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PREPARATION, CHARACTERIZATION AND *IN-VITRO* RELEASE OF CONTROLLED RELEASE KETOROLAC TROMETHAMINE CELLULOSE ACETATE BUTYRATE MICROSPHERES

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تم في هذا البحث تحضير الكريات الدقيقة لعقار كيتورولاك تروميثامين بطريقة تبخير المذيب من المستحلب بإستحدام سليلوزأسيتات بيوتيرات بنسب مختلفة. وقد أختير نظام بوكس بنكن لتحضير كيتورولاك تروميثامين ويعتمد هذا التصميم على استخدام ثلاث متغيرات بثلاث مستويات مختلفة وقد استخدمت سرعة الجهاز ونسبة العقار إلى البوليمر وكذلك نسبة سبان ٨٠ كمتغيرات ثابتة وبثلاث مستويات وهى ٥٠٠ ، ٧٠٠ ، ٩٠٠ لفة في الدقيقة لسرعة الجهاز و ١ : ١ ، ١ : ٢ ، ١ : ٣ لنسبة العقار إلى البوليمر ١ ، ١,٥ ، ٢% من سبان ٨٠. تم تعيين الناتج التصنيعي والمحتوى الدوائي للكريات الدقيقة المحضرة وكذلك تعيين الخواص السطحية وشكل الكريات باستخدام المجهر الضوئي الماسح.وأظهرت النتائج أن الناتج التصنيعي ينحصر بين ٧٩,٥٥% (الصياغة رقم ١١) إلى ٩٤,٦١% (الصياغة رقم ١٣) وأن الصياغة رقم ١٣ لها أحسن محتوى دوائي (٧٧,١٢%) بينما الصياغة رقم ١١ لها أقل محتوى دوائي (٥١,٩٠%). وقد أظهرت النتائج أن الصياغات التي لها توزيع صغير يتراوح متوسط قطر جسيماتها الحسابي بين ٢٠٠–٣١٥ ميكروميتر (الصياغات رقم ٤ ، ٧ ، ٨ ، ٩ ، ١٠ ، ١١ ، ١٥) وأن الصياغات التي لها توزيع حجمي متوسط يتراوح متوسط قطر جسيماتها بين ٣١٥–٤٠٠ ميكروميتر (الصياغات رقم ٢ ،٣ ، ١٣ ، ١٤) بينما الصياغات التي لها توزيع حجمي كبير يتراوح متوسط قطر جسيماتها بين ٦٣٠ ٨٩٠ ميكروميتر (الصياغات رقم ١، ٥ ، ٦ ، ١٢) وقد تبين أن سطح معظم الكريات منتظم فيما عدا رقم ١٢ ، ١٣ وذلك باستخدام المجهر الضوئي الماسح. وقد تم تحضير محافظ كيتورولاك تروميثامين من الكريات الدقيقة للعقار انطلاق العقار منها باستخدم طريقة تعيين الأس الهيدروجيني. أظهرت النتائج أن أفضل الصياغات في معدل الانطلاق المعملي للعقار هي ١٤ ، ١٢ ، ٦ ، ١١ ، ٨ ، ١٣ ، ٩. وقد تم ايضا تعيين ديناميكية انطلاق العقار من المحافظ باستخدام نماذج حركية مختلفة. وقد وجد أن الانطلاق المعملي للعقار من الصياغات المحضرة يتبع النماذج الحركية الاتية : الصياغات رقم ١ ، ٢ ، ٥ ، ٦ ، ٧ ، ٨ ، ١١ ، ١٣ ، ١٤ تتبع النظام الحركي صفر بينما الصياغات رقم ٣ ، ٤ ، ١٠ تتبع معادلة هيكسون.

The purpose of this study was to prepare and characterize controlled release ketorolac tromethamine microspheres. To achieve this goal, cellulose acetate butyrate microspheres loaded by ketorolac tromethamine were prepared by the emulsion solvent evaporation method.

The prepared ketorolac tromethamine microspheres were evaluated for their production yields, particle size distribution, morphology, drug content and drug release characteristics. Thermal Gravimetric Analysis (TGA) were performed on the drug polymer systems in order to shed a light on the possibility of solid state changes of ketorolac tromethamine with CAB.

A Box-Behnken design was selected for formulating ketorolac tromethamine microspheres with revolution per minute (X1), drug-polymer ratio (X2) and span 80 percent (X3) as independent variables. Three levels of the independent variables were used which equal to -1, 0 and +1 for the above design. The values of the corresponding variables were 500, 700 and 900 rpm for the machine speed; 1:1, 1:2 and 1:3 for drug-polymer ratio; 1%, 1.5% and 2% (w/w) for span 80 percent.

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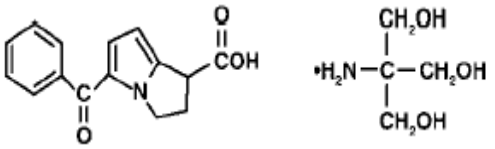
INTRODUCTION

Ketorolac tromethamine is a potent analgesic, anti-inflammatory drug. It is one of the few NSAIDs approved for parenteral administration. On the basis of animals studies it appears to have relatively more pronounced analgesic activity than most NSAIDS[1]. In the mouse writhing assay, it was found to be 350 times more potent as an analgesic than aspirin, on weight basis, 50 times as potent as naproxen, and six times as potent as indomethacin[2]. The biological half life of ketorolac is quoted to be 5.4 hrs with a range of 4.5-5.6 hrs which makes it suitable to be designed as a controlled release formulation.



(±)-1H-Pyrrolizine-1-carboxylicacid,5-benzoyl-2,3-dihydro-compound with 2-amino-2 hydroxy- methyl-1,3-propanediol.

Microspheres have been widely accepted as a means to achieve oral[3] and parentral controlled release drug delivery system[4]. The microspheres require a polymeric substance as a carrier and a core material. Among various methods developed for formulation of microspheres, the emulsion solvent evaporation method has gained much attention due to its ease of fabrication without compromising the activity of drug. In the present investigation, Cellulose acetate butyrate was used as encapsulating materials. Box-Behnken design was used for formulating ketorolac tromethamine cellulose acetate microspheres[5]. It deals with, optimization of formulation variables to improve the *in-vitro* release of ketorolac tromethamine dosage forms. Microspheres were prepared by emulsion solvent evaporation technique[6-8]. Cellulose esters widely used to impart controlled release properties to many drugs[7].

The main purpose of present research was to develop a controlled drug delivery system of ketorolac tromethamine for oral administration using cellulose acetate butyrate as a polymer via emulsion solvent evaporation technique applying Box-Behnken design to choose these formulae.

EXPERIMENTAL

Materials

Ketorolac Tromethamine (KT), El-Kahira Pharm. Chem. Co., (Cairo, Egypt). Cellulose Acetate Butyrate (CAB), Sigma Chem. Co., St. Louis (USA). Span 80, Sigma Chem. Co., Stoneham (Germany). Acetone, El-Nasr Pharm. Chem. Co., Cairo (Egypt). Liquid Paraffin, El-Gomhoria Chem. Co., Cairo (Egypt). Magnesium Stearate, El-Gomhoria Chem. Co., Cairo (Egypt). Hydrochloric acid, Potassium dihydrogen orthophosphate, disodium hydrogen phosphate, Sodium chloride and sodium hydroxide, El-Nasr Pharm. Co., Cairo (Egypt). n-hexane, El-Nasr Pharm. Co., Cairo (Egypt). Cyclohexan, Sigma Chem. Co., Stoneham (Germany). All the other reagents were analytical grade and were used recieved.

Methods

Design of the experiment

A Box-Behnken design was selected for formulating ketorolac tromethamine micro-spheres with revolution per minute (X1), drug-polymer ratio (X2) and span 80 percent (X3) as independent variables. Three levels of the independent variables were used which equal to -1, 0 and +1 for the above design. The values of the corresponding variable were 500, 700 and 900 rpm for the machine speed; 1:1, 1:2 and 1:3 for drug-polymer ratio and 1%, 1.5% and 2% (w/w) for span 80 percent.

Preparation of ketorolac tromethamine - cellulose acetate butyrate (CAB) micro-particles by emulsion solvent evaporation (w/o) technique

Ketorolac tromethamine was dispersed in the polymeric solution of cellulose acetate butyrate which dissolved in (25 ml) acetone forming the internal phase. The drug-polymer ratios 1:1, 1:2 and 1:3. Known amount of magnesium stearate (125 mg) was dispersed in the different internal phases as soothing agent. This dispersion was added drop wise to liquid paraffin (external phase) (150 ml) containing different concentrations of span 80 as emulsifying agent and was emulsified by stirring at different speeds. The stirring was continued at room temperature until complete evaporation of the solvent (acetone) about 5-7 hrs.

Liquid paraffin was decanted and the microspheres produced were filtered off, washed three times with n-hexane and three times with cyclohexane to remove the remaining oily phase and then dried overnight at room temperature.

Yield determination

The yield of the microspheres was determined by dividing the weight of the prepared microparticles by the original amount of the polymer and drug used. The results were expressed as a percentage.

Particle size determination

The dried microspheres were weighed and sized using USP standard sieve set. The fraction of microspheres remaining on each sieve was collected, and the mean particle size of the microspheres was determined as the percentage of microspheres retained at each sieve multiplied by the average particle size of this sieve.

Determination of drug content

The drug content of the prepared ketorolac tromethamine microspheres was determined by the following method[9].

Digestion method

One hundred mg of ketorolac tromethamine microparticles were crushed carefully in a glass mortar and transferred to a 100 ml volumetric flask using phosphate buffer pH 7.4. The volumetric flask was completed to the volume with phosphate buffer pH 7.4 then agitated for 5 min. each hour for 5 hrs. The sample was filtered and the drug concentration was determined specrophotometerically at 325 nm. The same procedure was applied for the plain formula, which was used as a blank. The concentration was calculated using the standard calibration curve of ketorolac tromethamine in phosphate buffer pH 7.4.

Photo-micrograph of ketorolac trome-thamine microspheres

Diluted suspension of ketorolac tromethamine microspheres in liquid paraffin was mounted on a slide. A photograph for each microsphere was taken from the prepared slide at magnification powers 40 and 100x.

Thermal gravimetric analysis (TGA)

TGA studies were carried out using previously prepared Ketorolac Tromethamine microspheres with drug to polymer ratio 1:1 and the corresponding physical mixtures as well as, drug alone in order to determine the extent of crystallinity of the drug in the presence of the studied polymers and to examine any possible interaction between Ketorolac Tromethamine and the used polymers. Samples were placed in an aluminum pan and heated at a rate of 10°C/min with indium in the reference pan, in an atmosphere of nitrogen up to 280°C.

Preparation of capsules

An appropriate amount of ketorolac tromethamine microspheres (prepared from Cellulose acetate butyrate) equivalent to 30 mg of ketorolac tromethamine was filled into hard gelatin capsules No.2.

***In-vitro* release of ketorolac tromethamine capsules**

Dissolution testing of the prepared microspheres equivalent to 30 mg of ketorolac tromethamine was performed with the rotating basket apparatus according to USP XXIV apparatus 2. Hard gelatin capsules No.2 filled with known amount of microparticles. The operating conditions were: Basket speed of 50 rpm and a temperature of 37°C±0.5, regarding the dissolution medium, the pH shift method[10-12].

First, 500 ml of 0.1N HCl pH 1.2, was used as the release medium for two hours, followed by the addition of (5.7) ml of 7 m KH_2 PO_4 containing 16.75% (w/v) NaOH in order to change the pH of the medium to 7.4 and the experiment was continued for another six hours. Filtered samples, 3 ml each, were removed at 0.25, 0.5, 1, 1.5, 2, 2.25, 2.5, 3, 4, 5, 6, 7 and 8 hrs. The samples were diluted appropriately with the release medium, and absorbance was measured at the predetermined λ_{max} of each medium against a blank of this medium. The withdrawn samples were replaced with equal volumes of the release medium kept at 37°C.

Kinetics of the *in-vitro* release of ketorolac tromethamine capsules

The kinetic parameters for the *in-vitro* release of ketorolac tromethamine were determined and then analyzed in order to find the proper order of the drug release using a specific computer program. Zero-, first-, and second order kinetic, as well as controlled diffusion model[13]. Hixson-Crowell cup root law and Baker-Lonsdale equation were investigated[14&15].

RESULTS AND DISCUSSION

Box-Behnken design, as shown in table 1, was used for formulating ketorolac tromethamine cellulose acetate microparticles[5]. It deals with, optimization of formulation variables to improve the *in-vitro* release of ketorolac tromethamine dosage forms.

Different concentrations of CAB were tried in this work, i.e, 2, 4, 6 and 8%. Both 2% and 4% CAB gave non spherical microparticles while 8% and more gave hard sheets of CAB. So, 6% CAB was used in this study.

Cellulose acetate butyrate containing ondanstron or butesonide were prepared by the emulsion-solvent evaporation method in an oily phase. Mixture of acetone and methanol in proper ratio (2:1 v/v, 3 ml) which was found to be excellent solvent for dissolving both drugs and polymers, polymer concentrations studied were 4, 6 and 8% and the drug polymer ratio was 1:10. The emulsified used was 1% of span 85 into liquid paraffin (70 ml) and 0.1% (w/w) of antifoam[9].

Magnesium stearate was added to the formulations as droplet stabilizer to overcome problem of droplet coalescence during solvent evaporation[16]. The action of magnesium stearate as soothing agent and liquid paraffin as external phase were used as a part of the emulsion solvent evaporation technique while the surfactant (span 80) was used as emulsifying agent.

Production yield determination

The range of the production yield of the prepared ketorolac tromethamine CAB – microspheres was found to be between 79.55% and 94.61% as shown in table 2. These data were represented as histogram in figure 2.

The best value appeared in the formula F13 (94.61%) while the worst value appeared in formula F11 (79.55%).

Drug content determination

The drug content determination measures the actual weight of ketorolac tromethamine inside the CAB microspheres. The rank order of the drug content was measured by the deviation from the theoretical weight. Formula 13 gave the best drug content of the prepared ketorolac tromethamine microparticles (77.12%), while formula F11 showed the worst value (51.90%) as shown in table 2 and illustrated as histogram in figure 1.

Particle size distribution

Table 3 shows the fraction percent of weight distribution of different formulae of ketorolac tromethamine CAB microspheres determined by sieve analysis. Formulae F4, F7, F8, F9, F10, F11, and F15 exhibit the best distribution pattern as the largest weight determined lied between 315-200 µm, while formulae F2, F3, F13 and F14 gave the second group of good distribution as a largest weight calculated lied between 400-315 µm. The remaining formulae F1, F5, F6 and F12 exhibit high distribution as the largest weight determined lied between (890-630 µm).

So, the formulated ketorolac tromethamine microspheres were arranged according to the mean particle size, in a descending order, as the following: F1, F12, F6, F5, F2, F13, F3, F14, F7, F8, F9, F4, F10 F11 and F15. Speed is the maximum parameters for controlling the drug/matrix dispersion's droplet size in the continues phase. It was shown that increasing the mixing speed generally results in decreased microsphere size, as it produces smaller emulsion droplets through stronger shear forces and increased turbulence[17-20].

In our study high stirring speed (900 rpm) produced microspheres with small particle size while low stirring speed (500 rpm) produced microspheres with large particle size. Similar results were obtained by Prongpaibul *et al*.[21].

Various manufacturing parameters (apparatus design, type of stirrer, stirring speed, viscosity of emulsion phase, polymer concentration and emulsifier concentration) affect particle size of the prepared microspheres[22&23].

Table 1: Composition of different suggested formulae of ketorolac tromethamine microparticles using cellulose acetate butyrate.

Formula No.	Drug (gm)	Cellulose acetate butyrate (gm)	Magnesim stearate (mg)	Liquid paraffin Ml	Span 80	Speed (rpm)	Total weight (gm)
F1	1.5	1.5	125	150	2.25	500	3.125
F2	1.5	1.5	125	150	1.5	700	3.125
F3	1.5	1.5	125	150	3	700	3.125
F4	1.5	1.5	125	150	2.25	900	3.125
F5	0.75	1.5	125	150	1.5	500	2.375
F6	0.75	1.5	125	150	3	500	2.375
F7	0.75	1.5	125	150	2.25	700	2.375
F8	0.75	1.5	125	150	2.25	700	2.375
F9	0.75	1.5	125	150	2.25	700	2.375
F10	0.75	1.5	125	150	1.5	900	2.375
F11	0.75	1.5	125	150	3	900	2.375
F12	0.5	1.5	125	150	2.25	500	2.125
F13	0.5	1.5	125	150	1.5	700	2.125
F14	0.5	1.5	125	150	3	700	2.125
F15	0.5	1.5	125	150	2.25	900	2.125

Independent variables	Level		
Speed	+1= 900	0 = 700	-1 = 500
Drug-polymer ratio	+1= 1:3	0 = 1:2	-1 = 1:1
Span 80%	+1= 2%	0 = 1.5%	-1 = 1%

Table 2: Production yield (percentage recovery) and drug content (percentage drug loading) of ketorolac tromethamine - Cellulose acetate butyrate microspheres.

Formula No.	Drug polymer ratio	Production yield %	Theoretical drug content (gm)	Actual drug content (gm)	Drug content %
F1	1:1	91.30	50.00	37.50	75.00
F2	1:1	91.00	50.00	35.05	70.10
F3	1:1	83.43	50.00	28.58	57.16
F4	1:1	81.32	50.00	27.16	54.32
F5	1:2	91.75	33.33	23.74	71.22
F6	1:2	86.52	33.33	19.43	58.29
F7	1:2	87.89	33.33	21.71	65.13
F8	1:2	90.35	33.33	23.15	69.46
F9	1:2	88.04	33.33	21.64	64.92
F10	1:2	88.80	33.33	21.51	64.53
F11	1:2	79.55	33.33	17.30	51.90
F12	1:3	82.57	25.00	13.03	52.12
F13	1:3	94.61	25.00	19.28	77.12
F14	1:3	81.79	25.00	13.26	53.04
F15	1:3	86.80	25.00	14.20	56.80

Table 3: Sieve analysis of ketorolac tromethamine-cellulose acetate butyrate microparticles (F1).

Formula (1)

Sieve size (µ)	Mean size (d) (µm)	Weight retained (W)	% Weight retained (%W)	Cumulative % weight retained	(d) x (%W)
890-630	760	38.21	38.21	38.9898	29632.24
630-400	515	28.256	28.256	67.82245	14848.82
400-315	357.5	15.258	15.258	83.39184	5566.056
315-200	257.5	11.06	11.06	94.67755	2906.071
200-160	180	3.016	3.016	97.7551	553.9592
160-100	130	4.2	4.2	100	291.8367
Sum		100	100		53798.98
(dav)	537.9898				

d_{av} = Arithmetic mean diameter in µm.

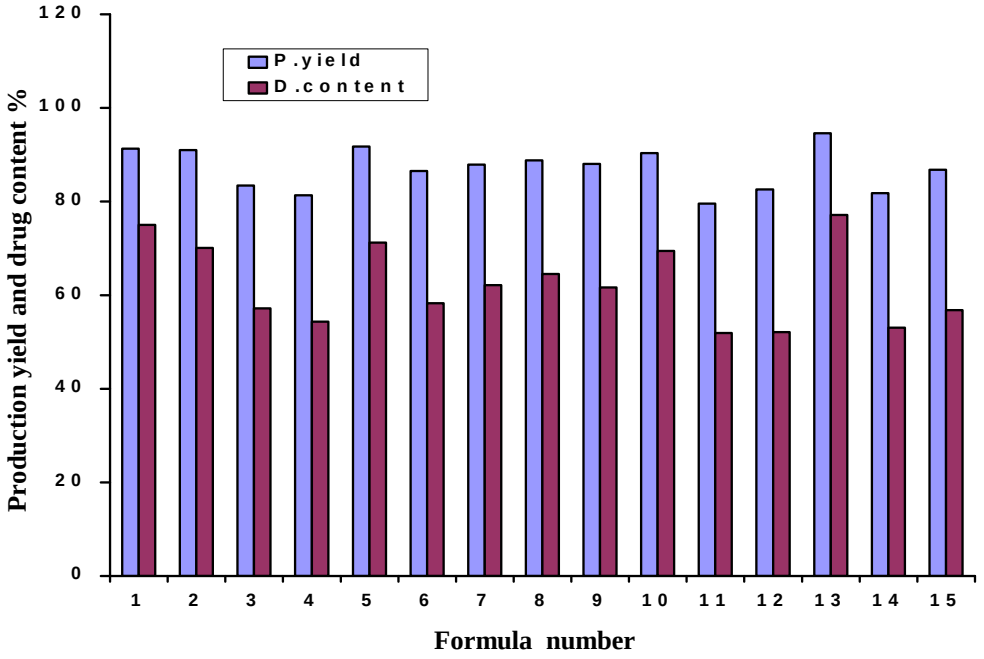


Fig. 1: Histogram showing the production yield and drug content of ketorolac tromethamine - cellulose acetate butyrate microspheres.

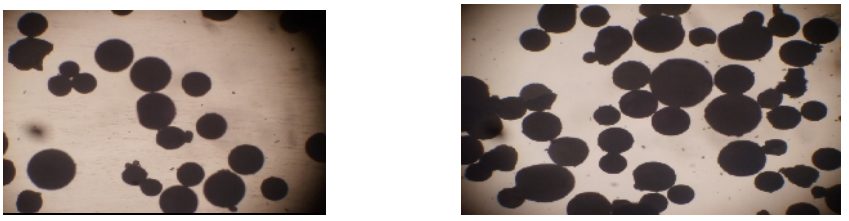


Fig. 2: Optical micrograph of ketorolac tromethamine – CAB microspheres, F3 and F14.

In this study evaporation process performed at room temperature because lower and higher temperature produce larger spheres whereas intermediate temperatures produced smaller spheres. The same finding was obtained by the work done by Yang *et al*.[24]. Also higher temperature resulted in highly porous skin and core due to rapid solvent evaporation[25].

Photo-micrographs of ketorolac trome-thamine-cellulose acetate butyrate micro-particles

Photo-microscopic technique was used to give as a clear picture about the shape and the surface of the prepared ketorolac tromethamine cellulose acetate butyrate microspheres. Also, this technique gave us an idea about the efficiency of the emulsion-solvent evaporation process.

Figure 2 illustrates the results of photo-micrographs. All the prepared ketorolac tromethamine cellulose acetate butyrate microspheres were spherical in shape with smooth surface except formulae F12 and F13 which were semispherical with irregular surface. The sizes of the tested formulae were different in diameters.

Thermal gravimetric analysis (TGA)

In order to shed a light on the possibility of solid state changes of ketorolac tromethamine with Cellulose Acetate Butyrate, TGA were performed on the drug polymer systems and their physical mixtures, as well as, individual components as shown in table 4 and figure 3.

The TGA scan of ketorolac tromethamine alone (Fig. 3, curve A), showed two endothermic indicative minima, the first at 156.6°C indicated dehydration process of ketorolac tromethamine salt, while the second at 166.22°C indicated it's melting point, ΔH values of - 196.37 J/g at 10°C/min. (Table 4).

The TGA tracing of CAB showed broad shallow peaks at about 227°C.

Upon scanning the TGA thermogram of ketorolac tromethamine-CAB physical mixture with drug to polymer ratio 1:1, it was clear that the characteristic endothermic peaks of the drug were seen at 156.17 and 166.56°C with ΔH value –376.8 J/g, indicating that there is no change on the drug in its Cellulose Acetate Butyrate physical mixture system. However the TGA thermogram of ketorolac tromethamine-Cellulose Acetate Butyrate microparticles revealed a reduction in the value of endothermic peak of the drug to 152.05 and 163.99°C with a pronounced reduction in the ΔH value to –129.09 J/g (Table 4 and Fig. 3, curve D).

The characteristic endothermic peaks of ketorolac tromethamine in its-polymer microparticles reduced in its intensity, shifted to lower temperatures and lost its sharpened distinct appearance. Also the drug exhibited lower values of ΔH in the prepared microparticles with the tested polymers, indicating that most of the drug was molecularly dispersed within the microparticles[26].

The appearance of melting peak of the drug in the prepared microparticles signified that the amount of polymers in these systems wasn't enough (drug-polymer ratio 1:1) to complete transformation of the drug to the amorphous form. TGA thermograms revealed that no notable thermal interaction occurred between the drug and the polymers used in this work.

***In-vitro* release of ketorolac tromethamine capsules**

Figures 4-6 show the *in-vitro* release of ketorolac tromethamine from their capsules containing formulae from F1 to F15. The maximum and minimum *in-vitro* release after 8 hrs of dissolution were found to be equal to 100% and 82.31%.

Figure 4 shows the *in-vitro* release of ketorolac tromethamine from their capsules containing formulae from F1-F4 using constant drug: polymer ratio 1:1 (X2) with variable span 80, 1% for F2; 1.5% for F1 and F4; 2% for F3 (X3), and the variable speeds, 500 rpm for F1; 700 rpm for F2 and F3; 900 rpm for F4 (X1). The maximum and minimum percent released were observed to be 19.24% and 13.9% at the end of two hours (Y1). The maximum and the minimum *in-vitro* release after four hours (Y2) of dissolution were found to be equal 88.35% and 72.65%, respectively. After eight hours of dissolution (Y3) the maximum and minimum *in-vitro* release was found to be equal to 100% and 92.36%, respectively.

Table 4: Endothermic peaks and ΔH values of ketorolac tromethamine- CAB microsphere (1:1 drug-polymer ratio) as well as the corresponding physical mixtures compared with the individual components.

Samples	Endothermic peaks (° C)		ΔH (Joule/g)
Drug alone	156.6	166.22	-196.37
Cellulose Acetate Butyrate	227		-25.64
Drug- CAB physical mixture (1:1)	156.17	166.56	-376.8
Drug-CAB microparticles (1:1)	152.05	163.99	-129.09

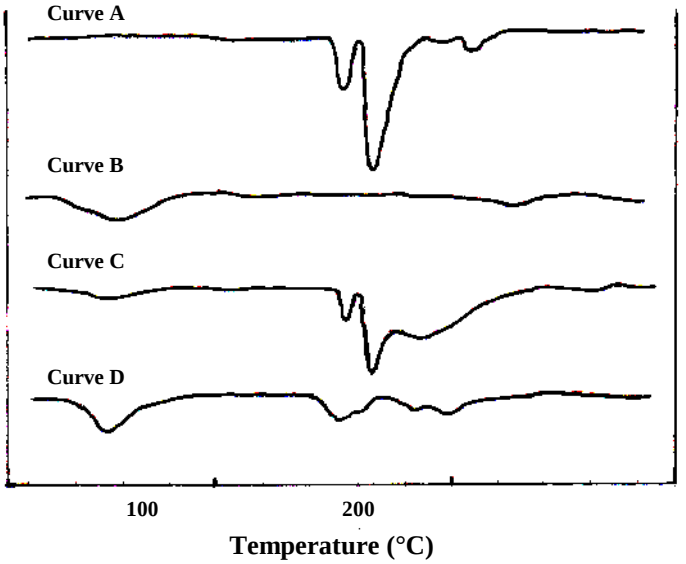


Fig. 3: TGA thermograms of ketorolac tromethamine with CAB at scanning speed of 10°C/min.: A, Drug alone; B, CAB; C, Ketorolac tromethamine-CAB physical mixture (1:1) and D, Ketorolac tromethamine-CAB microparticles (1:1).

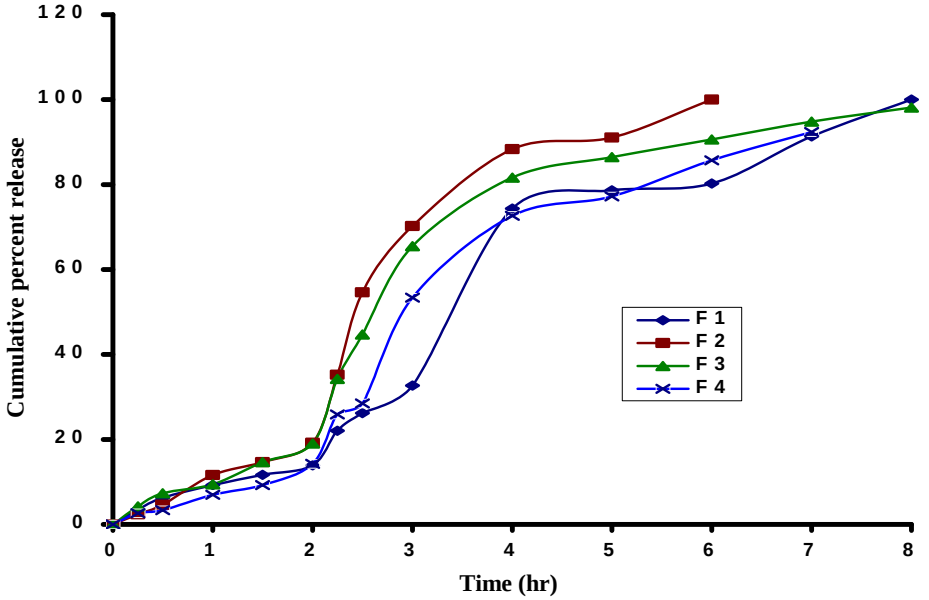


Fig. 4: *In-vitro* release of ketorolac tromethamine capsules containing drug : polymer ratio 1:1.

Similar finding obtained by *Abd El-Aziz* who studied the *in-vitro* release of diclofenac sodium microspheres from their capsule[10].

The investigated formulae containing ketorolac tromethamine capsules (F1–F4) can be arranged, in descending order, concerning the *in-vitro* release within 8 hrs as follows: F4 > F3 > F1 > F2, respectively.

Figure 5 shows the *in-vitro* release of ketorolac tromethamine from their capsules containing formulae F5–F11 using drug–polymer ratio 1:2 (X2) with variable span 80, 1% for F5 and F10; 1.5% for F7, F8 and F9; 2% for F6 and F11 (X3), and also variable speed, 500 rpm for F5 and F6; 700 rpm for F7, F8 and F9; 900 rpm for F10 and F11 (X1).

The maximum and minimum percent released were observed to be 17.02% and 11.52% at the end of two hours (Y1). The maximum and minimum *in-vitro* release after four hours of dissolution (Y2) were found to be equal 72.14% and 43.69%. Lastly, the maximum and the minimum *in-vitro* release after eight hours of dissolution (Y3) were found to be equal 100% and 82.90%.

The investigated formulae containing ketorolac tromethamine capsules (F5–F11) can be arranged, in descending order, concerning the *in-vitro* release within 8 hrs dissolution as follows: F6 > F11 > F8 > F7 > F9 > F5 > F10, respectively.

Figure 6 shows the *in-vitro* release of ketorolac tromethamine from their capsules containing formulate F12–F15 using constant drug-polymer ratio 1:3 (X2) with variable span 80, 1% for F13; 1.5% for F12 and F15; 2% for F14 (X3), and also variable speed, 500 rpm for F12; 700 rpm for F13 and F14; 900 rpm for F15 (X1). The maximum and minimum percent released were observed to be 13.75 and 11.95% after the end of two hours (Y1). The maximum and minimum *in-vitro* release after four hours (Y2) of dissolution were found to be equal 66.78 and 40.66. Lastly, the maximum and minimum *in-vitro* release after eight hours of dissolution (Y3) were found to be equal 97.90% and 82.31%.

The investigated formulae containing ketorolac tromethamine capsules (F12–F15) can be arranged, in descending order, concerning the *in-vitro* release within 8 hrs dissolution, as follows: F14 > F12 > F15 > F13, respectively.

The investigated formulae containing ketorolac tromethamine capsules (F1-F15) can be arranged, in ascending order, regarding the *in-vitro* release within two hours dissolution (Y1), as follows: F11 (8.87%), F6 (11.52%), F12 (11.95%), F8 (12.78%), F11 (12.87%), F9 (13.02%), F13 (13.06%), F14 (13.25%), F15 (13.75%), F1 (13.90%), F5 (14.24%), F7 (14.25%), F4 (14.25%), F13 (19.04%), F2 (19.24%), respectively.

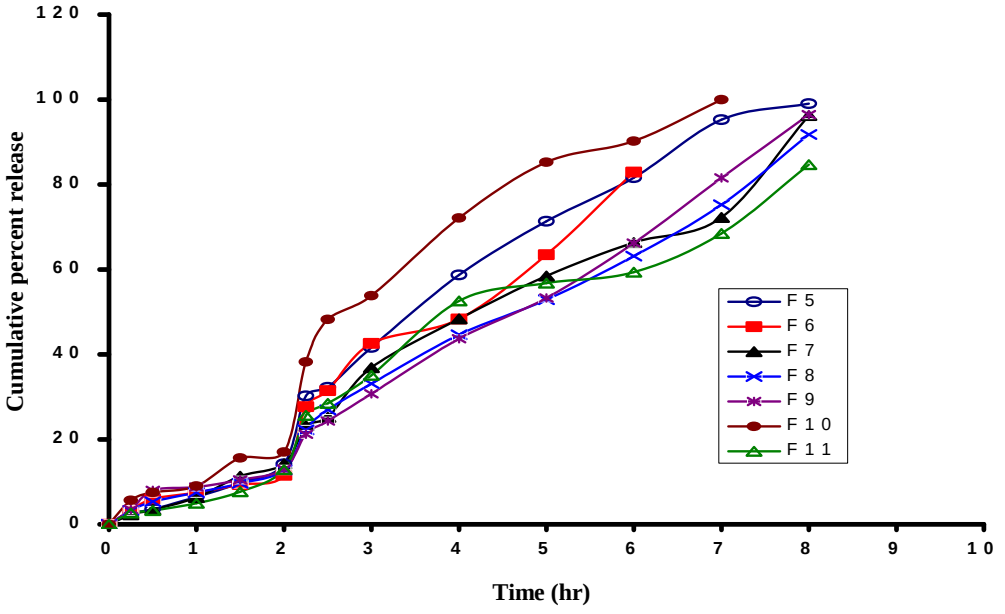


Fig. 5: *In-vitro* release of ketorolac tromethamine capsule containing drug : polymer ratio 1:2.

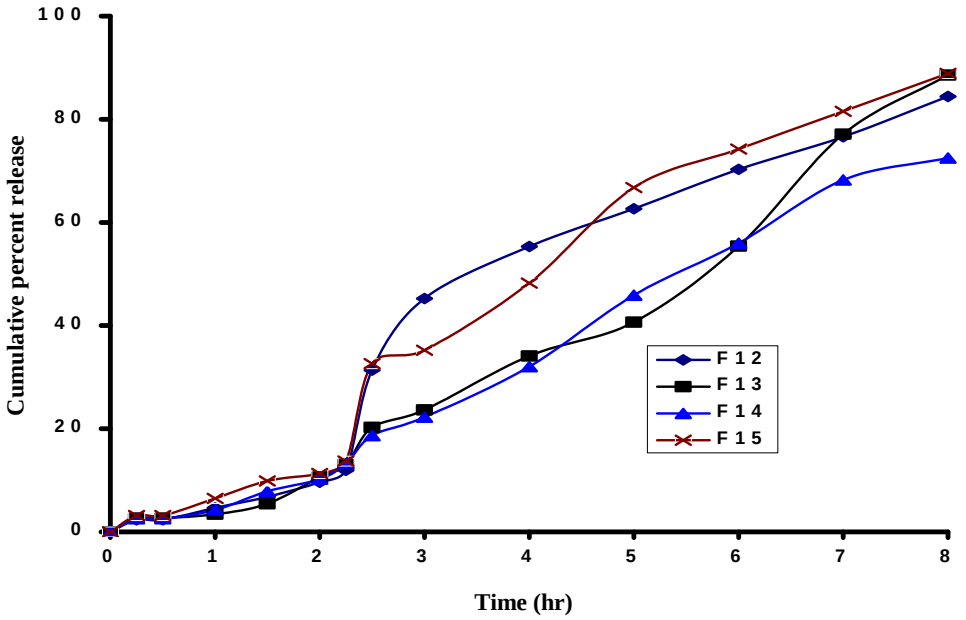


Fig. 6: *In-vitro* release of ketorolac tromethamine capsules containing drug : polymer ratio 1:3.

The investigated formulae containing ketorolac tromethamine capsules (F1-F15) can be arranged, in ascending order, regarding the *in-vitro* release within four hours dissolution (Y2), as follows: F13 (40.66%), F9 (43.69%), F8 (44.63%), F14 (45.89%), F6 (48.33%), F7 (48.35%), F11 (52.58%), F5 (58.69%), F12 (62.65%), F15 (66.78%), F10 (72.14%), F4 (72.65%), F1 (74.34%), F3 (81.65%), F2 (88.35%), respectively.

The investigated formulae containing ketorolac tromethamine (F1-F15) be arranged, in ascending order, regarding the *in-vitro* release within eight hours dissolution (Y3), as follows: F14 (82.31%), F6 (82.90%), F11 (84.69%), F12 (89.05%), F15 (90.18%), F8 (91.78%), F4 (92.36%), F7 (96.25%), F9 (96.45%), F13 (97.90%)a, F3 (98.15%), F2 (100%), F1 (100%) and F10 (100%), respectively.

The investigated formula containing ketorolac tromethamine can be arranged in descending order concerning production yield, drug content, mean particle size and the *in-vitro* release as follows: F13, F5, F1, F2, F8, F6, F7, F12, F9, F14, F10, F3, F15, F11 and F4 the results represented in table 5.

Kinetics of the *in-vitro* release of ketorolac tromethamine capsules

The kinetic treatment was done by plotting the time in hours versus the cumulative percent release of ketorolac tromethamine for zero-order; by plotting the time versus log percent of ketorolac tromethamine retained for first-order; by plotting the time versus the reciprocal of the percent of ketorolac tromethamine retained for second-order; by plotting the time versus cup root of KT, release for Hixson-Crowell cup root low and by plotting time versus percent of KT release according to Baker-Lansdale equation. The kinetic treatment for Higuchi diffusion model was calculated by plotting the square root of time in hours versus the cumulative percent of ketorolac tromethamine release.

In calculating the kinetic parameters for each order or system, the intercept, the slope, the correlation coefficient (r), the specific rate constant and the half-life were obtained in table 6. Table 7 represents the calculated correlation coefficients for each order or system employed.

It can be observed that the order of release for formulae: F1, F2, F5, F6, F7, F8, F9, F11, F13 and F14 were found to follow zero order with $t_{1/2}$ 3.360, 2.285, 3.576, 3.537, 4.189, 4.362, 4.145, 4.569, 3.789 and 4.489 respectively. While formulae F12 and F15 were found to obeyed first order kinetic with $t_{1/2}$ 2.377 and 2.121. While formulae F3, F4 and F10 were found to be based on Hixon-Crowell Cup root law with $t_{1/2}$ 2.046, 2.271 and 2.071, respectively.

Table 5: Rank order of ketorolac tromethamine-CAB microspheres concerning production yield, drug content, mean particle size and the *in-vitro* release from capsules.

Formula No.	Production yield	Drug content	Mean particle size	*In-vitro* release	Rank order	
					Total	C.R.O
F1	3	2	1	12	18	11
F2	4	4	5	11	24	10
F3	11	10	7	14	42	4
F4	14	12	12	10	48	1
F5	2	3	4	9	18	11
F6	10	9	3	2	24	10
F7	8	6	9	6	29	9
F8	5	5	10	4	24	10
F9	7	7	11	7	32	7
F10	6	8	13	13	40	5
F11	15	15	14	3	47	2
F12	12	14	2	2	30	8
F13	1	1	6	5	13	12
F14	13	13	8	1	35	6
F15	9	11	15	8	43	3

Table 6: Kinetic parameters for the *in-vitro* release of ketorolac tromethamine - CAB capsules according to the suitable order or system.

Formula No.	I	S	R	K	$T_{1/2}$	Order
F1	5.891	14.87	0.964	14.87	3.360	Zero
F2	8.907	21.87	0.959	21.87	2.285	Zero
F3	0.250	0.467	0.984	0.467	2.046	HC
F4	0.340	0.420	0.982	0.420	2.271	HC
F5	4.199	13.98	0.988	13.98	3.576	Zero
F6	5.618	14.13	0.980	14.13	3.537	Zero
F7	3.739	11.93	0.991	11.93	4.189	Zero
F8	3.413	11.64	0.994	11.46	4.362	Zero
F9	4.431	12.05	0.993	12.05	4.145	Zero
F10	0.279	0.461	0.980	0.461	2.071	HC
F11	1.996	10.94	0.982	10.94	4.569	Zero
F12	2.088	0.126	0.987	0.291	2.377	First
F13	7.269	13.19	0.992	13.19	3.789	Zero
F14	3.288	11.13	0.992	11.13	4.489	Zero
F15	2.114	0.141	0.998	0.326	2.121	First

I = Intercept S = Slope R= Correlation Coefficient

K= specific rate constant (hr^{-1})

Table 7: The calculated correlation coefficient for the *in-vitro* release of ketorolac tromethamine capsules.

Formula No.	Zero	First	Second	Diffusion	H-C	B-L
F1	0.964	0.957	0.877	0.935	0.963	0.939
F2	0.959	0.948	0.894	0.932	0.957	0.923
F3	0.944	0.981	0.796	0.958	0.984	0.979
F4	0.972	0.975	0.882	0.953	0.982	0.959
F5	0.988	0.923	0.669	0.972	0.976	0.936
F6	0.980	0.944	0.848	0.940	0.964	0.892
F7	0.991	0.879	0.651	0.968	0.945	0.859
F8	0.994	0.928	0.756	0.964	0.965	0.891
F9	0.993	0.888	0.671	0.953	0.946	0.872
F10	0.972	0.973	0.907	0.952	0.980	0.953
F11	0.982	0.968	0.868	0.970	0.981	0.934
F12	0.954	0.987	0.936	0.962	0.983	0.981
F13	0.992	0.901	0.668	0.956	0.956	0.987
F14	0.992	0.982	0.926	0.968	0.990	0.953
F15	0.968	0.988	0.940	0.967	0.987	0.976

Conclusion

Ketorolac tromethamine was successfully encapsulated into cellulose acetate butyrate using emulsion solvent evaporation method. A Box-Behnken design was selected for formulating ketorolac tromethamine microspheres with revolution per minute (X1), drug-polymer ratio (X2) and span 80 percent (X3) as independent variables. Three levels of the independent variables were used which equal to -1, 0 and +1 for the above design. The values of the corresponding variable are 500, 700 and 900 rpm for the machine speed; 1:1, 1:2 and 1:3 for drug-polymer ratio and 1%, 1.5% and 2% (w/w) for span 80 percent. All the prepared ketorolac tromethamine cellulose acetate butyrate microspheres were spherical in shape with smooth surface except formulae F12 and F13 which were semispherical with irregular surface. The investigated formulae containing ketorolac tromethamine can be arranged in descending order concerning production yield, drug content, mean particle size and the *in-vitro* release as follows: F13, F5, F1, F2, F8, F6, F7, F12, F9, F14, F10, F3, F15, F11 and F4. The order of release for ketorolac tromethamine- CAB were found to follow different kinetic orders or systems and no one kinetic order can explain the release of ketorolac tromethamine-CAB capsules.

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