A study on factors affecting the preparation and *in-vitro* evaluation of mucoadhesive propranolol HCl suppositories

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Abstract

Propranolol HCl is a beta-adrenoreceptor blocking drug which is subjected to extensive first pass metabolism after oral administration. In this study, attempts were made to prepare mucoadhesive suppositories composed of 80mg (4%) propranolol HCl by fusion method using fatty base, witepsol W-35 or water soluble bases polyethylene glycol (PEG) 4000 and mucoadhesive poloxamer 188.

Physical characteristics and dissolution profiles of the prepared formulas were studied. The results showed that all the prepared formulas have acceptable physical characteristics regarding weight variation, hardness, and melting time.

The release of drug from the prepared suppositories was found to be affected by the type of suppository base and additives. Fastest release was obtained with witepsol W-35 followed by PEG 4000 then poloxamer 188. Addition of carbopol 934 as a mucoadhesive polymer in a concentration of 1% or 2% to witepsol W-35 or PEG 4000 bases , retard the release of drug to unacceptable limit due to formation of an insoluble complex with the drug. On the other hand, the release of drug was enhanced by addition of propylene glycol to poloxamer 188 based suppositories in a concentration of 25% or 30% to a required limit for sustained release preparations that follow zero order kinetics. Furthermore, these last formulas were found to have mucoadhesive property.

Therefore, the results suggest that propylene glycol-poloxamer 188 mixture is a promising base for preparation of sustained release solid mucoadhesive propranolol HCl suppositories.

دراسة العوامل المؤثرة على تحضير وتقييم خارج الجسم لتحاميل هيدروكلوريد البروبرانولول اللاصقة مخاطيا

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الكلمات المفتاحية : هيدروكلوريد البروبرانولول، تحاميل لاصقة مخاطيا ، تحاميل بطيئة التحرر

الخلاصة:

هيدروكلوريد البروبرانولول هو من حاصرات مستقبلات الفعل الادرينالي نوع بيتا والمعرض الى الايض الشديد بواسطة الكبد عند استعماله كجرعة دوائية عن طريق الفم. في هذه الدراسة تمت عدة محاولات لتحضير تحاميل شرجية لاصقة مخاطيا تحوي على 80 ملغم (4%) لدواء الهيدروكلوريد البروبرانولول بطريقة الانصهار باستخدام قواعد دهنية مثل ويتبسول و-35 وقواعد ذائبة في الماء مثل البولي اثيلين كليكول 4000 وقاعدة البولوكسامر 188 ذات الخاصية اللاصقة مخاطيا.

لقد تمت دراسة الخواص الفيزياوية وتحرر الدواء من الصيغ المحضرة حيث أظهرت النتائج بأن جميع الصيغ المحضرة أعطت نتائج مقبولة من حيث الوزن والصلابة ووقت الانصهار.

كما أوضحت النتائج بأن تحرر الدواء من اللبوسات المحضرة يتأثر بنوع القواعد المستعملة والمواد المضافة. اسرع تحرر للدواء تم الحصول عليه من الويتبسول و-35 ثم من البولي اثيلين كلايكول 4000 وأخيرا من البولوكسامر 188 . كما أظهرت

النتائج بأن اضافة الكاربوبول 934 كمادة لاصقة بنسبة 1% او 2% الى الويتبسول و-35 او البولي اثيلين كلايكول 4000 يؤخر من تحرر الدواء بشكل غير مقبول نتيجة لتكوينه معقد غير ذائب مع الدواء. من الناحية الاخرى ، فقد وجد بأن تحرر الدواء يزداد بأضافة مادة البروبلين كلايكول بنسبة 25% او30% الى قاعدة البولوكسامر 188 الى الحد المطلوب لتحضير المستحضرات البطيئة التحرر. بالاضافة الى ذلك فقد وجد بأن الصيغ الاخيرة لها خاصية التصاق مخاطية .
لذلك فان النتائج تشير الى ان مزيج البروبلين كليكول والبولوكسامر 188 قاعدة واعدة لتحضير تحاميل لاصقة مخاطيا بطيئة التحرر لدواء هيدروكلوريد البروبرانولول.

Introduction

Suppositories are solid dosage forms intended for insertion into body cavity. They are an alternate dosage form for drugs which have unpleasant taste, gastrointestinal irritation and those undergo first pass metabolism [(1)]. Besides the conventional form, sustained release suppositories were prepared to provide a desirable blood concentration of the drug at nearly constant level for an appropriate period of time [(2)]. A variety of approaches have been used to prepare sustained release suppositories for different drugs; these include using of various additive substances acting as retardants [(3)] or by using solid matrix of poorly soluble carriers [(4)]. In addition, preparation of sustained release suppositories by the use of microspheres was also reported [(2, 5)].

Propranolol HCl, a non selective beta- adrenergic blocking agent, is widely used in treatment of hypertension, angina pectoris and many other heart or circulatory conditions. Propranolol HCl is subjected to extensive first-pass metabolism following oral administration with a reported systemic bioavailability between 15-23% with half life 3-5 hours [(6)]. Extended release tablets were prepared to provide a constant level of propranolol HCl for a long period of time [(7, 8)], while buccal [(9, 10)] and rectal preparations were prepared to avoid the first pass metabolism of the drug [(11-12)]. Furthermore, improvement in the bioavailability of propranolol HCl was obtained when it is formulated as matrix-based slow release suppositories [(13)]. In addition to retain the suppository at the site of application (lower-rectum) and prevent it to reach to the end of the canal of application because of its poor mucoadhesion properties , which may allow the carried drug to undergo first - pass effect [(14)] propranolol HCl was prepared as thermally gelling mucoadhesive liquid suppositories [(15)].

The objective of this study was to prepare mucoadhesive solid suppositories of propranolol HCl by fusion method using carbopol as a mucoadhesive polymer in combination with fatty or hydrophilic base.

Another trial was made by using poloxamer 188 as a mucoadhesive hydrophilic base. In addition the effect of the above bases on the physical and dissolution properties of the prepared suppositories was also studied.

Material and Method

Materials:

Propranolol HCl and witepsol W-35 were received as a gift from Samarra Drug Industry (SDI), polyethylen glycol (PEG) 4000 and propylene glycol (Hopkin and Williams, England), poloxamer 188 (BASF, United Pharmaceutical, Jordan), carbopol 934(Himedia laboratories, Pvt. LTD Mumbai), dialysis tubing 36/32 (Medicell Intrnational LTD, Liverpool, England). All other chemicals were of analytical grade.

Methods

Preparation of suppositories

Adult suppositories (weighing 2 gram) containing 80 mg. of propranolol HCl [(8, 9)] were prepared by fusion method in which the suppository base (witepsol W-35, PEG 4000, or

poloxamer 188) were melted at their appropriate temperature, then the drug alone or with other additives (carbopolol 934, propylene glycol) was added. Uniform dispersion was formed in the melted base which was then molded in a metal mold, allowing it to cool and congeal into suppositories. After then, suppositories were removed from the mold, wrapped in aluminum foil and stored in the refrigerator until use [16]. The composition of the formulas are shown in table (1)

Evaluation of the prepared propranolol HCl suppositories

Weight variation test

Twenty suppositories were weight individually and the average weights were determined. Not more than two of the individual of weights deviate from the average weight by more than 5% and non deviate by more than 10% [17]

Hardness test (Breaking strength)

This test was carried out to measure the brittleness and fragility of suppositories. Hardness was determined at room temperature using Erweka hardness tester. A good result is at least 1.8-2 Kg. pressure [18]. The purpose of this test is to verify that the suppository can be transported under normal conditions and administered to the patient.

Melting time test

This test was made on fatty based suppositories. The suppositories were placed into a glass tube (2.5 cm. diameter), 2 ml. Sorensen's phosphate buffer (pH 6.8) was added. The tube was placed in water bath at $37 \pm 0.5^{\circ}$ C. The time required for each suppository to completely melt was determined [19].

Dissolution test

Each suppository was inserted into a semipermeable membrane tubing of 7 centimeter in length [20]. Both sides of the tube were tied up with a thread to prevent leakage, and then placed into the dissolution jar. Dissolution test was performed at $37 \pm 0.5^{\circ}$ C using the USP dissolution apparatus type II (paddle method) at 100 rates per minute with 500 ml Sorenson's phosphate buffer pH 6.8 as a dissolution medium [21]. At appropriate intervals ranged from 0.5 - 8 hours [2], 5 ml. aliquots of the dissolution medium were withdrawn and immediately replaced by 5 mlliliters fresh medium were replaced to maintain the sink condition. Drug concentration was measured spectrophotometrically at 290 nm. [7, 10] .

In order to evaluate the percentage of drug released at different time intervals along the dissolution period, the monograph of extended release propranolol hydrochloride capsule in USP was used, since, there is no monograph for extended release suppositories was mentioned in the USP [22]. Based on this monograph, not more than 30% of the drug should be released after 1.5 hours, 35%-60% after 4 hours, and 55%- 80% after 8 hours [23]

Differential Scanning Calorimetry (DSC) study

Thermal analyses were performed using Differential Scanning Calorimeter (DSC- 60, Shimazu, Japan). DSC analyses were carried out on pure drug, suppository bases, carbopol 934 and formulation. Samples of 2 mg. were placed in aluminum pans. Thermal behavior of the sample was investigated under nitrogen gas at a scanning rate of 10°C/min. covering a temperature range 50-200° C [24, 25]. The scanning rate for witepsol W-35 and witepsole W-35 based suppositories was 1°C/min. in the temperature range 25-200°C [26]. The melting point of the samples was taken as the temperature at the melting peak in the DSC.

Kinetic analysis of the release data

In order to establish the release kinetics and mechanism of drug release from the selected formulas, the data obtained from their *in-vitro* release studies were fitted to zero-order, first-order and Higuchi's model. Based on the correlation coefficient (r^2) value in various models, the model that gives the highest (r^2) value is considered as the best fit of the release model. Furthermore, when the mechanism is not well known, the first 60% drug release data were fitted in Korsmeyer-Pepas equation:-

$$\frac{Mt}{M\infty} = Kt^n$$

Were $\frac{Mt}{M\infty}$ is the fraction of drug released at time t , K denotes the constant of suppository system and n is the release exponent related to the mechanism of the drug release. The n value of 1 corresponds to zero- order dissolution kinetics, $0.5<n<1$ means a non-fickian dissolution model and n=0.5 indicate fickian diffusion (Higuchi's model) [24, 27].

Mucoadhesive strength test

The prepared suppositories that pass the previous tests were subjected to the bioadhesive strength measurement. This study was carried out by simple modified double pan weight balance. One surface of mucoadhesive suppository was stick to the bottom of one pan of weight balance by sticky gum. Another surface of mucoadhesive suppository was adhered with agar media (2% agar in phosphate buffer pH 6.8) as mucous membrane in Petri dish as shown in photo (1). One by one calibrated fractional weight put in another pan until the suppository was detached from the agar media. The weight required to detach the suppository from the agar media give the bioadhesive strength. The experiment was performed in triplicate and the average value was calculated [28, 29].

Results and Discussion

Weight variation, melting time and hardness

The results of these physical properties are listed in table (1).The results of weight variation show that all the prepared suppositories were in conformity with British Pharmcopoeia, since no suppository deviated from average weight by more than 5%. The differences in the weight of suppositories of different formulas are due to the differences in the densities of the base used. The melting time for the suppositories prepared with fatty base was within the acceptable limit, since the time required for complete melting should be within 30 minutes [19]. In addition, the hardness of all tested suppositories was more than 2Kg, so they withstand handling and transportation [18]. The lowest hardness of F8 and F9 may be due to the presence of liquid propylene glycol in the formulation.

Dissolution test

Factors affecting the dissolution

Effect of type of suppository base

Two types of suppository bases were used in this study, fatty base (witepsol W-35), water soluble base (PEG 4000 and a mucoadhesive poloxamer 188[30]). The effect of type of suppository base on the release of propranolol HCl is shown in figure (1). Ranking the tested formulas in descending order, according to the percentage of drug release along the dissolution period was as follow, F1> F2>F3. The highest drug release from F1 (witepsol based suppository) can be explained to be due the nature of the base and the drug. This

base is fatty in nature with low melting point (33.5-35.5℃) and a high hydroxyl value (40-50), which may enhance the drug release by increasing the hydrophilic environment around the drug [31], also this drug, has high solubility in the dissolution medium with low affinity to fatty base [17]. All these characteristics may enhance the drug release and getting it free in the dissolution medium. On the other hand, within the hydrophilic bases the PEG-based suppositories (F2) showed a higher release of the drug compared to poloxamer- based suppositories (F3) which may be due to higher solubility of PEG 4000 in the dissolution medium than that of poloxamer. This finding is in agreement with that obtained by Ghorab, D *et al* [32]. The dissolution profiles of these formulas are not in consistent with USP monograph; further trials were made to prepare mucoadhesive sustained release suppositories.

Effect of addition of carbopol 934 on witepsol W-35 and PEG 4000 based suppositories

In an attempt to prepare mucoadhesive sustained release suppositories of propranolol HCl, 2% carbopol 934 [33, 34] was added to witepsol W-35 and PEG 4000 based suppositories (F4, F6 respectively). A very slow release of drug was obtained from both types of suppository bases falling outside the required limits of USP. Therefore, 1% carbopol 934 was used (F5, F7). It gives less retardation effect than that of 2%, but still the drug release not comply with the USP requirement for sustained release propranolol HCl preparations. The effect of concentration of carbopol on the release of drug from witepsol and PEG based suppositories is shown in figure (2 and 3) respectively.

The retardation effect of carbopol can be explained to be due to the properties of both carbopol and propranolol HCl.

Carbopol 934 is anionic polymer with large number of acid group, thus it tend to interact with cationic drug. At the pH of the dissolution, carbopol become increasingly ionized and possess negatively charges that interact with positively charged amino groups of propranolol HCl to form insoluble complex which retard the drug release [35, 36].

Complex formation was confirmed by formation of turbidity [35, 37]. Higher turbidity was observed in the dissolution sac at the end of the dissolution period with formulas containing 2% carbopol than those containing 1% compared with clear solution that remain in the dissolution sac of carbopol free witepsol and PEG based suppositories as shown in photos (2 and 3).

Effect of addition of propylene glycol on poloxamer 188 based suppositories

Propylene glycol was added to poloxamer 188-based suppositories, as a trial to increase the amount of drug released from this type of suppository base.

As shown in figure (3) it is obvious that addition of propylene glycol accompanied by enhancing the release of the drug along the dissolution period this result was in agreement with previous reports [21, 32].

The dissolution profiles of F8 and F9 which composed of poloxamer 188 / propylene glycol mixture with a ratio of 75/25% or 70/30% (w/w) respectively were comparable to each other and comply with USP requirement for sustained release preparations.

On the other hand, these mixtures can be considered as compatible mixture since a clear solution was obtained in the dissolution sac at the end of the dissolution period as shown in photo (4).

In addition, it was found that this mixture is safe and does not cause irritation or damage the rectal tissue [38]. Therefore, these formulas were selected as the best formulas and

further studies regarding investigation the mechanism of the release and mucoadhesion test were made on them.

Differential Scanning Calorimetry (DSC) study

According to the thermograms (figures 5-7) , pure propranolol HCl, witepsol W-35, PEG 4000 and poloxamer 188, show endothermic peaks around their melting points, while carbopol 934 show its characteristic peaks at 71.78℃ and 241℃. Furthermore, the DSC thermograms for the prepared formulas had no peaks for the drug, carbopol, but only one peak at a temperature around that of the pure base which may indicate that a homogenous phase was obtained during the preparation of the suppositories and the drug present as amorphous form rather than crystalline form [19, 26].

Kinetic analysis of the release data

As shown in table (2), the r^2 values for zero- order and first- order models for the selected formulas (F8 and F9) were nearly similar to each other. Therefore, to know the mechanism of drug release, the release exponent in Korsmeyer-Pepas equation was determined and it was≈1 which indicates that the release mechanism is near to zero-order. This result was similar to the previous studies [24, 38].

Mucoadhesive strength

The mucoadhesive strength for F8 and F9 were found to be 5.33± 0.516 and 5±0.577g. respectively. The slight higher value obtained with F8 may be due to its higher content of poloxamer 188 which has a mucoadhesive property [30].

Conclusion

The study findings suggests that poloxamer 188 / propylene glycol mixture with a ratio of 75/25% or 70/30% (w/w) based suppositories were superior to witepsol W-35 and PEG 4000 in terms of their ability to release propranolol HCl in sustained release pattern in zero-order kinetic with mucoadhesive property. Further study may be required to determine the stability and expiration date of the selected formulas.

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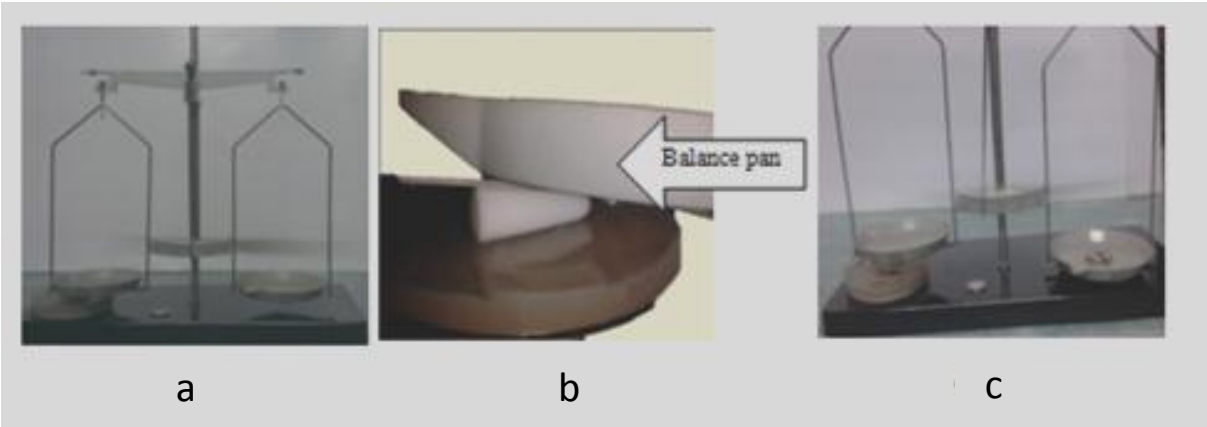


Photo (1):- Photography of simple modified balance for mucoadhesion strength study (a,b. attached suppository, c. detached suppository

Table (1):- Composition and characterization of tested suppository formulations *

Formula no.	Composition of suppository base **	Weight variation (g) n=20	Hardness (Kg) n=3	Melting time (Minutes) n=3
F1	Witepsol W-35	1.962±0.033	4.5±0.707	24.50±1.43
F2	PEG 4000	2.207±0.149	4.7±0.424	---
F3	Poloxamer 188	2.053±0.078	> 6	---
F4	Witepsol W-35 + 2% Carbopol 934	1.956±0.028	> 6	27.53±1.69
F5	Witepsol W-35+ 1% Carbopol 934	2.00±0.01	> 6	27.43±1.45
F6	PEG 4000 + 2% Carbopol 934	2,392±0.052	> 6	---
F7	PEG 4000 + 1% Carbopol	2.429±0.045	> 6	---
F8	Poloxamer/ Propylen glycol 75/25%	2.081±0.037	2.8±0.707	---
F9	Poloxamer/ Propylen glycol 70/30%	2.068±0.063	2.2±0	---

* All formulas contain 80mg propranolol HCl

** All percentages represent w/w% out of the total weight of the suppository

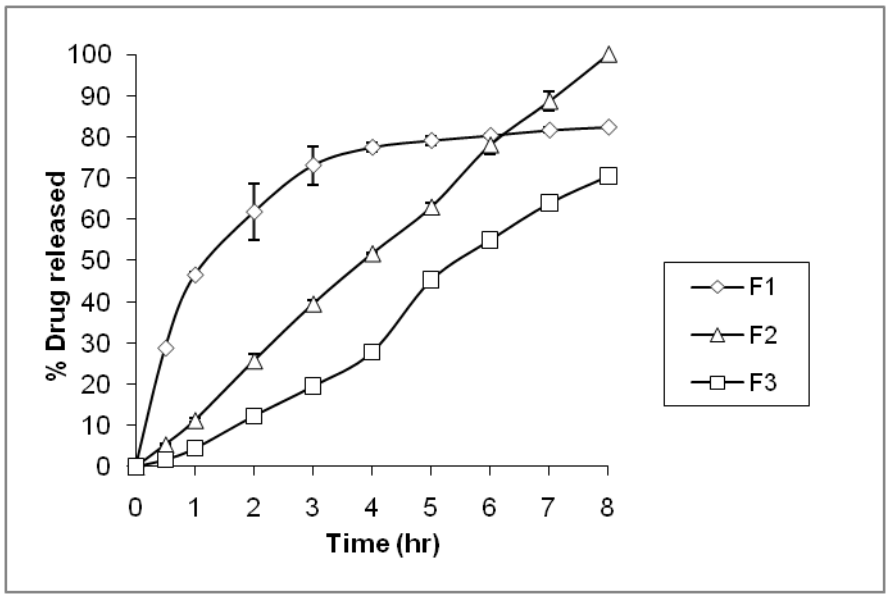


Figure (1):-Effect of type suppository base on the dissolution of propranolol HCl in pH 6.8 at 37±0.5℃

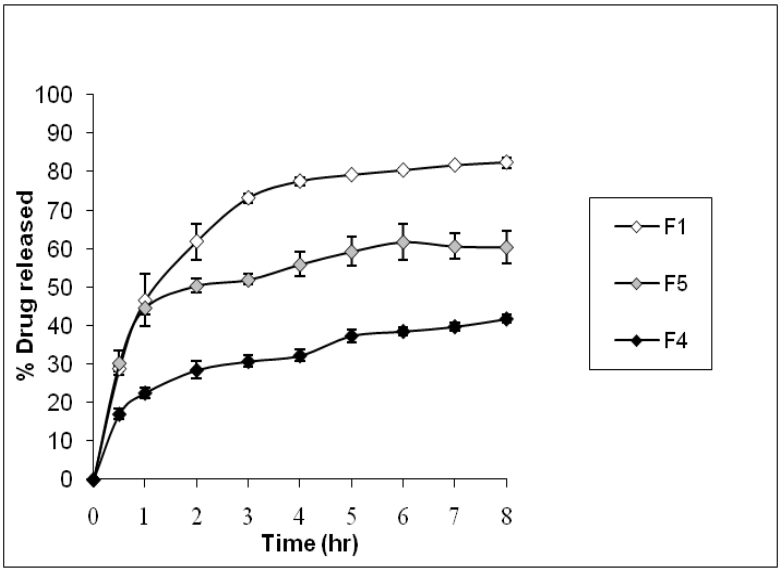


Figure (2):- Effect of addition of carbopol 934 to witepsol W-35 based suppositories on the dissolution of propranolol HCl in pH 6.8 at 37±0.5℃

Photo (2):- Photography showing the effect of addition of carbopol 934 to witepsol W-35 based suppositories after 8 hours of dissolution in pH 6.8 at 37±0.5℃
(F1 0% carbopol, F4 2% carbopol, F5 1% carbopol)

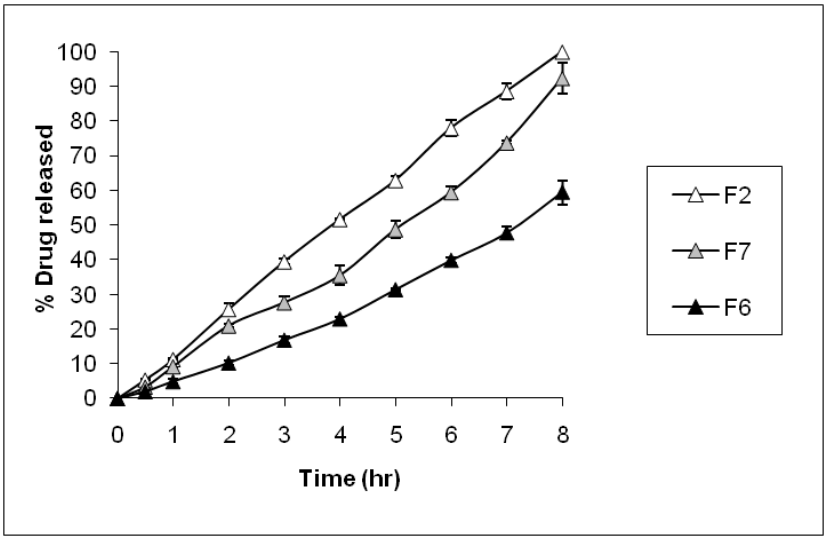


Figure (3):- Effect of addition of carbopol 934 to PEG 4000 based suppositories on the dissolution of propranolol HCl in pH 6.8 at 37±0.5℃

Photo (3):- Photography showing the effect of addition of carbopol 934 to PEG 4000 based suppositories after 8 hours of dissolution in pH 6.8 at 37±0.5℃
(F2 0% carbopol, F6 2% carbopol, F7 1% carbopol)

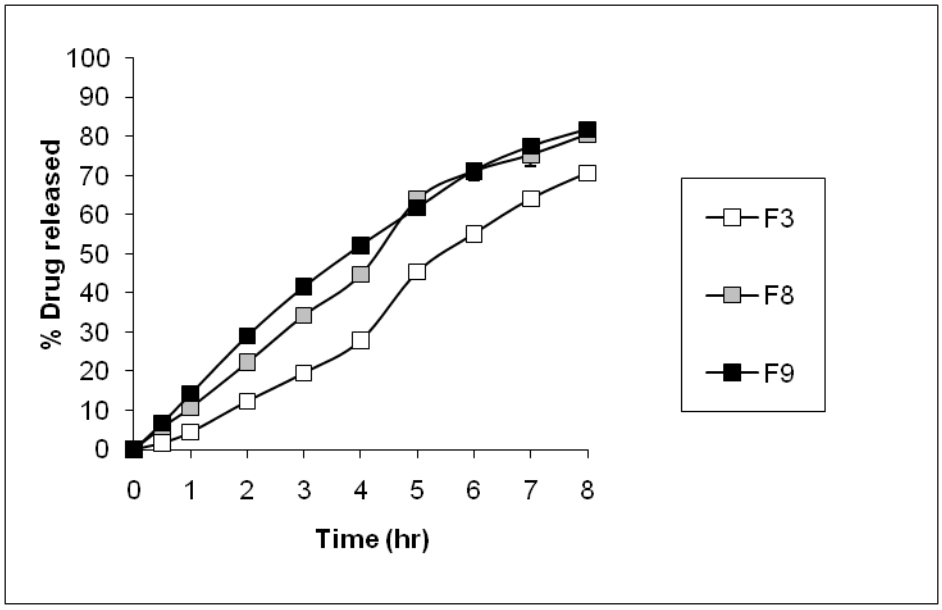


Figure (4):- Effect of addition of propylene glycol to poloxamer 188 based suppositories on the dissolution of propranolol HCl in pH 6.8 at 37±0.5℃

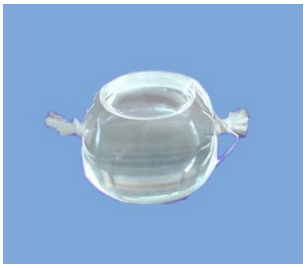


Photo (4):- Photography showing the effect of addition of propylene glycol to poloxamer 188 based suppositories after 8 hours of dissolution in pH 6.8 at 37±0.5℃
(F3, F8, F9)

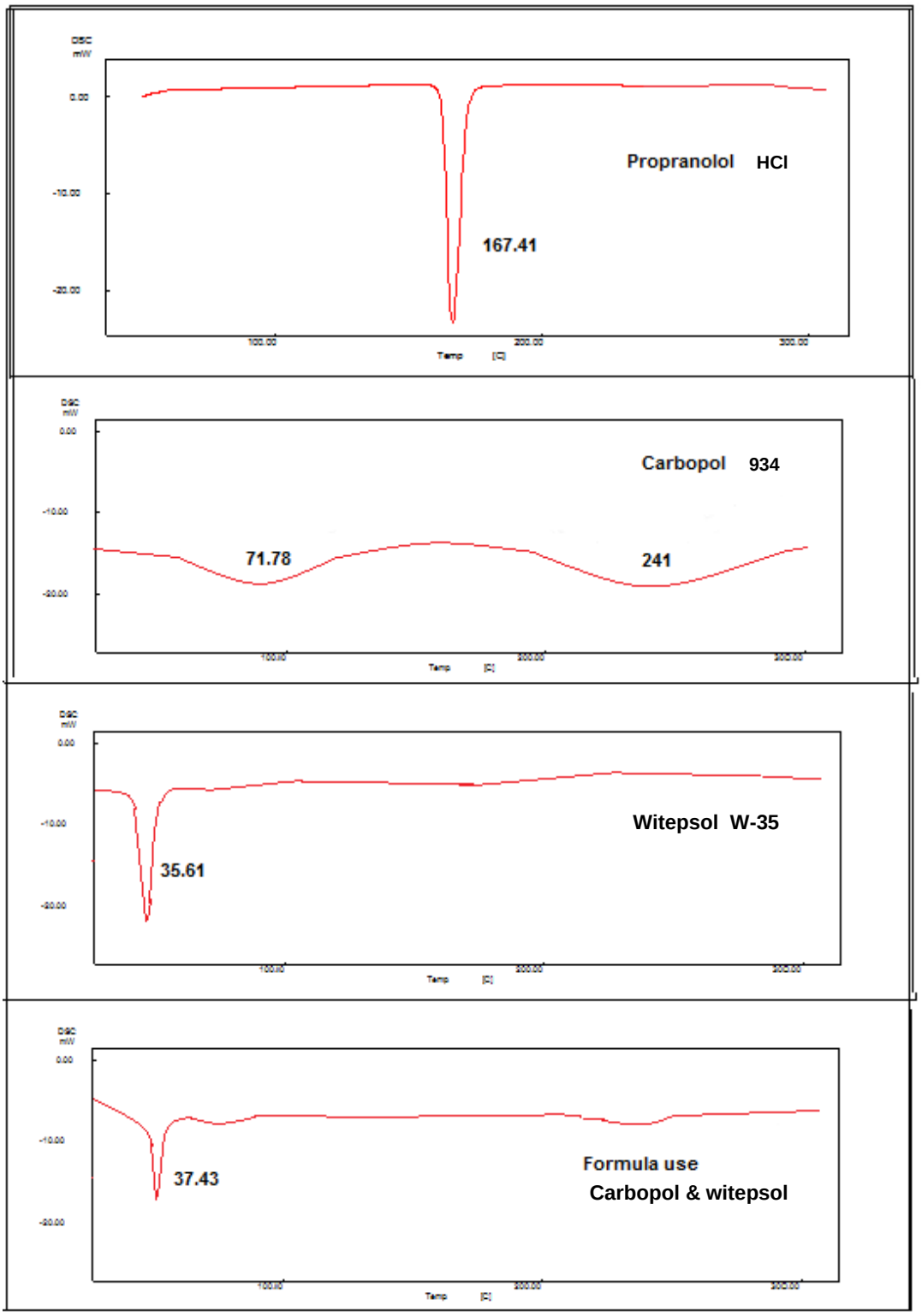
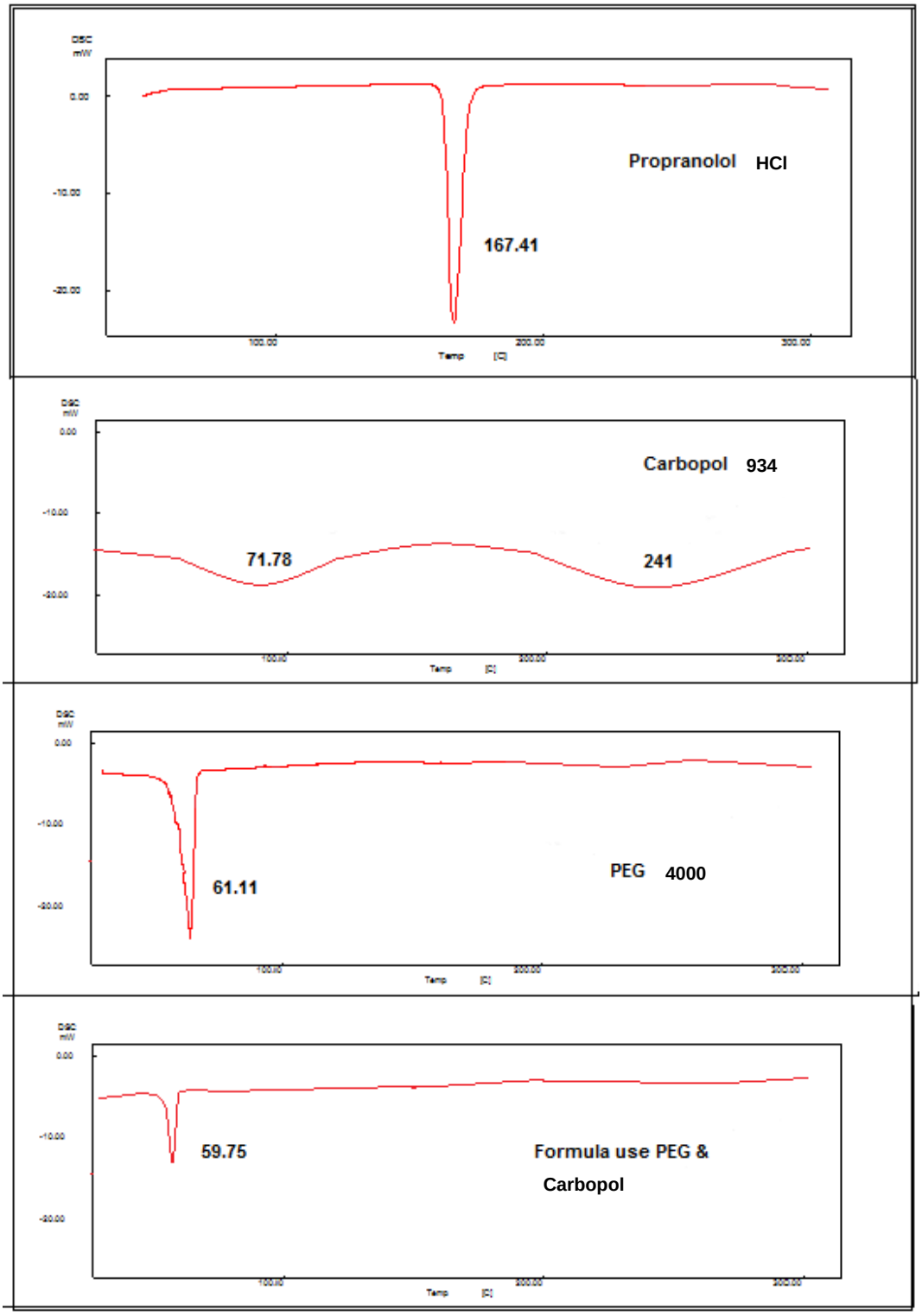


Figure (5) DSC thermograms of propranolol HCl, carbopol 934, witepsol W-35 and formula contains carbopol and witepsol



Figure(6) DSC thermograms of propranolol HCl, carbopol 934, PEG 4000 and formula contains PEG and carbopol

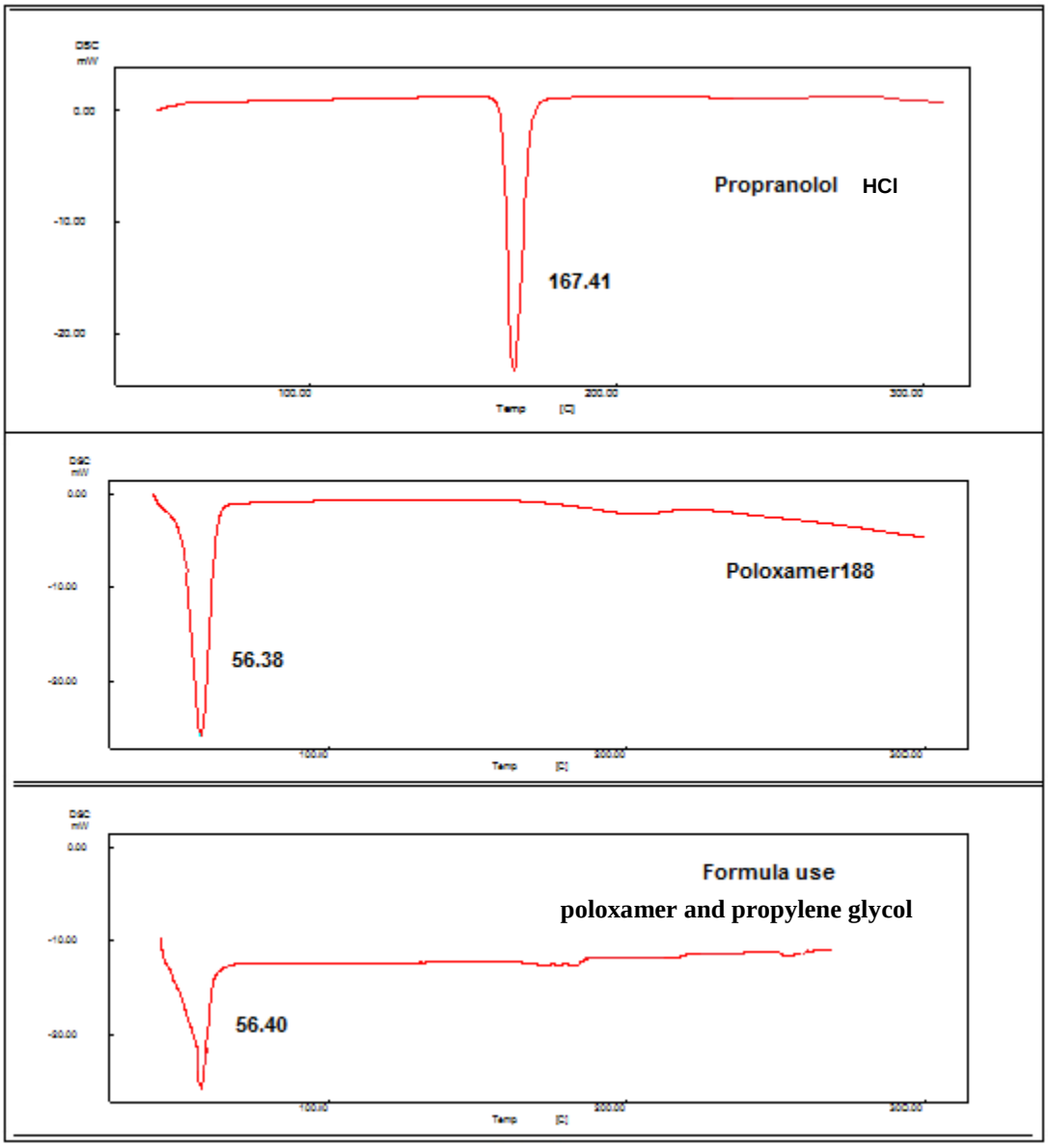


Figure (7) DSC thermograms of propranolol HCl, poloxamer188, and formula contains poloxamer and propylene glycol

Table (3):- Values for correlation coefficient (r^2) for zero-order, first-order and Higuchi's model with the release exponent in Korsmeyer-Pepas for F8 and F9

Formula no.	correlation coefficient (r^2)			n-values Korsmeyer-Pepas equti
	zero-order	first-order	Higuchi's model	
F8	0.98	0.97	0.89	1.034
F9	0.97	0.99	0.94	0.967

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