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Emulsion solvent evaporation method for preparing Eudragit RS100 microparticles loaded ketorolac tromethamine

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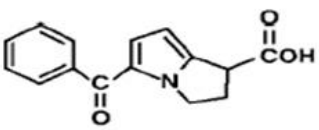
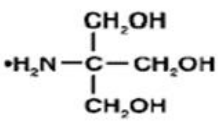
ABSTRACT

The purpose of this study was to prepare and characterize controlled release ketorolac tromethamine microparticles. To achieve this goal, Eudragit RS100 microparticles loaded by ketorolac tromethamine were prepared by the emulsion solvent evaporation method.
The prepared ketorolac tromethamine microparticles were evaluated for their production yields, particle size distribution, morphology, drug content and drug release characteristics. Thermal Gravimetric Analysis (TGA) was performed on the drug polymer systems in order to shed a light on the possibility of solid state changes of ketorolac tromethamine with Eudragit RS100. Via the emulsion solvent evaporation technique applying Box-Behnken design to choose these formulae. Box-Behnken design determined fifteen formulae containing specified amounts of the independent variables, which included revolution per minute (X1), drug: polymer ratio (X2) and span 80 percent (X3), the dependent variables studied were cumulative percent release after two hours (Y1), four hours (Y2) and eight hours (Y3).The prepared micro particles were characterized for their production yield, sizes, shapes and morphology, entrapment efficiency and ketorolac tromethamine in vitro release as well. The results showed that the production yield of the prepared ketorolac tromethamine microparticles was found to be between 77.80% and 93.66%. The formulated microparticles exhibited acceptable drug content values that lie in the range 53.24%-8018%. Also, the data obtained revealed that increasing the mixing speed (X1) generally resulted in decreased microparticles size. Kinetic treatment of the in vitro release from drug-loaded microparticles indicated that there is no one kinetic order can explain the release of KT-Eudragit RS100 capsules.

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 hours 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 [3,4] and parentral controlled release drug delivery system [5]**.** 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. Eudragit resins are synthetic cationic and anionic polymers of methacrylic acid and methacrylic acid esters in varying ratios [6].

Eudragit RS100 is copolymer of low content of quaternary ammonium group, because of its low permeability the drug release through the film was relatively retarded, and hence it was used as encapsulating materials [7]. The molar ratios of quaternary ammonium groups to polymer chain are 1:20 for Eudragit RL100 and 1:40, for RS100. Eudragit RS100 is water insoluble and pH independent polymer [6]. Box-Behnken design was used for formulating ketorolac tromethamine Eudragit RS100 microparticles [8]**.** It deals with, optimization of formulation variables to improve the *in vitro* release of ketorolac tromethamine dosage forms. Microparticles were prepared by emulsion solvent evaporation technique [9,10,11,12].The main purpose of present research was to develop a controlled drug delivery system of ketorolac tromethamine for oral administration using Eudragit RS100 as a polymer via emulsion solvent evaporation technique applying Box-Behnken design to choose these formulae.

MATERIALS AND METHOD

2.1. Design of the experiment

A Box-Behnken design was selected for formulating ketorolac tromethamine microparticles 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 Eudragit RS100 microparticles by emulsion solvent evaporation (w/o) technique.

Ketorolac tromethamine was dispersed in the polymeric solution of Eudragit RS100 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 hours.

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.

Production yield determination

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

Particle size determination

The dried microparticles were weighed and sized using USP standard sieve set. The fraction of microparticles remaining on each sieve was collected, and the mean particle size of the microparticles was assigned as the percentage of microparticles 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 [13].

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 minutes each hour for 5 hours. 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-microscopic determination of Ketorolac tromethamine microparticles

It has the advantage of providing a direct visual representation of the particles being measured. Photomicroscope can provide details about shape, crystal habit, and homogeneity of the tested sample.

According to the microscopic method, diluted suspension of ketorolac tromethamine in liquid paraffin was mounted on a slide. Then a photograph for each microparticle was taken from the prepared slide at magnification powers 40 and 100x.

Microparticles morphology by scanning electron microscopy:

The morphology of the microspheres surfaces was investigated using scanning electron microscopy. Microspheres were spread on a carbon double-adhesive layer on a metal holder, and gold-coated using Ion-Sputtering device (Jeol Fine-Coat JFC 1100E, Jeol LTD, Tokyo, Japan). The microspheres were scanned by Scanning Electron Microscope (SEM) (Jeol JSM-5400 LV, Jeol LTD, Tokyo, Japan).

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.

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.[14,15,16]

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 [14,17] was used. First, 200 ml of 0.1 N HCl pH 1.2, was used as the release medium for two hours, followed by addition of (5.7) ml of 7 M potassium dihydrogen orthophosphate

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 specific intervals throughout the whole 8 hours, namely 0.25, 0.5, 1, 1.5, 2, 2.25, 2.5, 3, 4, 5, 6, 7 and 8 hours. The samples were diluted appropriately with the release medium, and absorbance was measured at the predetermined $_{max.}$ of each medium against a blank of this medium. The withdrawn samples were replaced with equal volumes of the release medium.

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 kinetics, as well as controlled diffusion model [18], Hixson-Crowell cup root law [19] and Baker-Lonsdale equation [20] were investigated.

RESULTS AND DISCUSSION

Experimental Design

Box-Behnken design, as shown in table (1), was used for formulating Ketorolac Trometamine (KT) microparticles [7] deals with optimization of formulation variables to improve the in-vitro release of dosage forms. The three independent variables are stirring speed (X1), drug: polymer ratio (X2) and span 80% (X3). According to Box-Behnken design, 15 formulae of KT microparticles were prepared.

Three levels of the speed were used 500, 700 and 900 rpm

Table 1: Composition of different suggested formulae of Ketorolac Tromethamine Microparticles using Eudragit Rs100 according to pharmaceutical point of view

Formula NO.	Drug (gm)	Eud. RS 100 (gm)	Magnesium Stearate (mg)	Liquid paraffin (ml)	Span 80 (ml)	Speed (rpm)
F1	1	1	125	150	2.25	500
F2	1	1	125	150	1.5	700
F3	1	1	125	150	3	700
F4	1	1	125	150	2.25	900
F5	1	2	125	150	1.5	500
F6	1	2	125	150	3	500
F7	1	2	125	150	2.25	700
F8	1	2	125	150	2.25	700
F9	1	2	125	150	2.25	700
F10	1	2	125	150	1.5	900
F11	1	2	125	150	3	900
F12	1	3	125	150	2.25	500
F13	1	3	125	150	1.5	700
F14	1	3	125	150	3	700
F15	1	3	125	150	2.25	900

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 and percentage recovery (drug content) of Ketorolac Tromethamine - Eudragit RS100 Microparticles.

Formula No.	Drug-polymer ratio	Production Yield %	Theoretical Drug content (gm)	Actual drug content (gm)	Drug content %
F1	1:1	9 ±2.65	50.00	36.22±1.65	72.44±3.33
F2	1:1	9 ±4.55	50.00	40.09±3.55	80.18±4.35
F3	1:1	7 ±3.45	50.00	27.11±3.77	54.22±6.05
F4	1:1	8 ±2.21	50.00	32.01±3.85	64.02±5.55
F5	1:2	9 ±3.33	33.33	26.62±4.22	79.86±3.42
F6	1:2	8 ±2.77	33.33	18.90±2.37	56.71±3.77
F7	1:2	8 ±3.88	33.33	2 ±3.47	6 ±4.82
F8	1:2	8 ±4.35	33.33	2 ±1.75	6 ±2.73
F9	1:2	8 ±4.25	33.33	21.45±2.95	6 ±3.95
F10	1:2	8 ±3.75	33.33	18.01±4.45	54.03±3.89
F11	1:2	8 ±4.55	33.33	19.62±1.27	58.86±4.29
F12	1:3	9 ±3.35	25	17.32±1.95	69.28±3.74
F13	1:3	9 ±1.62	25	15.66±2.95	62.64±2.79
F14	1:3	8 ±1.75	25	13.31±3.67	53.24±3.88
F15	1:3	8 ±3.63	25	14.68±4.25	58.72±4.22

Table 3: Observed values of responses for Box-Behnken design of Ketorolac Tromethamine - Eudragit RS100 capsules.

Formula No.	Variable level in coded form			Cumulative percent release		
	X1	X2	X3	Y1 (2hrs)	Y2(4hrs)	Y3 (8hrs)
F1	-1	-1	0	14.46	57.89	72.72
F2	0	-1	-1	18.42	85.03	91.08
F3	0	-1	+1	24.75	93.15	100
F4	+1	-1	0	21.47	84.8	89.2
F5	-1	0	-1	12.67	62.6	84.19
F6	-1	0	+1	9.43	44.12	79.54
F7	0	0	0	19.9	43.73	98.87
F8	0	0	0	13.5	45.73	93.15
F9	0	0	0	14.89	42.75	95.16
F10	+1	0	-1	18.17	72.14	100
F11	+1	0	+1	16.68	72.99	100
F12	-1	+1	0	7.01	41.23	65.34
F13	0	+1	-1	16.97	43.65	76.23
F14	0	+1	+1	18.59	28.37	73.05
F15	+1	+1	0	15.17	50.36	88.35

denoted the values -1, 0 and +1 in the above design, respectively. Drug: polymer ratio was varied to be (1:1), (1:2) and (1:3), also denoted the values -1, 0 and +1, respectively. Moreover, span 80% was chosen to be 1%, 1.5% and 2% denoted -1, 0 and +1 value, respectively. The dependent variables to be tested for the prepared KT microparticles were chosen to be the *in vitro* release of the drug capsules after 120 minutes (Y1), 240 minutes (Y2) and 480 minutes (Y3).

Production yield determination

The range of the production yield of the prepared Ketorolac Tromethamine was found to be between 77.80% and 93.66% as shown in table 2. The highest microparticles crop was obtained in case of formula 3 (93.66%) in which stirring speed was intermediate value (700 rpm) in combination with lower span concentration (1%). In addition, at the same stirring speed (700 rpm) but at the highest span concentration (2%), a lowest

Table 4: The calculated correlation coefficient values and Kinetic parameters for the in-vitro release of Ketorolac Tromethamine - Eudragit RS100 capsules according to the suitable order or system

Formula	Zero order	First order	Higuchi	Hexon-Crowel	B-L	($t_{1/2}$) Hr	Specific rate constant	Order
F1	0.981	0.960	0.940	0.971	0.901	3.147	15.88	Zero
F2	0.932	0.960	0.924	0.955	0.947	1.246	0.555	First
F3	0.942	0.937	0.915	0.946	0.916	1.225	0.780	H-C
F4	0.919	0.949	0.918	0.941	0.939	1.323	0.523	First
F5	0.984	0.967	0.947	0.977	0.931	3.131	15.96	Zero
F6	0.983	0.986	0.966	0.988	0.964	3.490	0.273	H-C
F7	0.982	0.934	0.958	0.971	0.941	3.613	13.83	Zero
F8	0.990	0.965	0.965	0.983	0.945	3.874	12.90	Zero
F9	0.974	0.962	0.951	0.970	0.943	3.561	14.03	Zero
F10	0.974	0.982	0.971	0.989	0.967	2.227	0.429	II-C
F11	0.959	0893	0.933	0.943	0.885	2.341	21.35	Zero
F12	0.979	0.961	0.923	0.969	0.906	4.152	12.03	Zero
F13	0.987	0.956	0.942	0.970	0.907	3.965	12.60	Zero
F14	0.983	0.948	0.934	0.963	0.899	6.248	8.002	Zero
F15	0.991	0.971	0.974	0.987	0.944	4.411	11.33	Zero

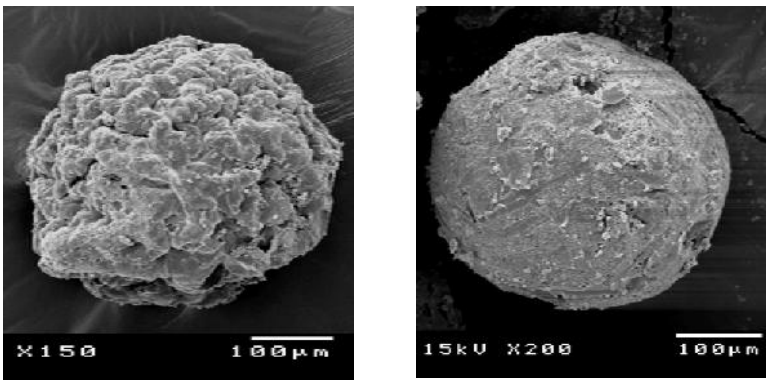


Figure 1: Scanning electron micrograph of Ketorolac Tromethamine Microparticles, F5, F7.

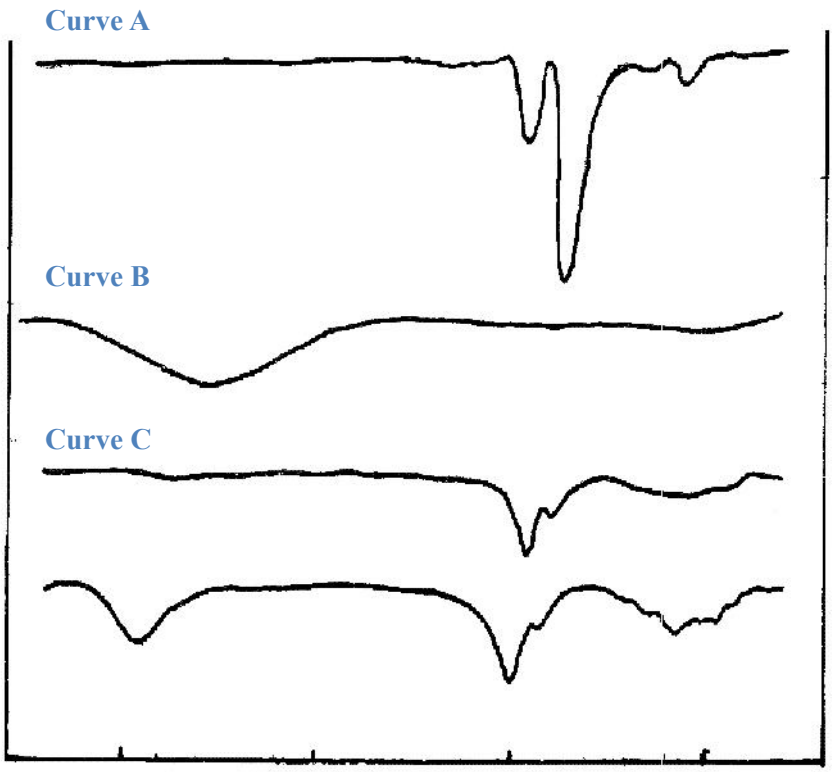
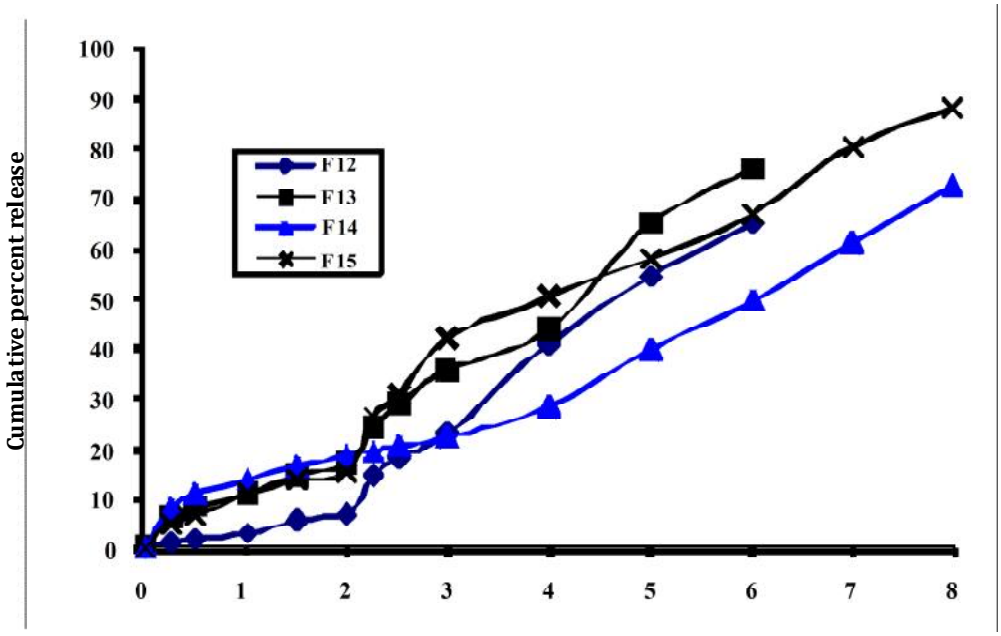


Figure 2: TGA thermograms of ketorolac tromethamine with Eudragit RS100 at scanning speed of 10 oC/min. : A, Drug alone; B, Eudragit RS100 ; C, Ketorolac Tromethamine - Eudragit physical mixture (1:1) and D, Ketorolac Tromethamine - Eudragit Microparticles (1:1).



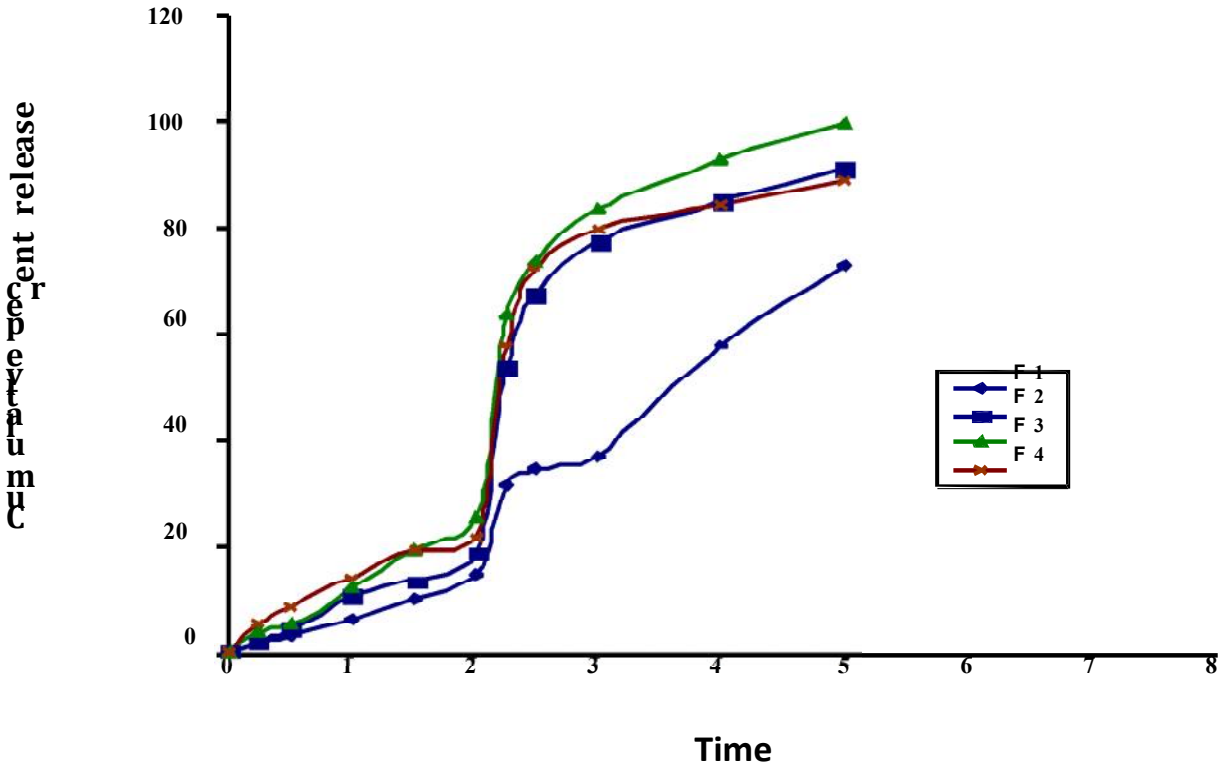


Figure 3: In vitro release of Ketorolac Tromethamine capsules containing drug : polymer ratio 1:1

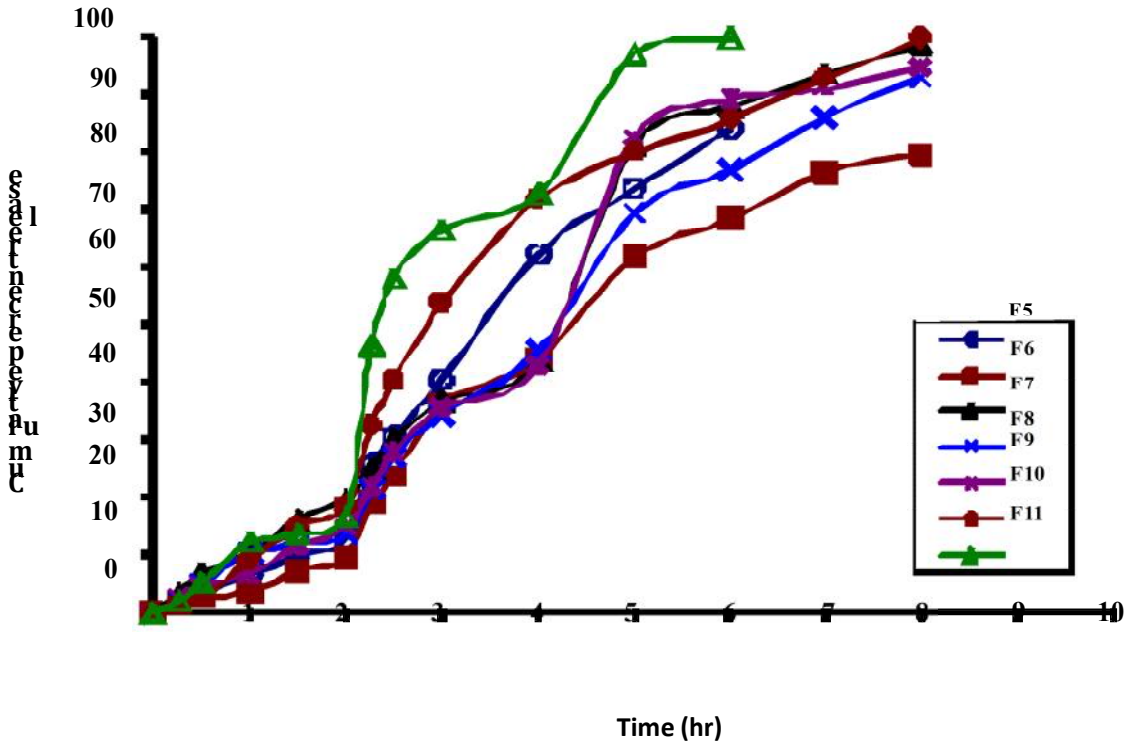


Figure 4: In vitro release of Ketorolac Tromethamine capsule containing drug: polymer ratio 1:2

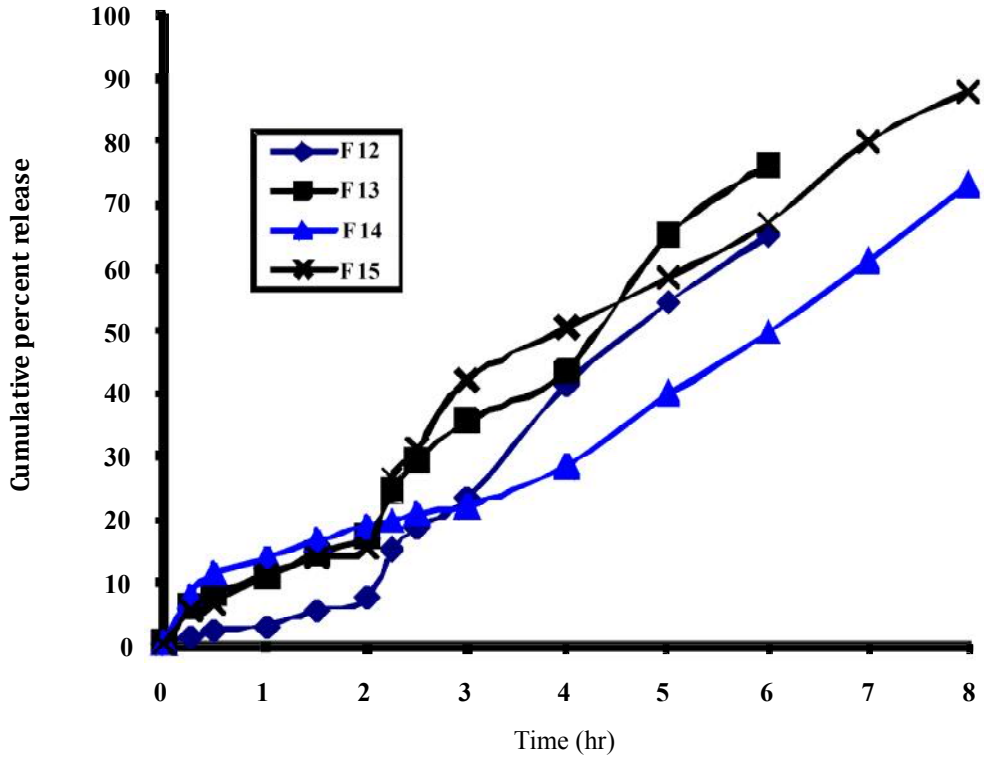


Figure 5: In vitro release of Ketorolac Tromethamine capsule containing drug: polymer ratio 1:3

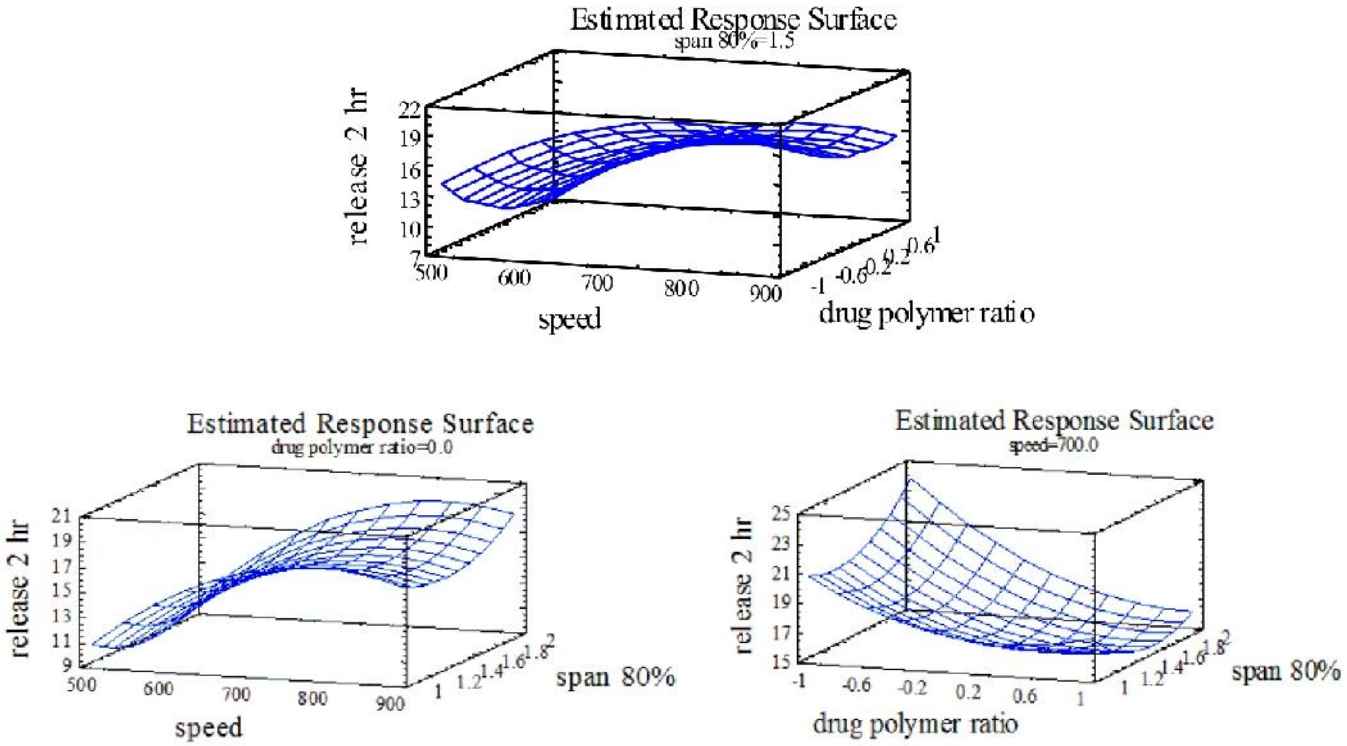


Figure 6: Three dimensional contour plots for the effect of speed (X1), drug-polymer ratio (X2) and Span 80 percent (X3)) on the cumulative percent release after two hours (Y1).

microparticles yield was obtained as the case of formula 3 (77.80%).

Drug content determination

The drug content determination measures the actual weight of KT itself inside the microparticles. The rank order of the drug content was measured by the deviation from the theoretical weight. Microparticles formulated by using intermediate or lower speed (700 and 500) in combination with lower or intermediate span concentrations were found to have higher ketorolac contents (for example, F2, F5, F1), table 2. On the other hand, the formulations prepared by using higher or intermediate stirring speeds and/or higher span concentrations have lower drug contents, as the case of F14 (53.024%).

Particle size distribution

The fraction percent of weight distribution of different formulae of ketorolac tromethamine Eudragit RS100 microparticles determined by sieve analysis. The range of sieve employed ranged from 890 m100 m.

The formulated ketorolac tromethamine microparticles were arranged according to the mean particle size, in a descending order, as the following: F5 (485.74±3.03), F1(474.84), F6(474.79), F12(450.19), F3(429.44), F7(420.78), F2(416.04), F8(411.31), F9(394.93), F13(368.16), F15(363.61), F14(354.99), F10(343.26), F11(335.96) and F4(335.08).

Speed is the maximum parameters for controlling the drug/matrix dispersion's droplet size in the continuous phase. It was shown that increasing the mixing speed generally results in decreased microparticle size, as it produces smaller emulsion droplets through stronger shear forces and increased turbulence [6,21,22,23].In this study high stirring speed (900 rpm) produced Eudragit RS100 microparticles with small particle size while low stirring speed (500 rpm) produced microparticles with large particle size.

Microparticles shapes and surfaces (SEM)

Scanning electron microscopy was used to characterize the shapes and the surfaces of the prepared ketorolac tromethamine microparticles. Figure 1 displays SEM images of the formulations F5 and F8 as representatives of all microparticles formulae. For comparison, F5 (1% span and 500 rpm stirring) microspheres showed wrinkled, but smooth, surfaces and no aggregation was observed. Upon increasing the span concentration and stirring speed, as the case of F8 (1.5% span and 700 rpm stirring), microspheres' surfaces become more smooth and slightly porous. In addition, the fraction percent of the fines (160-100 µm) was found to increase by increasing span concentration and stirring speed (F8). All other ketorolac tromethamine microparticles formulae were spherical in shape with smooth surface except formula F2 with irregular surface.

Thermal Gravimetric Analysis (TGA)

In order to shed a light on the possibility of solid state changes of Ketorolac Tromethamine with Eudragit RS100, TGA were performed on the drug polymer systems and their physical mixtures, as well as, individual components as shown in figure (2). The TGA scan of ketorolac tromethamine alone figure (4) curve (A), this curve 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/minute.

The TGA tracing of Eudragit RS100 showed broad shallow peaks at about 69.15 °C. The TGA thermogram of ketorolac tromethamine-Eudragit RS100 physical mixtures with drug to polymer ratio 1:1 exhibit the endothermic peaks of the drug at 154.74 and 161.86 °C with ΔH value 71.01 J/g. In the other hand these characteristic endothermic peaks appeared were shifted to a lower temperature (150.51 and 157.73 °C) in case of ketorolac tromethamine-Eudragit RS100 microparticles in drug to polymer ratio 1:1, this shift in the endothermic peak was accompanied with a reduction in ΔH value to 56.17 J/g figure (2) 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 []. 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 Eudragit Rs100.

In-vitro release of Ketorolac tromethamine microparticles

The *in vitro*-release of ketorolac tromethamine from Eudragit RS100 polymer was evaluated by measuring the cumulative percent release. The results showed that at pH 1.2, all the microcapsules retained intact nearly without swelling. This behavior depends on the nature of the used polymer.

Figure (3) showed the in-vitro release of ketorolac tromethamine from their capsules containing formulae from F1F4 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 24.75% and 14.46% 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 93.15% and 57.89%, respectively. After eight hours of dissolution (Y3) the maximum and minimum in-vitro release was found to be equal to 100% and 72.72%, respectively.

The *in-vitro* release of ketorolac tromethamine from its microparticles containing microparticle formulations F5F11 is illustrated in Figure 4. Different formulation variables were studied in these formulae including drug: polymer ratio (X2), span 80 concentration (X3), and variable stirring speed (X1). The maximum and minimum percent released were observed to be 19.9% and 9.43% released at the end of two hours (Y1), while 72.99% and 42.75% release values were recorded after four hours for F11 and F9, respectively. After eight hours of dissolution (Y3), 100% and 79.54% released for F11 and F6 respectively.

Moreover, Figure 5 illustrates the *in-vitro* release of ketorolac tromethamine from its-loaded microparticles formulae F12F15, using constant drug: polymer ratio (1:3) (X2) with varying both span 80 weight ratio (X3) and stirring speed (X1). At the first two hours, F12 formula was found to release the drug more slowly in comparison to the other formulae. This might be due to a fact that using lower stirring speed even in combination with a medium span 80 concentration resulted in relatively larger size microparticles, from which a slower release rate was observed. The *in vitro* release of the drug from these microparticle formulae in the alkaline pH, however, is quietly different. Slower release

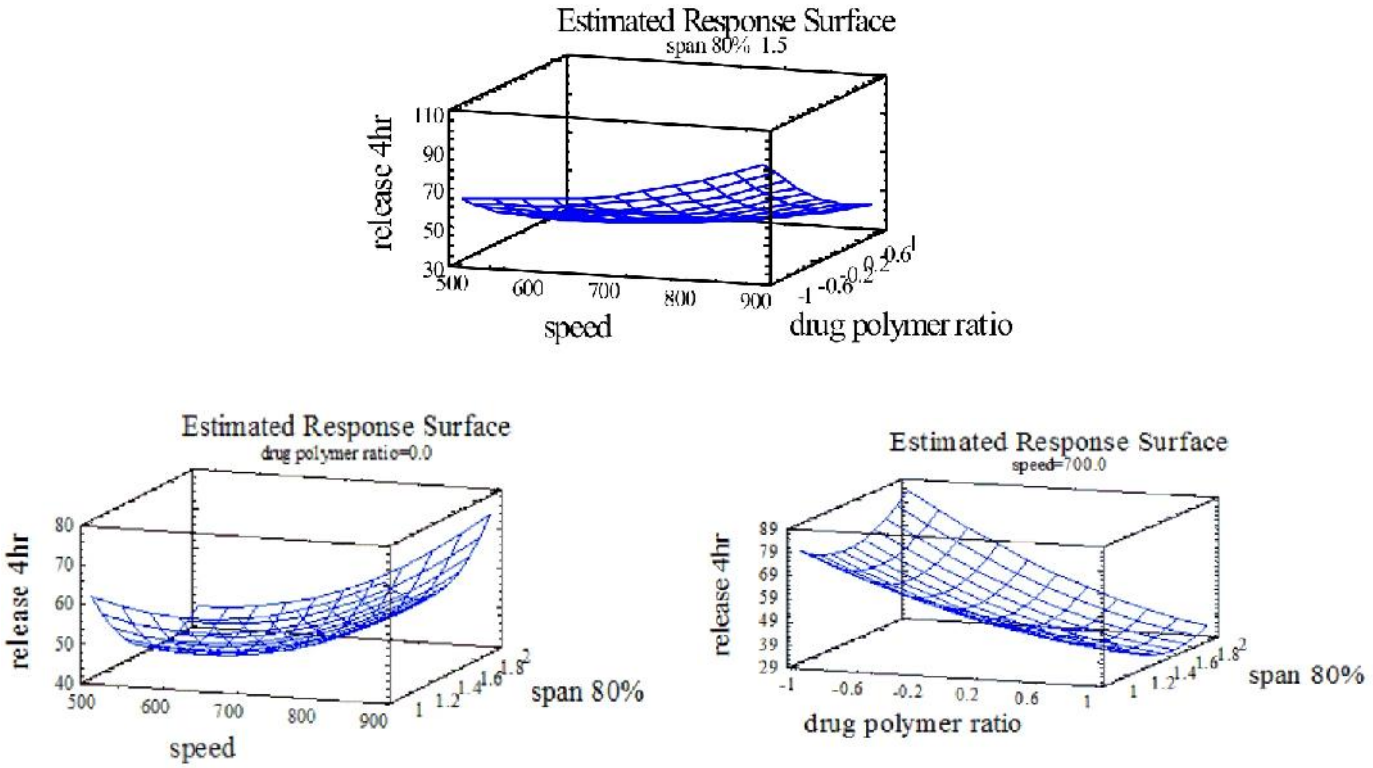


Figure 7: Three dimensional contour plots for the effect of speed (X1), drug-polymer ratio (X2) and Span 80 percent (X3)) on the cumulative percent release after two hours (Y1).

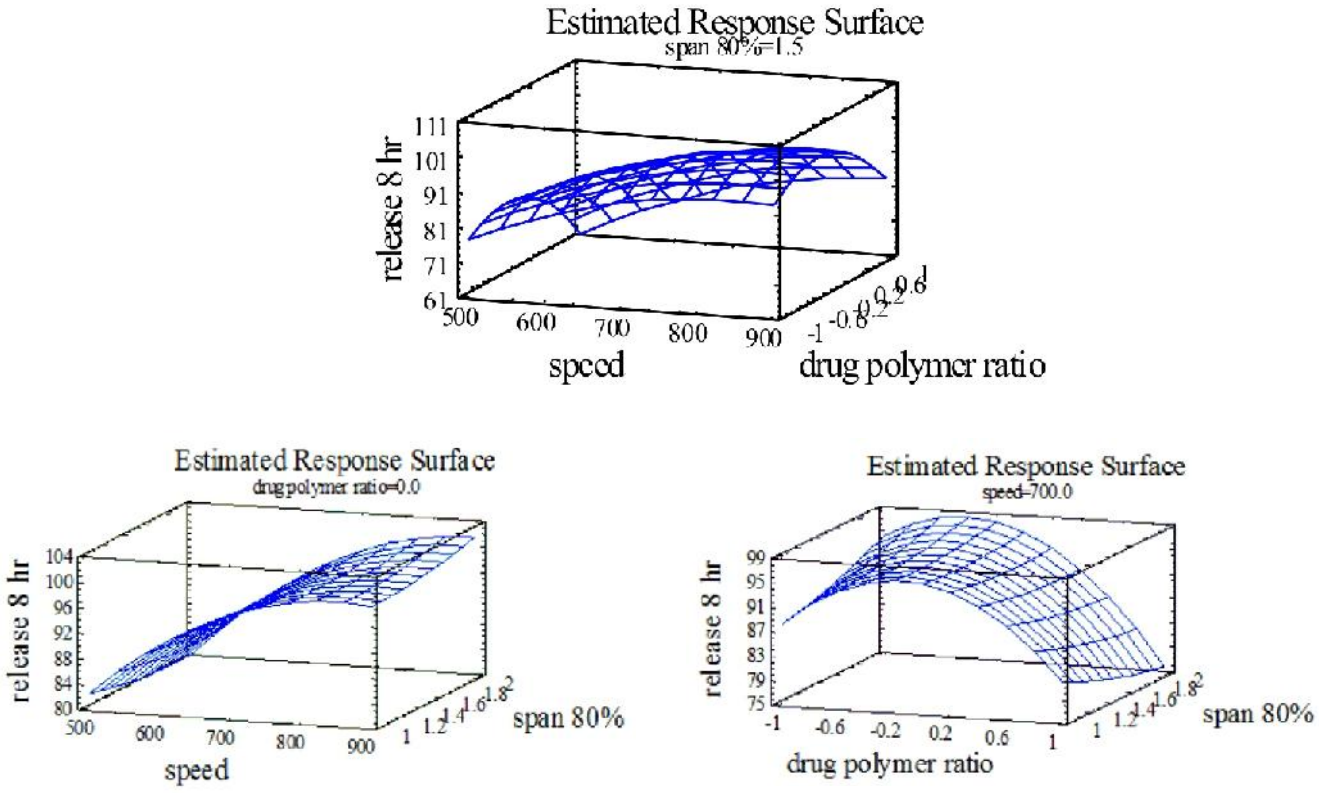


Figure 8: Three dimensional contour plots for the effect of speed (X1), drug-polymer ratio (X2) and Span 80 percent (X3)) on the cumulative percent release after eight hours.

was recorded in case of using slower stirring speed with medium span concentration (F12). In contrast higher stirring speed with medium span concentration resulted in faster *in vitro* release (F15).

From table 3 and Figures 6-8, it could be concluded that by increasing X2 and increasing X1, the drug release (Y3) decreased at fixed X3 levels. This indicates a negative correlation between Y3 and X2, in Figures 6-8.

At fixed X3 at high level (2%) when X1 at medium level (700 rpm) Y3 decreased from 100% to 73.05% when X2 increased from low level (1:1) to high level (1:3). However, the effect of increasing X1 level on the *in vitro* release rate is only pronounced at a combination of higher X2 and X3 levels indicating a positive correlation between Y3 and X1. For example, When X2 was fixed at low level (1:1) and X3 at medium level (1.5%) Y3 increased from 72.72% to 89.2% by increasing X1 from low level (500 rpm) to high level (900 rpm). At fixed X1 (900 rpm high level) when X2 at medium level (1:2) when X3 increased from low level (1%) to high level (2%), Y3 didn't change (constant). So we can conclude that, there is both negative and positive correlation between Y3 and X3.

The results obtained indicated that insignificant effect of span 80% (X3), significant effect of speed and drug- polymer ratio, so speed must be in low level (500 rpm) while drug- polymer ratio must be in high level (1:3).

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 released of Ketorolac Tromethamine for zero, first, Hixson-Crowell cup root low and Baker-Lonsdale 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. The calculated correlation coefficient values and Kinetic parameters for the in-vitro release of Ketorolac Tromethamine - Eudragit RS100 capsules according to the suitable order or system were obtained in table 4.

In can be observed that the order of release for formulae F2, F4 were found to follow first-order with t1/2 1.246 and 1.323 hours respectively, while formulae F1, F5, F7, F8, F9, F11, F12, F13, F14 and F15 were found to follow zero order with t1/2 3.147, 3.131, 3.613, 3.874, 3.561, 2.341, 4.152, 3.965, 6.248, and 4.411.

Formulae F3, F6 and F10 was observed to be based on HixonCrowell cup root law with t1/2 1.225, 3.490 and 2.227.

CONCLUSION

Ketorolac tromethamine was successfully encapsulated into Eudragit RS100 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 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.

The dependent variables to be tested for the prepared KT microparticles were chosen to be the *in vitro* release of the drug capsules after 120 minutes (Y1), 240 minutes (Y2) and 480 minutes (Y3). There is a negative correlation between the cumulative percent release (Y3) and drug-polymer ratio (X2); positive correlation between the cumulative percent release (Y3) and speed (X1) and there are both negative and positive correlation between the cumulative percent release (Y3) and span 80% (X3), indicated that insignificant effect of span 80% (X3). So speed must be in low level (500 rpm) while drug- polymer ratio must be in high level (1:3).

All the prepared ketorolac tromethamine microparticles were spherical in shape with smooth surface except formula F2 with irregular surface.The best formulae for the in-vitro release of KT-Eudragit RS100 capsules after whole dissolution period (8 hours) were observed to be F12, F6, F1, F5, F8 and F9.

The investigated formulae containing KT-Eudragit RS100 can be arranged in descending order concerning production yield, drug content, mean particle size of KT microparticles and the in-vitro release of capsules as follows: F5, F1, F12, F2, F8, F9, F13, F6, F7, F14, F15, F4, F3, and F11and F10.The order of release for KT-Eudragit RS100 was found to follow different kinetic orders or systems and no one kinetic order can explain the release of KT-Eudragit RS100 capsules. TGA thermograms revealed that no notable thermal interaction occurred between the drug and Eudragit Rs100.

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