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FORMULATION AND EVALUATION OF TRAMADOL HYDROCHLORIDE MICROSPHERES.

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ABSTRACT

Tramadol hydrochloride microspheres with cellulose acetate butyrate (CAB) polymer were prepared using water-in-oil emulsion non solvent evaporation technique, in an attempt to decrease the frequency of the dose from 4 to 6 times daily to twice daily. The Influence of different parameters such as drug to polymer ratio, concentration of span 80, stirring rate and viscosity of oil on the actual entrapment and yield percentage were studied. The actual entrapment and yield percentage were increased by increasing drug: polymer ratio, decreasing the stirring rate, decreasing span 80 concentration and decreasing the oil viscosity. The microsphere particle size was decreased by decreasing drug: polymer ratio, increasing the stirring rate, increasing span 80 concentration and increasing the oil viscosity. the effect of different parameters on the in-vitro release of tramadol hydrochloride from the prepared microspheres was also studied. The release rate was decreased by decreasing the drug: polymer ratio, decreasing span 80 concentration, decreasing stirring rate and decreasing oil viscosity. Analgesic activities of intact tramadol HCl alone and tramadol HCl microsphere were evaluated using hotplate method. The analgesic activities of the tested microspheres in-vivo were prolonged compared to that of the uncoated drug.

INTRODUCTION

Numerous microspheres preparation methods and materials, which can be incorporated in microspheres, enable precise optimization of controlled release in different physiological conditions. Due to their microscopic size, microspheres can be used alone or incorporated in other drug delivery systems and are suitable for various routes of application[1]. Tramadol HCl is a centrally acting analgesic, which possesses opoid properties. It may be administered orally, rectally, intravenously or intramuscularly. Many clinical studies have evaluated analgesic effects of tramadol HCl in comparison with morphine and other analgesics. The results showed that tramadol HCl is effective for relief of postoperative pain, moderate surgical pain, and surgical pain in children[2]. A dose of 50 to 100mg may be given every 4 to 6 hours. Tramadol may also given orally as modified release preparation twice daily[3]. It has been reported that, as the number of doses per day increases there is a greater risk that the patient will either forget or neglect to take every dose[4] .This is a major reason that considerable attention has been focused on the development of controlled release dosage forms[5]. Microspheres can achieve sustained drug release with additional taste abatement and better gastrointestinal tolerability[6]. Microspheres are often distributed through the gastrointestinal tract (GIT) after oral administration; this potentially improves drug absorption and reduces local irritation to GI mucosa[7]. The emulsion non-solvent evaporation technique has been described in the literatures, and has been applied to polymer such as cellulose acetate butyrate (CAB)[8]. The aim of this investigation was to develop sustained release microspheres of tramadol HCl using CAB polymer. The morphology, size distribution of the microspheres, and the effect of drug-to-polymer ratio on release rate of drug from the prepared microspheres were evaluated.

EXPERIMENTAL

Materials

Tramadol hydrochloride was kindly supplied by the Egyptian International Pharmaceutical Industrial Co., Egypt; Cellulose acetate butyrate (CAB) was obtained from Sigma Chemical Co st. Louis, Mo.USA; Acetone, n-hexane, HCl, potassium dihydrogen phosphate, disodium hydrogen phosphate, Light liquid paraffin (L.L.P) and Heavy liquid paraffin (H.L.P) were of analytical grade and purchased from El-Gomhouria Co.; Sorbitan monooleate 80 (Merck Sharpe and Dohmn International, Germany). All other solvents and chemicals were of analytical grade.

Equipment

Mechanical stirrer (Heidolph PZP-2000, Germany); -Digital pH meter (Cole-Parmer Instrument Co., U.S.A); -Dissolution apparatus (Type PTWl l, Pharma test, Germany); Sieve Shaker (Model RX-86-1.USA.); Intel digital computer camera (model C110. USA); Electronic Digital Balance (Metter-Toledo, CH 8606, Greifensee, Switzerland); Visco Star- R FUNGILAB viscometer; Hot plate

Preparation of Microspheres.

Microspheres were prepared by the emulsion non-solvent evaporation technique[9]. CAB in different concentrations, was dissolved in acetone and kept over night in a refrigerator to form the polymer solution, into which tramadol HCl was dispersed. Mineral oil was the dispersion medium for the polymer solution; the drug-polymer dispersion was then emulsified in the mineral oil containing different concentrations of span 80, with vigorous agitation. After 5 min, 60 ml of n-hexane (non-solvent) were added to the emulsion at a rate 1ml / min. Stirring was maintained until all the acetone was evaporated. The microspheres were separated from the dispersion medium by filtration using sintered glass filter G4, washed with three portions of n-hexane (100 ml each). The washed microspheres were dried at room temperature over night. Formulations with different drug to polymer ratios were prepared as shown in Table (1)

Table 1: The compositions of different microsphere formulations

Formula No.	Drug / polymer ratio	Stirring rate R.P.M	Emulsifier concentration	Oil type
1	1: 3	800	1%	100% LLP
2	1: 4	800	1%	100% LLP
3	1: 5	800	1%	100% LLP
4	1: 4	1200	1%	100% LLP
5	1: 4	1600	1%	100% LLP
6	1: 4	800	0.1%	100% LLP
7	1: 4	800	0.6%	100% LLP
8	1: 4	800	2%	100% LLP
9	1: 4	800	1%	25% HLP
10	1: 4	800	1%	75% HLP
11	1: 4	800	1%	100% HLP

LLP: Light Liquid Paraffin.
HLP: Heavy Liquid Paraffin

Particle size analysis of microspheres

The particle size distribution of microspheres was determined by using a set of standard sieves with shaker. As specific weight (1gm) of microspheres was placed on the top of the sieves of aperture size (1180, 850,355,250,180,150um) and shaken for 10 min. The size of the microspheres was calculated according to the equation of Ansel et al.[10].

Recovery of microspheres

The dried microspheres were weighed to determine the total recovery (%) by the following equation:

Recovery (%) =

$$\frac{\text{weight of the collected microspheres}}{\text{total weight of drug and polymer used}} \times 100$$

Drug content analysis

Twenty milligrams of microspheres were placed in 150 ml separating funnel and 25 ml chloroform were added to dissolve the polymer and shacked well for 5 min. Distilled water (100 ml) were added and shacked well for another 5 min then allowed to stand for 20 min. 5 ml of the aqueous layer were taken and the concentration of the drug was determined spectrophotometrically at 272 nm. The coating material showed no interference with the absorbance of the drug.

Entrapment efficiency =

$$\frac{\text{actual drug content}}{\text{theoritical drug content}} \times 100$$

Optical Microscopy

The surface characters of microsphere Formula number 2 were examined with an optical microscope.

***In vitro* dissolution studies.**

The USP basket apparatus was used for all the in vitro release studies. Acidic solution 0.1 N HCl of pH 1.2 and sorensen's phosphate buffer pH 7.4 were used as the release media. The release test was carried out for 2 hours in acidic solution, then the acidic solution was replaced by an equal volume of sorensen's phosphate buffer and the release test was continued for 6 hours, the samples were taken and determined at different time intervals. Each determination was performed in triplicate and the mean value was recorded

Evaluation of analgesic activity.

Twenty-five mice weighing 15-20 gm of both sexes were used in the present investigation. The standard tramadol hydrochloride was dissolved in distilled water. Formulae 1, 2 and 3 which gave the highest yield and highest actual entrapments among all formulations were selected as models for pharmacological evaluation of the tramadol hydrochloride microspheres and they were distributed in distilled water.

Analgesic activity using hot plate method.-

The hot plate method of Jacob and Bosoviski[11], was applied to evaluate the analgesic activity of different tramadol HCl formulations. Twenty-five mature albino mice of both sexes, weighing 15- 20 gm, were divided into five groups (5 in each). The first group received distilled water orally and kept as control. The second one received tramadol hydrochloride in distilled water in a dose of (6.7 mg/kg/oral)[12]. Each group from the remaining three groups received the test formulae in a dose equivalent to (6.7 mg/kg/oral). Thirty minutes after the drug administration each mouse was placed in a two liters beaker placed over a hot plate thermostatically controlled at 56±0.5°C with a cutoff time 30 seconds. The time elapsed until the mouse licks the paws was calculated as a measure for the analgesic effect. Recordings were taken at 30, 60, 90, 120, 180, 300, 420, 540 and 720minutes after administration.

RESULTS AND DISCUSSION

Factors affecting particle size distribution:

A- Drug: polymer ratio

Table 2 shows that, the drug polymer ratio affected the particle size diameter of tramadol HCl microspheres. The data obtained showed that, the mean diameter of microspheres was 386µm and decreased to 297µm when the drug: polymer ratio changed from 1:3 to 1:5 respectively. Increasing the proportion of the polymer resulted in a decrease in the mean diameter of microspheres. These results are in agreement with Zinutti et al.[13]. Who found that, the mean diameter of 5-fluorouracil microspheres was decreased from 458µm to 443µm when the drug: polymer ratio was changed from 1:1 to 1:3 respectively. This can be ascribed to an increase in the viscosity of the internal phase that may form large emulsion globules thus increasing the particle size[14].

B- Effect of stirring rate.

Table 2 shows the effect of different stirring rates on the particle size distribution of tramadol HCl microspheres. Results indicate that, the particle size was decreased from 309 µm to 246µm when stirring rate increased from 800 to 1600 rpm. These results are

in agreement with those of Arabi et al.[15] who reported that, the average diameter of allopurinol microspheres was decreased by increasing the stirring rate. This may be attributed to an increase in the mechanical stress and therefore, the formation of an emulsion of small globules.

C- Effect of span 80 concentration.

Table 2 shows the effect of different span 80 concentrations on the particle size distribution of tramadol HCl microspheres. The data illustrate that, increasing the concentration of span 80 from 0.1% to 2% resulted in a decrease in the mean diameter from 415μm to 285μm respectively. The low concentration of span 80 result in coalescence of emulsion globules consequently increasing microspheres particle size. These results are in agreement with those Al-Helw et al.[16] who found that, increasing the concentration of span 80 resulted in a decrease in the particle size of chitosan microspheres containing phenobarbitone.

D- Effect of Oil Viscosity.

Table 2 shows the effect of increasing the viscosity of mineral oil on particle size of tramadol HCl microspheres. It is clear that, increasing the viscosity of continuous phase from 58.24 cp (LLP) To 140 cp (HLP) resulted in a decrease in the particle size from 309 to 221μm respectively. Sanghvi and Nairn[17] also reported that, increasing the viscosity of mineral oil from 100% LLP to 100% HLP resulted in a decrease in the particle size of cellulose acetate trimelitate microspheres from 700μm to 100μm respectively.

Factors affecting drug entrapment, yield percentage.

A- Drug: polymer ratio.

Table 2 shows the yield % of the microspheres obtained after filtration and drying in respect to the initial weight. The yield percentage of different microspheres formulations varied from 81.25% to 86.25% when the drug: polymer changed from 1:5 to 1:3 respectively. The reduction in the yield percentage with increasing polymer: drug ratio may be due to the loss of the smallest and lightest particles during filtration[18]. The data obtained from Table 2 shows that the actual entrapment percentage of microspheres prepared with 1:5 and 1:3 drug: polymer ratios increased from 13.9% to 22.8% respectively. These results are in agreement with those of Chiao and Price[14] who reported that, increasing the theoretical drug contents results in an increase in the actual drug content.

B- Effect of stirring rate.

Table 2 shows that, the actual entrapment % was 18.13%, 15.30% and 14.55% when the stirring rate was 800, 1200 and 1600 respectively. The data indicated that, the actual entrapment percentage decreased with increasing the stirring rate. These results are in agreements with those of Khidr et al.[19], who found that, lower percentage of drug was entrapped at the highest stirring speed and they attributed this to a less amount of drug encapsulated in the smaller microspheres size.

C- Effect of span 80 concentration.

Table 2 shows the effect of span 80 concentration on the yield% and actual entrapment % of CAB microspheres. The data revealed that, increasing the span 80 concentration from 0.1% to 2% results in a decrease in the actual entrapment percentage from 18.90% to 15.36% respectively. The decrease in the actual entrapment percentage could be attributed to the fact that, at low concentration of span 80 the surface of microspheres was smooth and intact while increasing span 80 concentration resulted in a brittle surface of microspheres which lead to a drug loss during washing of n-hexane[20].

D-Effect of oil viscosity.

Table 2 shows the effect of different LLP and HLP ratios on the yield percentage of tramadol HCl microspheres . It is clear that, increasing the oil viscosity from 58.24 to 140 cp (formulae 8 and 11 respectively) resulted in a decrease in the yield percentage and actual entrapment percentage of tramadol HCl Microspheres. This may be attributed to the decrease in the particle size[21].

Table 2: Effect of different parameters on the properties of tramadol Hcl CAB microspheres.

Formula No.	Actual Entrapment (%)	Entrapment efficiency. (%)	Yield (%)	Mean diameter (μm)
1	22.83	91.32	86.25	386
2	18.13	90.65	82.50	309
3	13.90	83.43	81.25	297
4	15.30	76.5	75	293
5	14.55	72.75	72.50	246
6	18.90	94.50	89.25	415
7	18.22	91.10	87.23	382
8	15.36	76.80	77.50	285
9	16.40	82	80	297
10	14.90	74.50	75	240
11	12.75	63.75	71	221

N.B: The compositions of the formulae are shown in Table 1.

***In vitro* release studies of Tramadol HCl CAB microspheres.**

A-Effect of drug: polymer ratio on the in vitro release of tramadol HCl CAB microspheres.

Figure 1 shows that, the release rate of the drug from the microspheres appeared to be directly proportional to the amount of drug used. The higher the amount of the drug the faster the rate of release. On the other hand, those with reduced amount of the drug gave bitter results in retarding the rate of release. For instance, the 1:3, 1:4 and 1:5 drug: polymer preparations (formulae 1, 2 and 3, respectively) gave good retardation effect. This can be ascribed to that, the high amount of the drug results in a thinner coating which, coupled with the pore formation

tendency, obviously results in faster drug release. On the contrary, the low amounts of drug resulted in thicker coating with no pore formation, that hinder the diffusion of the drug from microspheres[22,23,24].

B- Effect of span 80 concentration on the in vitro release of tramadol HCl from CAB microspheres.

Figure 2 shows the effect of different concentrations of span 80 on the percentage released of tramadol HCl. It is clear that, the release of the drug was dependent on the concentration of span 80, the higher the concentration of span 80 the greater the amount released. This may be explained on the base that, the microspheres formed at higher concentrations of span 80 were more porous than those made lower concentrations[20,25].

C- Effect of stirring rate on the in vitro release of tramadol HCl CAB microspheres.

Figure 3 shows that, increasing the stirring rate resulted in an increase in the rate of release of the drug. These results can be attributed to that the smaller particle size microspheres are produced at the higher agitation rates. Smaller particles possess a larger surface area, and hence higher dissolution rate. The results are in agreement with those obtained by Khidr et al.[26], who found that, the release of meclofenamic acid increased by increasing the stirring rate.

D- Effect of oil viscosity rate on the in vitro release of tramadol HCl CAB microspheres.

From Figure 4 it is clear that, the oil viscosity plays an important role in the percentage released of tramadol HCl from CAB microspheres. Increasing the oil viscosity resulted in an increase in the percentage released. It was mentioned previously that, increasing the oil viscosity resulted in a decrease in the particle size of the microspheres, accordingly, an increase in the percentage released was obtained. The results are in agreement with those of Bhalero et al.[27] who found that, the percentage released of diltiazem HCl from microspheres increased with increasing the oil viscosity.

Surface Scan of CAB microsphere.

Figures 5 and 6 show photomicrographs of CAB microspheres (Formula 2) at 2 different magnification powers. Spherical microspheres with uniform and smooth surface were obtained.

Analgesic Activity

Table (3) and Figure (7) illustrate that, tramadol hydrochloride and its prepared formulations have a significant analgesic activity almost over the period of experiment. The maximum analgesic effect for tramadol solution was observed after 90 minute, while the maximum analgesic effect for the test formulation was observed after 120 min for Formula 1 and 300 minutes for Formulae 2 and 3 respectively. It is clear that, the time for maximum analgesic effect increased with increasing the polymer ratio , and this may be due to the slower release of the drug from the polymer.

In the present study, it was predicted that uncoated tramadol HCl reached its maximum analgesic effect faster than that of the three formulations used . In addition, it was found that, the maximum analgesic activity for the tramadol HCl microspheres varied according to the percent of the drug to polymer ratios. Table (4) shows that the three formulations differed significantly from the data of tramadol HCl solution. The results obtained are in agreement with the data of Samy et al.[28] who found that increasing the polymer to drug ratio (phenyltoloxamine citrate) was accompanied by an increase in maximum analgesic effect. From the previously mentioned data, it can be concluded that, Formula 3 is considered to be the most preferable one since it gave the most significant sustained analgesic effect.

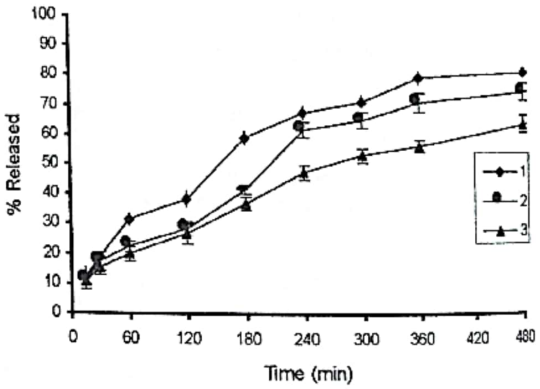

Fig. 1: Effect of drug/polymer ratio on percentage tramadol HCl released from CAB microspheres (pH change method)

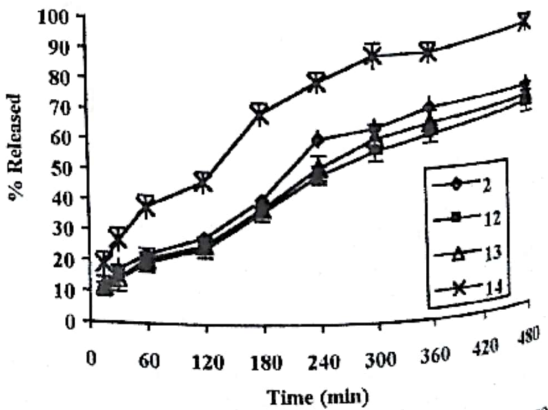

Fig. 2: Effect of span 80 concentration on percentage tramadol HCl released from CAB (pH change method)

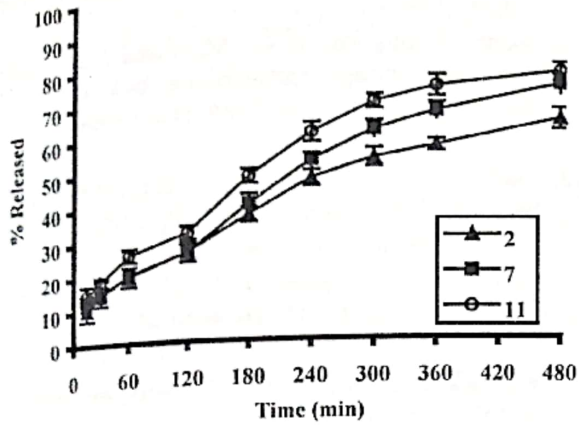

Fig. 3: Effect of stirring rate on percentage tramadol HCl released from CAB microspheres (pH change method).

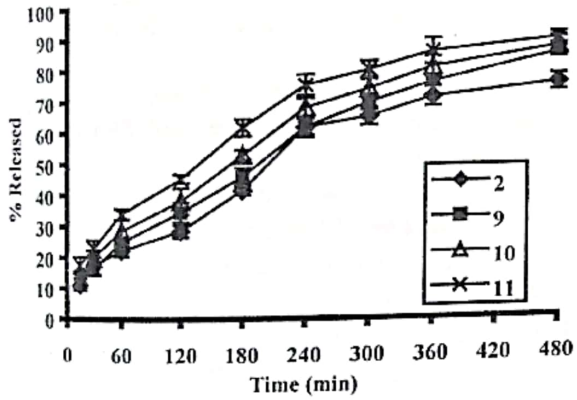

Fig. 4: Effect of oil viscosity on percentage tramadol HCl released from CAB microspheres (pH change method).

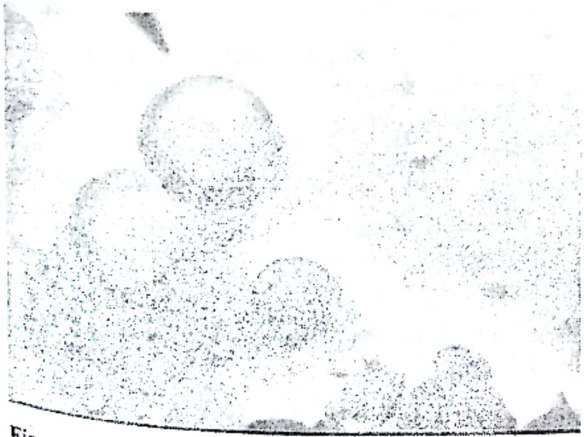

Fig. 5: Photomicrograph of CAB formula 2 magnification power 200x.

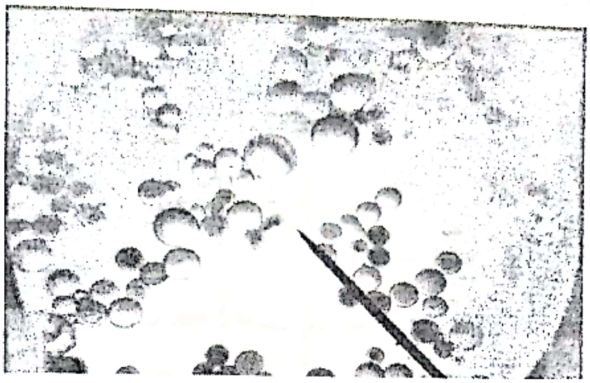

Fig. 6: Photomicrograph of CAB formula 2 magnification power 60x.

Table 3: Effect of different ratios of tramadol hydrochloride -cellulose acetate butyrate microspheres on the latencies of pain threshold on mice using hot plate method.

Time (min.)	Reaction time in seconds after varying time periods ± S.D.				
	Control	Pure drug	Form.1	Form.2	Form.3
30	6.65 ±0.53	9.21 *±0.48	7.19 ±0.74	7.21 ±1.60	6.60 ±1.26
60	7.93 ±0.96	14.08 *±1.13	11.46 *±0.99	9.21 ±2.23	7.96 ±0.95
90	7.97 ±0.59	18.86* ±3.20	14.44 *±1.11	9.45 ±1.28	9.81 ±0.70
120	6.46 ±0.37	11.94 *±2.49	17.10 *±0.65	10.66 *±0.96	11.16 *±1.53
180	7.33 ±0.96	7.09 ±1.67	15.41 *±0.77	12.77 *±2.21	11.82* ±0.68
300	6.59 ±1.59	6.82 ±2.34	13.86 *±1.13	15.39 *±1.91	16.39 *±0.76
420	7.07 ±1.41	7.23 ±1.32	11.36 *±1.10	11.86 *±2.76	15.56 *±1.37
540	7.08 ±0.45	6.82 ±0.82	11.31 *±0.97	10.32 *±3.13	14.45 *±0.52
720	6.6 ±0.46	6.66 ±0.66	9.42 *±0.72	8.52 *±2.89	10.86 *±1.12

- Values are expressed as mean difference ± SD. n = 5
(*) Significant difference from the control group at $p<0.05$.

Table 4: Time for maximum response and area under the curve for tramadol HCl standard and different microspheres formulations.

Preparation Data	Tramadol HCl standard	Formula 1	Formula 2	Formula 3
t_{max} (min)	90	120	300	300
AUC_{0-12}	5669.2 ± 660.6	8774* ± 473.4	8049* ±519.8	9372.6* ±365.3

Results represents mean of 5-observation ±S.D.
* Significant difference from tramadol HCl standard group at $p<0.05$.

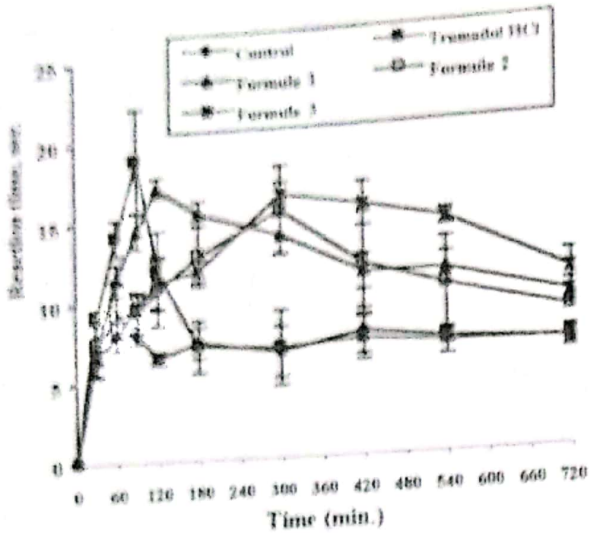

Fig 7: Mean reaction time versus time profiles in mice of Control group, tramadol hydrochloride oral solution, Formula1, 2 and 3.
- Values are expressed as mean difference ± SD, n = 5
* Significantly different from control group at $p<0.05$.

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صياغة وتقييم الحويصلات الدقيقة لأيدروكلوريد الترامادول

فخر الدين سليمان غازي ، أميمه أحمد أمين سمور ، محمد السيد ابوسليم و تامر محمد شحاته

قسم الصيدلانيات والصيدلة الصناعية – كليه الصيدلة – جامعه الزقازيق – الزقازيق – مصر

تم تحضير حويصلات دقيقة لعقار أيدروكلوريد الترامادول من مادة خلات بيوترات السليلوز بطريقة تبخير الوسط المنتشر. وذلك بهدف لتخفيض عدد مرات تعاطى العقار من ستة مرات إلى مرتين يوميا. وقد تمت دراسة تأثير عدة عوامل مثل نسبة العقار إلى البوليمر، نسبة سبان ٨٠ ، سرعة التقليب أثناء التحضير وكذلك تأثير لزوجة زيت البرافين على احتواء الحويصلات الدقيقة ،الكميه الناتجة بعد التحضير، حجم الحويصلات وكذلك مدى انطلاق العقار. وقد أظهرت النتائج أن حجم الحويصلات قد نقص تبعا لنقص كمية العقار إلى البوليمر ، زيادة سرعة التقليب ، زيادة نسبة سبان ٨٠ وكذلك زيادة لزوجة زيت البرافين. ومن ناحية أخرى فان انطلاق العقار من الحويصلات الدقيقة حديثة التحضير قل تبعا للاتي نقص نسبة العقار إلى البوليمر، نقص نسبة سبان ٨٠ ، نقص سرعة التقليب وكذلك نقص لزوجة الزيت. وقد تم أيضا تقييم التأثير الفرماكولوجي للحويصلات الدقيقة باستخدام طريقة السطح الساخن مقارنة بجرعات مساوية من ذات العقار في محلول مائي وقد وجد أن فاعلية العقار كمسكن للألم في الحويصلات الدقيقة كانت أفضل منها في المحلول المائي للعقار.