Zagazig J. Pharm. Sci., June, 2010
Vol. 19, No. 1, pp. 12-16

ISSN 1110-5089

IN VITRO EVALUATION OF SUSTAINED RELEASE SUPPOSITORIES CONTAINING PROPRANOLOL HYDROCHLORIDE MICROSPHERES.

Tamer M. Shehata and Mahmoud M. Ibrahim

Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt

ABSTRACT

Microspheres of propranolol HCl were successfully prepared using cellulose acetate butyrate (CAB) polymer by emulsion solvent evaporation technique. The effect of drug:polymer ratio on the produced microspheres particle size, drug encapsulation efficiency and drug release properties were evaluated. Conventional suppositories containing free drug and sustained release (SR) suppositories containing microspheres of propranolol HCl were formulated with hydrophilic polyethylene glycol (PEG) and lipophilic Witepsol H15 bases. Increase in drug content and particle size were observed with an increase in drug:polymer ratio. In vitro release studies were performed in phosphate buffer (pH 7.4). Results have shown that drug release from microspheres was affected by drug:polymer ratio. When the polymer:drug ratio was increased, the release of the drug was highly decreased. Witepsol base showed higher release rates of the drug compared with PEG base from conventional suppositories. On the other hand, slower release rates were obtained by dispersing microspheres of the drug into suppositories and also, Witepsol suppositories showed higher rates of drug release compared to PEG suppositories.

This study suggested that incorporation of propranolol HCl microspheres into a lipophilic or hydrophilic suppository base can give SR properties for the drug which is promising as being more useful than conventional formulations in therapy.

INTRODUCTION

Propranolol HCl is a non selective β blocker which is widely used as antihypertensive and antiarrhythmic agent. The drug undergoes excessive first-pass elimination after oral administration showing low bioavailability of about 15%-23% [1-2]. The poor bioavailability of the drug after oral administration leads to multiple dose administration and great variability in drug plasma concentrations [3]. The SR drug delivery systems (DDS) can be a major solution for the problem of fluctuating plasma drug level [4]. However, the bioavailability still poor after oral administration of SR DDS of drugs undergoing first-pass metabolism. Hence, the prime aim in designing suppositories is to avoid the first pass metabolism and to improve drug bioavailability. Conventional suppositories showed high bioavailability of incorporated drugs, however, rapid release, absorption, and drug elimination suggested also multiple rectal administrations of drugs [5]. A solution for such problem is to formulate suppositories with a SR patterns in order to control and prolong drug effects. Furthermore, formulating SR suppositories could have high patient acceptability and compliance due to reduced number of dosing regimen. Another advantage of SR suppositories is the help in obtaining a desirable blood concentration of the drug and maintaining such concentration at a nearly constant level for appropriate period of time [6]. Several technologies were designed to have SR suppositories like incorporation of microcapsules, micropellets and microspheres of the drug into suppository bases [7-10]. Moreover, suppositories that are liquids at room temperature and gel at body temperature have been developed and proposed as alternatives to conventional suppositories for administration of drugs [11]. The prolonged effect of liquid suppositories is due to the muco-adhesion properties of incorporated polymers. However, liquid suppositories have the disadvantages of difficulty in packaging, protection and transport at high climate temperatures [10].

This investigation was aimed to formulate SR suppositories of propranolol HCl via incorporation of microspheres containing propranolol HCl into conventional suppository bases like PEG or Witopsol. The in vitro characterization of the prepared microspheres and the drug release from microspheres, suppositories, and their combinations were also evaluated.

EXPERIMENTAL

Materials

Propranolol HCl was kindly supplied by Egyptian International Pharmaceutical Industrial Co., Egypt. Witepsol H15 was obtained from Chemikalien-Mulheim, West Germany. PEG 400 was purchased from Fluka chemical Switzerland. PEG 4000 was from Riedel-DE Haen AG Seelze, Germany. PEG 6000 was purchased from Morgan chemical works, Egypt. CAB was purchased from Sigma Chemical Co. st. Louis, Mo. USA. Acetone, n-hexane, potassium dihydrogen phosphate, disodium hydrogen phosphate, Light liquid paraffin (LLP) were of analytical grade and purchased from El Gomhouria Co. Egypt. All other chemicals and solvents were of analytical grades.

Equipment

PH-meter 300 (Jenway LTD, UK.); U.V. Spectrophotometer (1291 Shimadzu Company, Japan.); Analytical balance digital 100A (Denver Instrumental Company, Colorado, USA.); Thermostatic shaker water bath (Julabo, SW- 20C, Germany); Mechanical stirrer (Heidolph PZP-2000, Germany); Sieve Shaker (Model RX-86-1.USA).

Preparation of propranolol HCl microspheres.

Microspheres were prepared by the emulsion solvent evaporation technique [12]. CAB in different concentrations was dissolved in acetone and kept over night in a refrigerator to form polymer solutions. Propranolol HCl was then dispersed into the polymer solutions. The drug-polymer dispersion was then emulsified in LLP containing 1% span 80 with vigorous agitation. After 5 min, 60 ml of n-hexane were added to the emulsion in a drop-wise manner. Stirring was maintained until all the acetone was evaporated. Then, the formed microspheres were filtered, washed with n-hexane and finally dried overnight at room temperature.

Formulations with different drug: polymer ratios were prepared as shown in table (1).

Table (1): The composition of different propranolol HCl microsphere formulations.

Formula No.	Drug: polymer ratio	Stirring rate R.P.M	Emulsifier concentration (Span 80)	Oil type
F1	1: 1	800	1%	100% LLP
F2	1: 2	800	1%	100% LLP
F3	1: 3	800	1%	100% LLP
F4	1: 4	800	1%	100% LLP

Particle size analysis of the prepared microspheres.

The particle size distribution of microspheres was determined by using a set of standard sieves with a shaker. A specific weight (2 gm) of microspheres was placed on the top of the sieves (1180, 850,355,250,180,150 µm) and allowed to be shaked for 10 min. The size of the microspheres was calculated according to the equation reported by Ansel et al. [13]

$$\text{Average particle size} = \frac{\Sigma(\%\ Retained \times Average\ size)}{100}$$

Drug content analysis.

10 mg of microspheres were accurately weighed and added to 30 ml chloroform to dissolve the polymer. The drug was then extracted with 100 ml distilled water. The amount of propranolol HCl in the aqueous phase was assayed spectrophotometrically at 289 nm, where no detectable interferences with excipients were observed. The entrapment efficiency % of the drug was then calculated from the following equation according to Chang and Bodmeier[14].

$$\text{Drug entrapment efficiency \%} = \frac{Actual\ drug\ content}{Theoretical\ drug\ content} \times 100$$

Optical Microscopy of the prepared microspheres

The surface characters of microspheres of formulae number 3 and 4 were examined with an optical microscope at 40x magnification power.

Preparation of suppositories

I- Conventional suppositories:

Suppositories of infantile size (1gm) each containing 10 mg of propranolol HCl were prepared by fusion method. The required amount of propranolol HCl was accurately weighed then incorporated into the melted bases on a hot water bath at either 38°C for Witepsol H15 (W) or 48°C for PEG mixture (PEG 6000 40% and PEG400 60%) (P), and stirred gently until the drug was uniformly distributed through the base. When the melted base started congealing, it was poured into a clean mold and allowed to cool until mass solidification occurred. The prepared suppositories were stored in a refrigerator at 4°C for further investigation.

II- Sustained release suppositories:

Equivalent amounts of propranolol HCl microsphere (F1, F2, F3 and F4) were incorporated into both Witepsol H15 (W) and PEG (P) bases by fusion method described above giving eight formulae namely: WF1, WF2, WF3, WF4, PF1, PF2, PF3 and PF4, respectively.

Characterization of the prepared suppositories:

A) Weight variation and content uniformity

Twenty suppositories from each patch taken at random were weighed and average weight was determined. Not more than two of the individual weights should deviate from the average weight by more than 5 per cent, and none deviates by more than 10 percent (B.P 1998). Although the USP did not specify the content uniformity test for suppositories, the relative potency of each group of suppositories was determined. Only suppositories with a drug content of 100% ± 5% were included in this study[15].

B) Disintegration time of the prepared suppositories

Selected suppositories were placed in a dialyzing membrane and placed in a beaker containing 100 ml of water at 37±0.5°C and shaken gently. The time of complete disintegration of the suppositories was recorded in minutes [15].

In-vitro release of propranolol HCl from the prepared microspheres, conventional suppositories and sustained release suppositories:

The method of Hassan and Mahfouz [16] was adopted with certain modifications. The system was prepared as follows: A cellulosic membrane (4x4 cm) was soaked in distilled water over night. The membrane was stretched firmly over the end of a glass tube (28 mm internal diameter) and tied with a cotton thread as shown in the diagrammatic sketch (Fig. 1). A volume of 5 ml Sorensen's phosphate buffer pH7.4 at 37 ± 0.5°C was poured into the tube. The prepared tube was suspended vertically in a 250 ml beaker containing 100 ml of Sorensen's phosphate buffer pH 7.4 at 37 ± 0.5°C so that the buffer inside the tube and outside the tube was at the same level. The system was placed into a mechanically shaker water bath adjusted at 50 rpm. The absorbance of each sample was determined spectrophotometrically at λ_{max} 289 nm, where no detectable interferences with excipients were observed.

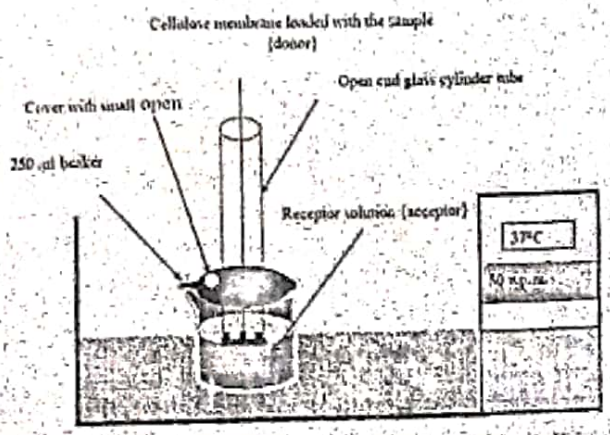

Fig. 1. Diagrammatic sketch of the diffusion cell in thermostatic shaker water bath

Zagazig J Pharm Sci, June 2010
Vol. 19 No 1 pp 12-16

ISSN 1110-5089

RESULTS AND DISCUSSION

Particle size analysis of the prepared microspheres and drug content

Table 1 summarizes the average particle size, actual drug loading (%) and encapsulation efficiency (%) of propranolol HCl loaded microspheres which were affected by the drug: polymer ratio. The data obtained indicated that, the mean diameter was 394 µm and decreased to 240 µm when the drug: polymer ratio was changed from 1:1 to 1:4 respectively. Increasing the proportion of the drug: polymer ratio resulted in decreasing the mean diameter of microspheres. The results are consistent with those of Jelvehgari et al [15] who have found that, changing the drug polymer ratio from 1:1 to 0.25:1 resulted in decreasing the mean particle size from 401 um to 189 um, respectively. This can be attributed to the fact that with the higher diffusion rate of inner solvent to polymer solution, the smaller size of microcapsule is easily obtained [16]. The data listed in table 2 shows that the actual entrapment percentage of microspheres prepared with 1:4 to 1:1 drug: polymer ratios increased from 16.2 to 45.6%, respectively.

Table (2): Average particle size, actual drug loading (%) and encapsulation efficiency of propranolol HCl microspheres.

Formulae	Average particle size (µm)	Actual drug loading (%)	Drug encapsulation efficiency (%)
F1	394	45.6	91.2
F2	367	29.9	89.8
F3	311	21.4	85.8
F4	240	16.2	81.3

These results were in agreement with those of Chao and Price [17] who reported that increasing the theoretical drug contents results in increasing the actual drug content. It is preferable to encapsulate water-soluble drug by using the w/o emulsion than o/w emulsion evaporation method since, w/o emulsion will increase the encapsulation efficiency. The poor encapsulation efficiency of o/w was attributed to the partitioning of the drug out from the organic dispersed phase into the aqueous continuous phase [18].

Surface scan of propranolol HCl CAB microspheres.

Figures 2-3 show photomicrographs of CAB microspheres (F3 and F4) at magnification powers 40x. Spherical microspheres with uniform and smooth surface were obtained. No free propranolol HCl crystals appeared in the preparations.

Fig. 2. Photomicrograph of CAP microspheres F3 (40X)

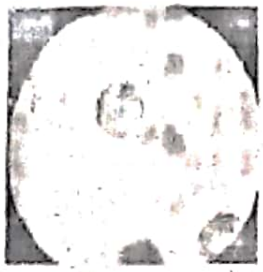

Fig. 3. Photomicrograph of CAP microspheres F4 (40X)

In vitro release studies of propranolol HCl microspheres.

Figure 4 shows that the release rate of the drug from the microspheres is directly proportional to the amount of drug incorporated. The higher the amount of the drug, the faster the rate of release. It was clear that formulae 1 and 2 are characterized by initial drug release which corresponds to about 30-47 % in the first 30 minutes of the test, followed by slower phase of drug release. Interestingly, 100% of the drug was released after 240 and 360 minutes from F1 and F2, respectively. The initial burst release could be attributed to the part of the drug located just at the surface of the microspheres within a thinner coating [19-21]. On the other hand, those with reduced amount of the drug gave better results in retarding the rate of release. For instance, the 1:3 and 1:4 drug: polymer preparations (F3 and F4, respectively) gave SR characteristics. About 5% -10% of the drug was released in the first 30 minutes and 30% - 43% was released after 360 min from F3 and F4, respectively. The previous behavior could be explained due to the low amounts of drug and the higher polymer ratio results in thicker coating with no pore formation that hinder the diffusion of the drug from the corresponding microspheres [22-24].

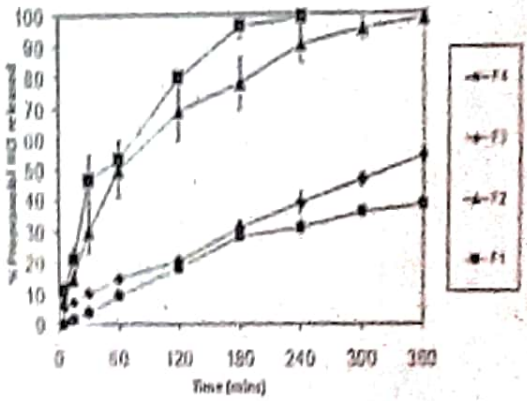

Fig. 4. Release profiles of propranolol HCl from microspheres in sorensen's phosphate buffer pH 7.4. (Data represented as mean±SD; n=3).

Physical properties of propranolol HCl conventional and SR suppositories:

A- Weight variation and content uniformity

All the prepared suppositories comply with the acceptable limits.

B- Disintegration time.

It was found that, no big difference in disintegration time between conventional and sustained release suppositories. The disintegration time of Witepsol H15 conventional and sustained release suppositories was 16 and 16.6 minutes, respectively, where the disintegration time of PEG conventional and sustained release suppositories was 20 and 21.5 minutes, respectively.

In vitro release studies of propranolol HCl conventional suppository

A- Release of propranolol HCl from conventional suppositories

The rate of release of propranolol HCl from conventional Witepsol H15 suppository was higher than PEG suppository (Fig. 5). It is clear that the difference in the drug release from the tested

suppositories was greatly affected by the type and composition of the utilized bases. The release rate was rapid from Witepsol H15, which may be due to the hydrophilic nature of propranolol HCl and its low affinity to fatty bases and the faster disintegration time of Witepsol H15 suppository than PEG suppository. These assumptions are in accordance with those obtained by Ibrahim et al. [25] and Sammour et al. [26]. The release of propranolol HCl from PEG base was also high. This may be attributed to the higher water solubility of PEG and their compatibility with the dissolution medium, which increases the solubility and diffusion rate of the drug [6].

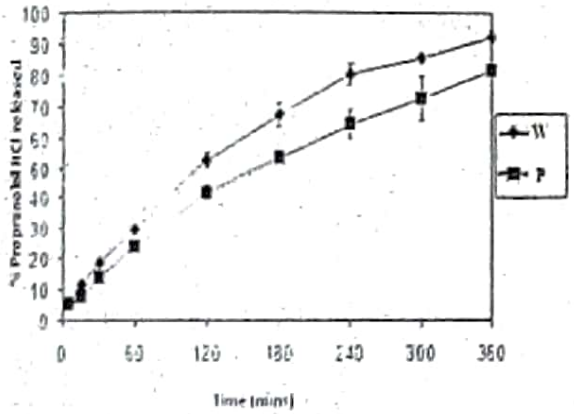

Fig. 5. Release profiles of propranolol HCl from conventional suppositories in sorensen's phosphate buffer pH 7.4. (Data represented as mean±SD; n=3).

B- Release of propranolol HCl from SR suppositories.

The rate of release of propranolol HCl from SR suppositories is shown in figure 6. All formulations of the drug loaded microspheres incorporated in Witepsol H15 and PEG bases showed slower rates of release when compared to either the drug release from powdered microspheres or conventional suppositories. It is clear that only formulae WF1 and WF2 gave drug release of about 70% and 60% after 6 hours, respectively. The result may be attributed to the combination of the effects of rapid bursting of the microspheres, the hydrophilicity of the drug and the oily nature of Witepsol H15.

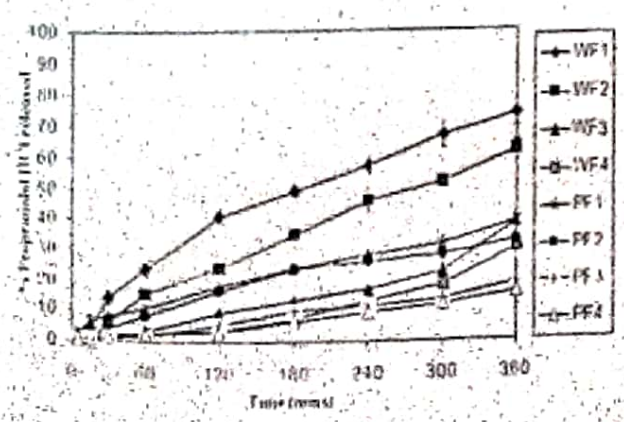

Fig. 6. Release profiles of propranolol HCl from sustained release suppositories in sorensen's phosphate buffer pH 7.4. (Data represented as mean±SD; n=3).

These results were consistent with those obtained by Arra et al[8] who have found that the dissolutions of both pure micropelets and conventional suppositories of the terbutalin sulfate were higher than PEG suppositories containing terbutalin sulfate micropellets. The same formulae of microspheres F1 and F2 in PEG base showed slow release patterns which could be ascribed to the slow disintegration and dissolution characteristics of PEG suppositories [10]. On the other hand, formulae WF3, WF4, PF3 and PF4 gave less than 30% of total drug release after 6 hours, where the release rates were higher from Witepsol base than from PEG base as discussed previously. This can be explained on the basis that the microspheres were of thick coating and reduced drug amounts which require longer time for drug diffusion through microsphere coats giving sustained release properties. Other studies performed release test for suppositories of indomethacin encapsulated in ethylcellulose and found that the drug released was almost the same for PEG and Witepsol suppositories, where others tested ibuprofen microspheres in suppositories and found that lipophilic bases slightly affected the dissolution which is due to the fact that ibuprofen is more soluble than indomethacin[10, 27]. This revealed that the drug dissolution from SR suppositories containing microparticulate dosage forms depends on the solubility of the drug and lipophilicity or hydrophilicity of the base used.

CONCLUSION

From the obtained results, it was concluded that, sustained release suppositories composed of propranolol HCl microspheres dispersed in hydrophilic or lipophilic suppository base can be suggested as alternative way to conventional dosage forms. This can lead to reduction of the frequency of administration, expected improvement of drug bioavailability and providing more patient compliance. The drug physical properties, the base nature, the microsphere characteristics are factors affecting the SR properties of the prepared suppositories. Therefore, SR suppositories of propranolol HCl are promising as being more useful formulations in therapy.

REFERENCES

1- Cid E., Mella F., Lucchini L., Carcamo M., Monasterio M.J. **J. Biopharm. Drug Dispos.** 7: 559–566. (1986).

2- Malladi S.P.S., Satyanarayama N.V., Divan P.V., Krishna D.R. **Drug Dispos. Ind. Pharm.** 19: 1089–1096. (1993).

3- Phutane P., Shidhaye S., Lotlikare V., Ghule A., Sutar S., and Kadam V. **J. Young Pharm.** 2(1): 35-41. (2010).

4- Baumgartner S., Kristl J., Vrecer F., Vodopivec P., Zorko B. **Int. J. Pharm.** 195:125-135. (2000).

5- Al-Dossary B. N., Al-Gohary O. M. N. and El-Khawas M. M. **Scientia Pharmaceutica.** 74: 31-51. (2006).

6- Baria A. H., Patel R. P., Suthar A. M., Parmer R. B. **Int. J. Pharm. Sci. and Drug research.** 1(2): 71-73. (2009).

ISSN 1110-5089

7- Kuroda T, Yokoyama T, Umeda T, Matsuzawa A, Kuroda K, Asuda S. **Chem. Pharm. Bull.**, 31: 3319-3325. (1982).
8- Arra GS, Biswanath SA, Krishna DR, Arutla S, Bandyopadhyay AK. **Drug Dev. Ind. Pharm.**, 23: 1233-1237. (1997).
9- Uzunkaya G. and Bergisadi N. **IL Farmaco.** 58: 509-512. (2003).
10- Tamer G., Mesut A., Gökhan E. **FABAD. J. Pharm. Sci.**, 29: 177-184. (2004).
11- Ryu Jei-Man, Chung Suk-Jae, Lee Min-Hwa, Kim Chong-Kook, Shim Chang-Koo. **J. Controll. Rel.** 59: 163–172. (1999).
12- Sprockel, O. L. and Prapaitrakul, W. **Int. J. Pharm.** 58:123. (1990).
13- Ansel, H. C., Popovich, N. G. and Allen, J. R. In Pharmaceutical Dosage Forms and Drug Delivery Systems. 6th ed. Williams and Wilkins. London P:175. (1995).
14- Chang M. and Bodmeier. **Int. J. Pharm.** 130:187. (1996).
15- Babar, A., Bellete, T. and Plakogiannis, F.M. **Drug. Dev. Ind. Pharm.**25(2): 241. (1999).
16- Hassan, M. A. and Mahfouz, N. M. **Bull. Pharm. Sci. Assiut Univ.**24(1): 47. (2001).
17- Jelvehgari M., Nokhodchi A., Rezapour M., Valizadeh H. **Indian J. Pharm. Sci.** 72(1): 72-78. (2010).
18- Sahoo S.K., Mallick A.A, Barik B.B., Senapati P.C. **Tropical J. Pharm. Res.** 4: 369-375. (2005).
19- Cihao, C. S. and Price, J. C. **J. Microencapsul.** 11(2): 153. (1994).
20- Patrick B. O'Donnell and James W. McGinity, **Advanced Drug Delivery Reviews**, 28(1): 25-42. (1997).
21- Ghaderi R., Struesson C., Carlfors J. **Int. J. Pharm.** 141: 205-216. (1996).
22- Mogi T., Ohtake N., Yoshida M., Chimura R., Kamaga Y., Ando S., Tsukamoto T., Nakajima T., Uenodan H., Otsuka M., Matsuda Y., Ohshima K., Makino K. **Colloid Surface B.** 17: 153-165. (2000).
23- Giunchedi, P., Torre, M. L., Maggi, L., Conti, B. and Conti, U. **Drug Develop. Ind. Pharm.** 21(3):315. (1995).
24- Kilicarslan, M., Baykara, T. **Int. J. Pharm.** 252(1-2):99. (2003).
25- Ibrahim, S. A., El-Faham, T. H., Shawky, T. S. and Mostafa, E. M. **Int. J. Pharm.**, 61:1. (1990).
26- Sammour, O. A., Bosela, A. A., El-Ghamry, H. A. and Mahdy, M. A. **J. Bio. Med. Sci. Ther.** 7, (9-1):124. (1991).
27- Nakajima T., Takashima Y., Iida K.I., Mitsuta H., Furuya T., Koishi M. **Chem. Pharm. Bull.** 35, 4249-4254. (1987).

Received: Feb., 07, 2010
Accepted : March, 30, 2010

التقييم المعملي للتحاميل ممتدة المفعول المحتوية علي الحويصلات الدقيقة للبروبرانولول هيدروكلورايد

تامر محمد شحاته و محمود مختار ابراهيم

قسم الصيدلانيات و الصيدلة الصناعية – كلية الصيدلة – جامعة الزقازيق – الزقازيق – جمهورية مصر العربية

تم تحضير الحويصلات الدقيقة للبروبرانولول هيدروكلورايد بنجاح باستخدام بوليمر السليولوز أستات بيوتيرات و طريقة المستحلب و تبخير المذيب. و قد تم تقييم تأثير نسبة العقار الي نسبة البوليمر علي الحويصلات الدقيقة المنتجة من حيث حجم الجزيئات وكفاءة احتواء العقار و خصائص انطلاق العقار. و قد تمت صياغة التحاميل ذات الانطلاق الممتد باضافة الحويصلات الدقيقة للبروبرانولول هيدروكلورايد الي قواعد دهنية مثل وايتبسول هـ١٥ و قواعد محبة للماء مثل عديد اثيلين جليكول. و قد أوضحت الدراسة أن كمية العقار المحتواه و حجم الحويصلات الدقيقة يزيد بزيادة نسبة العقار الي البوليمر. وقد تمت دراسة انطلاق العقار في المعمل في محلول فوسفات ذو الأس الهيدروجيني ٧,٤. و قد تبين أن انطلاق العقار من الحويصلات الدقيقة يتأثر بنسبة العقار الي البوليمر. فكلما زادت نسبة البوليمر بالنسبة الي العقار كلما قلت نسبة العقار المنطلق. و قد أوضحت الدراسة أن التحاميل التقليدية المتكونة من وايتبسول هـ١٥ تعطي انطلاقا سريعا للعقار مقارنة بالتحاميل المكونة من عديد ايثلين جليكول. وزيادة علي ذلك فان التحاميل المحتوية علي الحويصلات الدقيقة للعقار قد أعطت انطلاقا بطيئا للعقار و أيضا في حالة الوايتبسول كان أسرع منه في حالة عديد اثيلين جليكول.

و بذلك فان هذه الدراسة تقترح أنه باحتواء الحويصلات الدقيقة للعقار في التحاميل المكونة من قواعد محبة أو كارهة للماء يعطي الانطلاق الممتد للعقار وهو أمر واعد لأنه يعد أكثر نفعا من الصياغات التقليدية في العلاج.