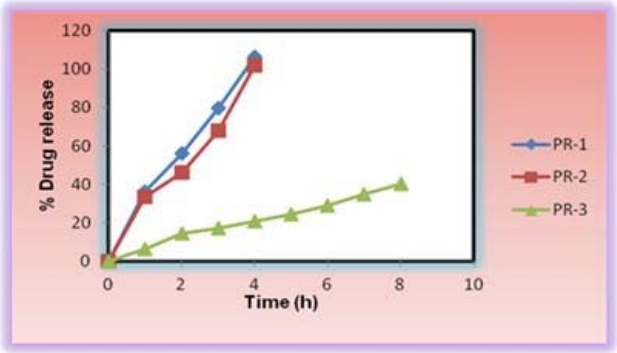

Figure 2: Comparative *in vitro* drug release profiles of the conventional Propranolol hydrochloride suppositories

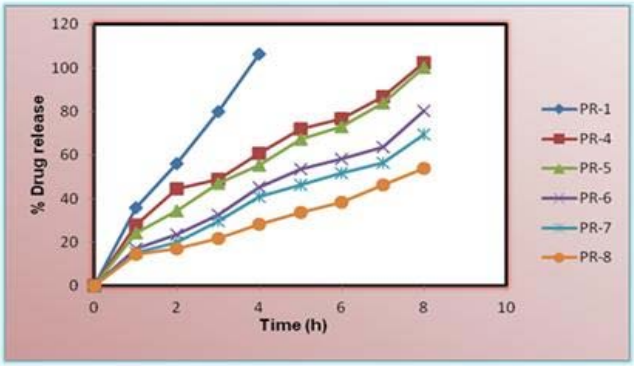

Figure 3: Comparative *in vitro* drug release profiles of the conventional and sustained Propranolol hydrochloride suppositories using PEG 4000 base.

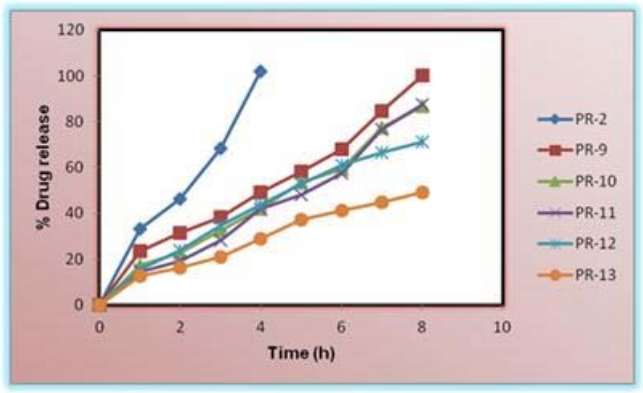

Figure 4: Comparative *in vitro* drug release profiles of the conventional and sustained Propranolol hydrochloride suppositories using PEG 6000 base.

***In vitro* permeability studies**

The *in vitro* permeability studies were carried out to know about the probable drug absorption through rectal mucosa. The percentage of drug permeated through pre treated cellophane membrane is shown in Table 6. PEG bases underwent higher permeation as they are likely to act as permeation enhancers. The permeation rate from the conventional suppositories using PEG 4000, PEG 6000 was almost 95 % and 89 % within 4 h, whereas from the stearic acid it was only 36 % at the end of 8 h. Thus the permeability rate from PEG 6000 was slow compared to the suppositories formulated from PEG 4000. Practically, the permeation rate is always less than the release rate, hence the rate controlling step is the permeation of the drug through rectal mucosa and not the release of the drug in the rectal or dissolution medium.

Table 4: *In vitro* drug release, *in vitro* permeability and melting characteristics of suppositories

Formulation code	*In vitro* drug release (%)	*In vitro* drug permeability (%)	Melting point (°C) ± S.D	Melting range (°C)	Melting time (min)
PR-1	106.28	95.51	40 ± 1.527	37-42	8'15"
PR-2	101.78	89.55	44 ± 1.466	40-47	14'12"
PR-3	40.14	36.88	57 ± 1.270	55-61	21'26"
PR-4	102.36	91.61	43 ± 1.620	40-46	17'5"
PR-5	100.28	79.40	42 ± 1.324	39-45	15'29"
PR-6	80.27	76.00	40 ± 0.993	37-43	16'33"
PR-7	69.42	70.86	45 ± 0.982	40-48	14'21"
PR-8	53.76	61.06	43 ± 1.202	38-46	13'47"
PR-9	100.21	90.74	46 ± 1.389	42-50	15'46"
PR-10	86.62	75.99	47 ± 1.426	44-50	16'17"
PR-11	87.47	72.97	43 ± 1.267	40-46	14'56"
PR-12	71.29	51.09	49 ± 1.253	45-53	15'24"
PR-13	49.26	44.05	48 ± 1.732	45-52	16'32"

Drug release kinetics

The drug release kinetics from the formulations of Propranolol hydrochloride suppositories was found to be of peppas, Zero order, 1st order and Hixon–Crowell models. The mechanism of drug release was found to be Non fickian diffusion as its n value lies between 0.5 and 1. The polymer here swells and then diffusion occurs. Diffusion is related to transport of drug from the dosage matrix into the *in vitro* study fluid depending up on the concentration. The non fickian diffusion from the porous membrane of the microspheres as well as from the high molecular weight polyethylene glycols is an indication of sustained release property of formulation. Hence it can be proved that the sustained action can be achieved till 8 h.

CONCLUSION

The microspheres of Propranolol hydrochloride, an antihypertensive drug had been successfully developed using ethyl cellulose as a release regulating polymer by solvent evaporation method to improve the bioavailability with prolonged drug release for 8 h. The drug was found to be in unchanged physical state without undergoing any transition as indicated by FT-IR and DSC studies. The prime importance of developing the microspheres was to provide the sustained release of the drug as its half life is very short. Conventional suppositories were formulated using PEG 4000, PEG 6000 and stearic acid as suppository bases. The results were compared and it was decided not to choose stearic acid as a base for formulating a sustain release dosage form as the nature of stearic cid is very hard and it showed only 40 % of drug release at 8 h. Sustained release suppositories was formulated using PEG 4000 and PEG 6000 at different concentration using different ratios of microspheres by fusion molding method. The drug release kinetics of suppositories signified that the formulated dosage forms can be used as a sustained drug release pattern comprising of microspheres, especially from water soluble bases of high molecular weight, either alone or in combination.

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