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Design and Characterization of Gastroretentive Microspheres of Ketoprofen

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ABSTRACT

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the GIT is to control the gastric residence time (GRT) using gastroretentive dosage forms. The aim of the present study is to prepare the floating microspheres of ketoprofen to sustain the drug release for longer time to overcome the short half life of the drug. The microspheres were prepared by emulsification-solvent evaporation technique using ethyl cellulose and heat denaturation technique using egg albumin as a natural polymer. The optimization of microspheres was carried out based on pentagonal design using response surface methodology. The floating microspheres were evaluated for micromeritic properties, particle size, percentage yield, *in-vitro* buoyancy, entrapment efficiency, drug polymer compatibility, scanning electron microscopy and *in-vitro* drug release studies. The prepared microspheres exhibited prolonged drug release (> 9 h) and remained buoyant for > 24 h. The mean particle size increased and the drug release rate decreased at higher polymer concentration. The optimized formulation of ethyl cellulose microspheres (KEC-OP) exhibited prolonged drug release of 88.31 % up to 10 h demonstrating zero order kinetics and Case II transport release mechanism where as optimized formulation of egg albumin (KEA-OP) showed drug release of 96.78 % up to 9 h demonstrating peppas kinetics and Case II transport release mechanism.

Keywords: Ketoprofen, ethyl cellulose, egg albumin, floating microspheres, bioavailability, pentagonal design.

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INTRODUCTION

Oral sustained drug delivery system is complicated by limited gastric residence time. Rapid gastrointestinal transit can prevent complete drug release in absorption zone and reduce the efficacy of administered dose since the majority of drugs are absorbed in stomach or upper part of small intestine. So to develop oral drug delivery systems, it is necessary to optimize both the residence time of system within the gastrointestinal tract and release of drug from the system[1]. Dosage forms that can be retained in stomach are called gastroretentive drug delivery systems (GRDDS)[2]. Gastroretentive floating drug delivery systems has bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time [3].

The concept of floating microspheres can also be utilized to minimize the irritant effect of weakly acidic drugs on stomach by avoiding direct contact with the mucosa and providing a mean of getting low dosage for prolonged periods [4].

Floating system made of multiple unit forms has relative merits compared to a single unit preparation because the single unit floating systems are more popular but have a disadvantage owing to their "all-or-nothing" emptying process, leading to high variability of the gastrointestinal transit time[5]. Still the multiple unit dosage forms may be better suited because they are claimed to reduce the intersubject variability in absorption and lower the probability of dose dumping. A floating multiparticulate system is expected to produce a prolonged release of the drug without irritant particles lodging in the mucosa[6].

Ketoprofen is a well known non-steroidal anti-inflammatory agent, absorbed from upper portion of the intestine, requiring a high dose for efficacy in arthritis. Therefore, multiparticulate floating microspheres of ketoprofen ensuring sustained drug release into the proximal part of intestine with enhanced gastric residence time will be investigated.

MATERIALS AND METHODS

Materials

Ketoprofen was procured from Yarrow Chem Products, Mumbai. Ethyl cellulose and sodium CMC were obtained from Central Drug House (P) Ltd. Chloroform and liquid paraffin were purchased from Rankem RFCL Limited, New Delhi. Egg albumin and dichloromethane were obtained from Qualigens Fine Chemicals, Navi Mumbai. All the other chemicals used were of analytical grade.

Drug excipient interaction

The drug-polymer interactions were studied by Fourier Transform Infra-Red (FTIR) spectroscopy and Differential Scanning Calorimetry (DSC) techniques.

FTIR spectra of pure drug ketoprofen, polymers (ethyl cellulose and egg albumin), physical mixture of drug and polymers were obtained in KBr pellets at moderate scanning speed between 4000-400 cm^{-1} using a Shimadzu FTIR 1601 PC[7].

The DSC analysis of pure drug, polymer and the physical mixture of both drug and polymer were carried out to evaluate any possible interaction between drug and polymers using Mettler-7 DSC, Germany. Samples of about 5 mg were placed in 50 µl perforated aluminium pans and sealed. Heat runs for each sample were set from 5 to 300 °C, using nitrogen as purging gas. The apparatus was indium-cyclohexane calibrated.

Preparation of Microspheres Using Ethyl Cellulose

Microspheres were prepared by emulsification-solvent evaporation technique. Ketoprofen and ethyl cellulose were incorporated into a mixture of chloroform: dichloromethane (3:2 v/v, 10ml) at room temperature separately. The drug-polymer solution was poured slowly as a thin stream into 200 ml of water containing 0.7 % w/v sodium CMC that was thermally controlled at 40^0C. The emulsion was continuously stirred for 3 h to allow the volatile solvents to evaporate completely. The microspheres formed were collected by vacuum filtration using whatmann filter paper. The collected microspheres were washed several times with distilled water, then dried overnight at room temperature and subsequently stored in desiccators over fused calcium chloride. Various batches of microspheres were prepared based on the pentagonal design using drug polymer ratio and rate of stirring as independent variables by response surface methodology by using Design-Expert Software.

Preparation of Microspheres Using Egg Albumin

Albumin microspheres were prepared by heat denaturation method. Egg albumin was dissolved in distilled water and then the drug ketoprofen was added to the albumin solution and mix well. The drug-polymer solution was poured slowly as a thin stream into a beaker containing 100 ml of preheated (60 ºC) heavy liquid paraffin containing Tween 80 as emulsifying agent and stirred for 1 h. The temperature was reduced to 40 ºC for hardening process and was maintained for 25 min. The resulting microspheres were stabilized using gluteraldehyde solution (25 %v/v) for a period of 15 min. The microspheres were collected by decantation and washed with petroleum ether and dried at room temperature[8].

Optimization of the microsphere formulation

The optimizations of ethyl cellulose and egg albumin microspheres were carried out based on pentagonal design using response surface methodology. Drug-polymer ratio and agitation intensity were selected as independent variables and percentage drug entrapment efficiency and percentage drug release were fixed as dependent variables or responses. Design Expert Version 8.01 software was used for optimization studies. Formulation trials of ketoprofen-ethyl cellulose microspheres and ketoprofen-egg albumin microspheres as per pentagonal design using Response Surface Methodology were shown in Table 1 and Table 3 respectively. Table 2 and 4 shows the optimized formulae of ketoprofen-ethyl cellulose microspheres and ketoprofen-egg albumin microspheres respectively.

Table 1: Formulation trials of Ketoprofen-Ethyl cellulose microspheres as per pentagonal design using Response Surface Methodology

S.No	Formulation	Runs	Std	Factor 1A: RPM	Factor 2 B: DPR (mg)
1	KEC F1	1	5	1061.80	524.50
2	KEC F2	2	2	1061.80	1475.50
3	KEC F3	3	8	1000.00	1000.00
4	KEC F4	4	1	1200.00	1000.00
5	KEC F5	5	4	838.20	706.00
6	KEC F6	6	6	1000.00	1000.00
7	KEC F7	7	3	838.20	1294.00
8	KEC F8	8	7	1000.00	1000.00

Table 2: Optimized formulae and formulation code of Ketoprofen-Ethyl cellulose microspheres

Method	Drug (mg)	Amount of Polymer (mg)	Rate of stirring (rpm)	Formulation Code
Solvent evaporation	500	500	990.32	KEC-OP

Table 3: Formulation trials of Ketoprofen-Egg albumin microspheres as per pentagonal design using Response Surface Methodology

S.No	Formulation code	Std	Runs	Factor 1A: RPM (rpm)	Factor 2 B: DPR (mg)
1	KEA F1	1	1	1500.00	1000.00
2	KEA F2	2	2	1154.50	1190.20
3	KEA F3	7	3	1000.00	1000.00
4	KEA F4	8	4	1000.00	1000.00
5	KEA F5	5	5	1154.50	809.80
6	KEA F6	6	6	1000.00	1000.00
7	KEA F7	3	7	595.50	1117.60
8	KEA F8	4	8	595.50	882.40

Table 4: Optimized formulae and formulation code of Ketoprofen-Egg albumin microspheres

Method	Drug (mg)	Amount of Polymer (mg)	Rate of stirring (rpm)	Formulation Code
Solvent evaporation	500	1500	800.00	KEA-OP

Evaluation of Microspheres

Micromeritic studies: The prepared microspheres were evaluated for micromeritic properties such as percentage yield, bulk density, tapped density, bulkiness, carr's index, hausner's ratio and angle of repose[9].

Particle size and shape: The surface morphology and internal structure of the products were observed by Scanning electron microscopy (JEOL JSM-T scanning electron microscope, Japan) and particle size was determined using optical microscope (Olympus LITE image)[10].

Drug entrapment efficiency: Accurately weighed 50 mg of microspheres were taken in 50 ml volumetric flask and dissolved in 50 ml with methanol. The resulting solution was diluted suitably with methanol and filtered through Whatman filter paper. The absorbance of the solution was measured at 255 nm[11].

$$\% \text{ Drug entrapment efficiency } = \frac{\text{Amount of drug actually present}}{\text{Theoritical drug loaded expected}} \times 100$$

***In-vitro* buoyancy studies:** This study was carried out using 0.1N HCl as a dispersion medium containing tween 20 (0.02 w/v) to simulate gastric fluid. 100 mg microspheres were weighed and placed over the surface of 900 ml of 0.1N HCl at 37 ± 0.5 ^{0}C with continuous agitation at 100 rpm using Electrolab dissolution apparatus (8 basket) for 12 h. The microspheres which were floating after 12 h were collected separately and dried properly and weighed[12].

$$\% \text{ Buoyancy } = \frac{\text{weight of floating microspheres}}{\text{initial weight of microspheres}} \times 100$$

***In-vitro* drug release studies:** *In-vitro* drug release was studied in Electrolab dissolution apparatus (8 baskets) using 900 ml phosphate buffer pH 7.4 as dissolution medium, maintained at 37 ± 0.5 ^{0}C for 10 h at 100 rpm. 2 ml of sample was withdrawn and diluted to 25 ml with phosphate buffer pH 7.4. Samples were analyzed spectrophotometrically at 255 nm and the percentage drug release was calculated.

Drug release kinetics: Data obtained from *in-vitro* drug release studies were fitted to various kinetic models like zero-order, 1st order, Higuchi, Korsemeyer and Peppas using PCP Disso V3 to predict the drug release mechanism.

Residual solvent analysis: Residual solvents present in traces in the optimized formulations were determined as per ICH Harmonised Tripartite Guideline on Impurities: Guideline for Residual Solvents Q3C (R4). Since there is no therapeutic benefit from the residual solvents, all residual solvents should be removed to the extent possible to meet product specifications or other quality-based requirements. The presence of volatile solvents chloroform (Class 2) and dichloromethane (Class 2) in the optimized formulation of ketoprofen-ethyl cellulose microspheres was determined by Gas Chromatography, concentration limit was expressed in terms of ppm[13].

Stability studies: Stability studies of the optimized formulation were carried out for accelerated stability testing at 40 ^{0}C ±2 ^{0}C with 75% RH ± 5% for a period of 6 months. The selected optimized formulations were packed in high density polyethylene containers, which were tightly plugged with cotton and capped. They were then stored for 6 months and evaluated for their physical appearance, percentage drug entrapment and percentage drug release at specified intervals of time.

RESULTS AND DISCUSSION

Floating microspheres of ketoprofen using ethyl cellulose were prepared by emulsification solvent evaporation technique and ketoprofen-egg albumin microspheres were prepared by heat denaturation method. The micromeritic properties of all the formulations of ketoprofen-ethyl cellulose and ketoprofen-egg albumin microspheres were found to be in acceptable range. The drug-excipient interaction study was carried out by FTIR spectroscopy revealed that there was no interaction between the drug and the polymers (ethyl cellulose and egg albumin) as there was no significant shift in the principle peaks of ketoprofen (Figure 1). DSC thermogram of the drug and polymers were shown in Figure 2, it was clearly evident from the thermogram of the physical mixture of drug and polymers that the drug has not undergone any physical change being in its natural form as there is a sharp endothermic peak at 94.58^{0}C corresponding to melting point of the drug.

The mean particle size of the microspheres were significantly increased with increasing the polymer concentration and was in the range of 324.52 µm to 434.28 µm in case of ethyl cellulose microspheres and 186.31 µm to 411.24 µm in case of egg albumin microspheres. The viscosity of the medium increased at a higher polymer concentration resulting in enhanced interfacial tension and diminished shearing efficiency resulting in the formation of larger particles. The percentage drug entrapment efficiency of ethyl cellulose microspheres were found to be in the

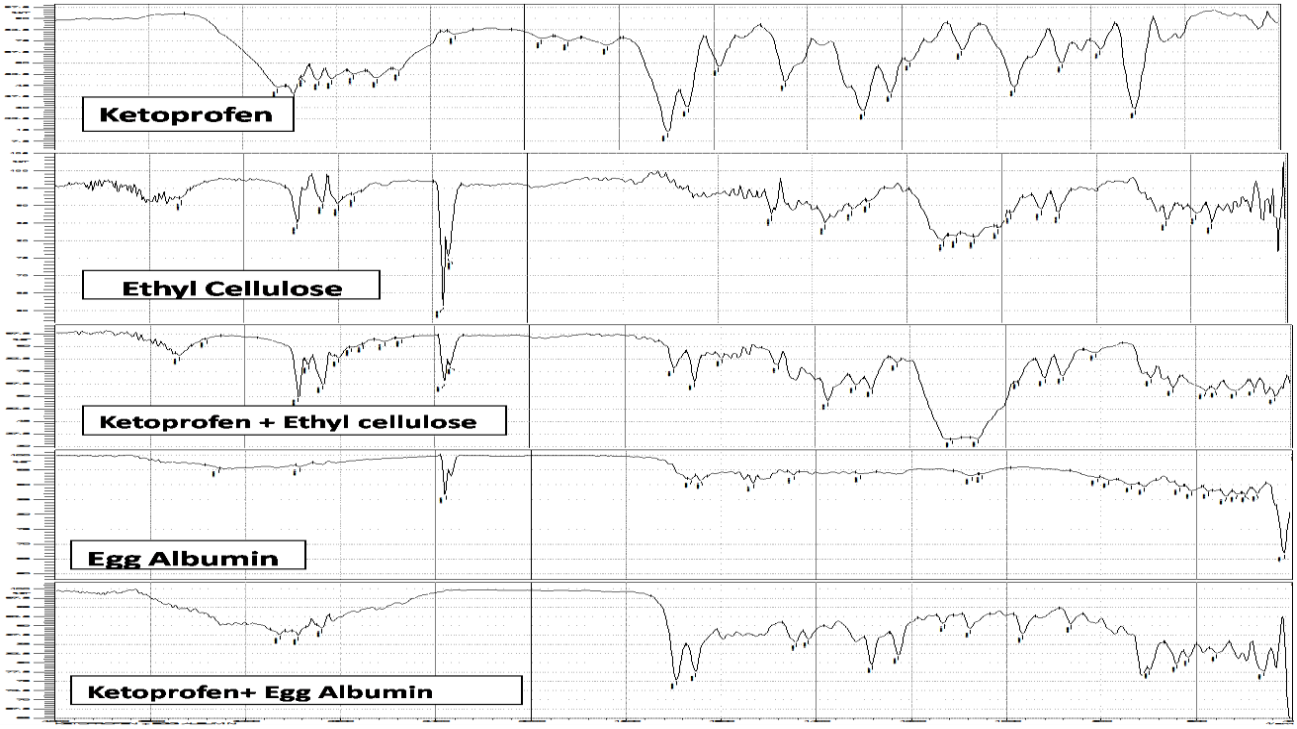


Figure 1: IR spectra of drug and polymer

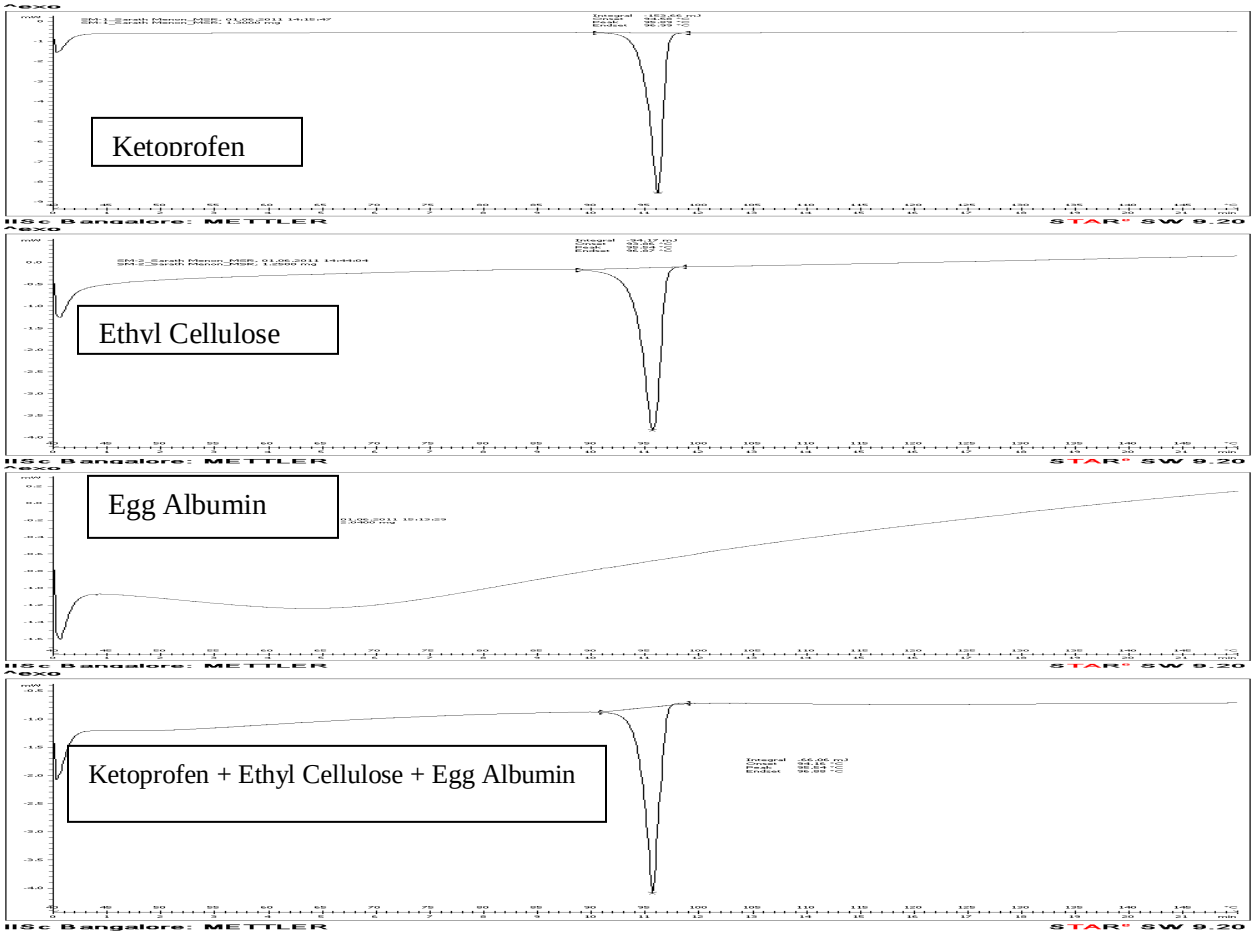


Figure 2: DSC thermogram of drug and polymers

range of 67.89 % to 76.60 % whereas egg albumin microspheres were in the range of 66.23 % to 76.80 %. The microspheres floated for prolonged time over the surface of dissolution medium without any apparent gelation. Percentage buoyancy of all the batches of microspheres was found to be above 80 %. The *in-vitro* dissolution studies of all the formulations of ethyl cellulose microspheres were in the range of 66.21 % to 81.35 % at the end of 10 h and egg albumin microspheres showed the drug release for 9 h, indicating as the polymer concentration increases the drug release decreases. The results of mean particle size, percentage drug entrapment, and percentage drug release and percentage buoyancy of all the trial formulations of ethyl cellulose and egg albumin microspheres were shown in Table 5 and 6 respectively. The comparative *in-vitro* dissolution profiles of different trial formulations of ethyl cellulose and egg albumin microspheres were shown in Figure 3 and 4 respectively. The three-dimensional response surface graph indicated that with the higher polymer concentration, maximum drug release and drug entrapment could be achieved. It was observed that an increase in the ratio of drug to polymer concentration resulted in an increase in the entrapment efficiency and percentage drug release (Figure 5 and 6). from the optimized trial formulations the software generated optimized formula was found to be 500 mg of drug and 500 mg of polymer at 1000 rpm for ethyl cellulose microspheres and 500 mg of drug and 1500 mg of polymer at 800 rpm for egg albumin microspheres.

Table 5: Results of the optimized trial formulations of ketoprofen-ethyl cellulose microspheres

S.No	Formulation Code	Mean particle size* (µm)	% Drug Entrapment Efficiency	%Drug Release at 10 h	% Buoyancy after 12h	Floating time (h)
1	KEC F1	324.52 ± 3.7	67.89	81.35	92.45	>24
2	KEC F2	434.28 ± 3.5	75.30	66.21	97.80	>24
3	KEC F3	362.30 ± 1.2	70.0	70.11	94.55	>24
4	KEC F4	326.54 ± 2.2	73.76	73.66	93.20	>24
5	KEC F5	394.68 ± 3.1	69.09	77.81	92.78	>24
6	KEC F6	374.69 ± 1.7	72.50	70.71	93.85	>24
7	KEC F7	412.54 ± 2.6	73.88	70.96	93.95	>24
8	KEC F8	356.74 ± 2.8	70.33	70.38	94.75	>24

*n=100 particles

Table 6: Results of the optimized trial formulations of ketoprofen-egg albumin microspheres

S.No	Formulation Code	Mean particle size* (µm)	% Drug Entrapment Efficiency	% Drug Release at 9 h	% Buoyancy after 12 h	Floating time (h)
1	KEA F1	382.11 ± 3.8	75.54	93.60	86.80	>24
2	KEA F2	305.46 ± 3.3	73.34	92.66	87.50	>24
3	KEA F3	273.61 ± 1.9	70.54	93.63	85.15	>24
4	KEA F4	285.13 ± 2.0	70.40	93.01	84.90	>24
5	KEA F5	341.66 ± 1.7	71.00	97.25	83.65	>24
6	KEA F6	280.12 ± 1.3	70.48	92.75	85.30	>24
7	KEA F7	198.45 ± 3.6	68.48	92.39	87.10	>24
8	KEA F8	209.57 ± 2.4	66.23	95.73	82.12	>24

*n=100 particles

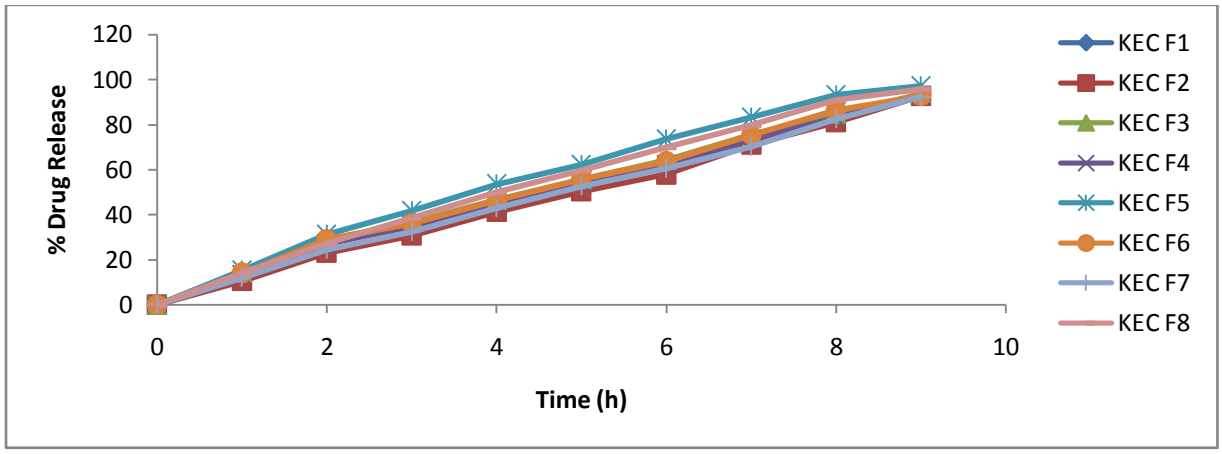


Figure 3: Comparative *in-vitro* drug release profiles of the optimized trial formulations of ketoprofen-ethyl cellulose microspheres

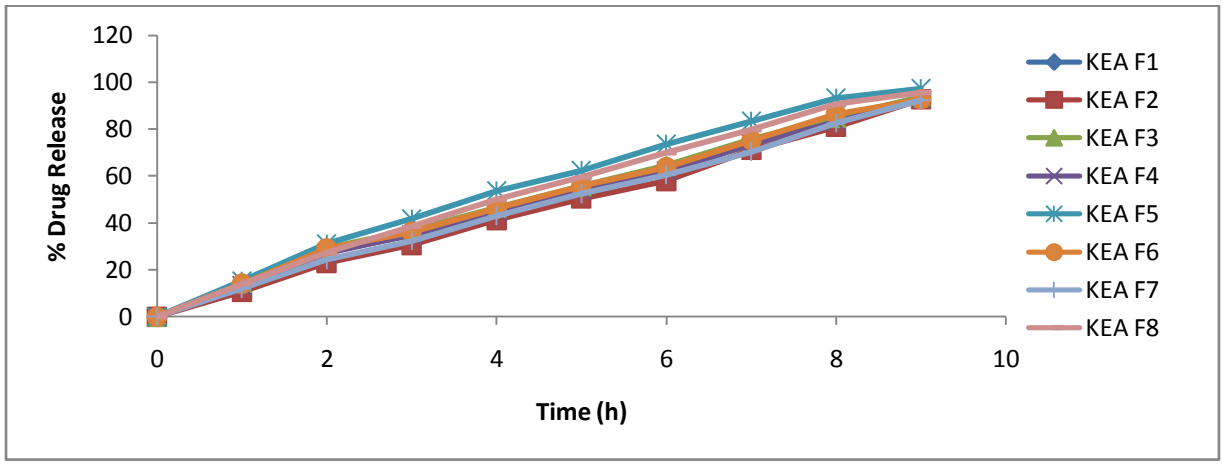


Figure 4: Comparative *in-vitro* drug release profiles of the optimized trial formulations of ketoprofen-egg albumin microspheres

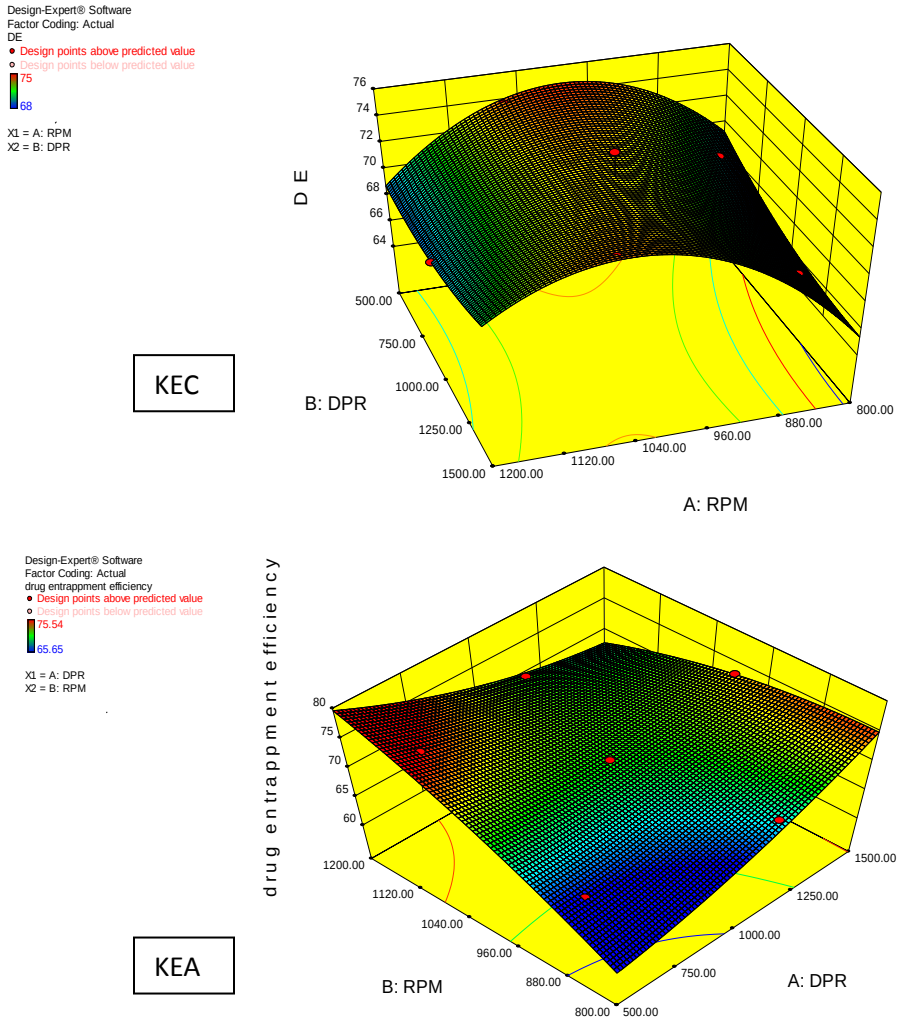
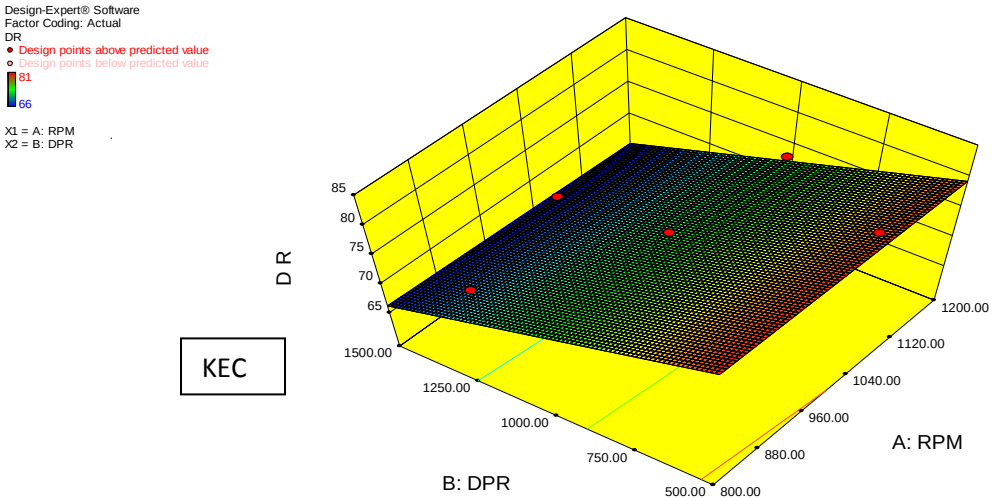


Figure 5: 3D RSM Graphs of KEC and KEA microspheres. Factor-Percentage Drug Entrapment



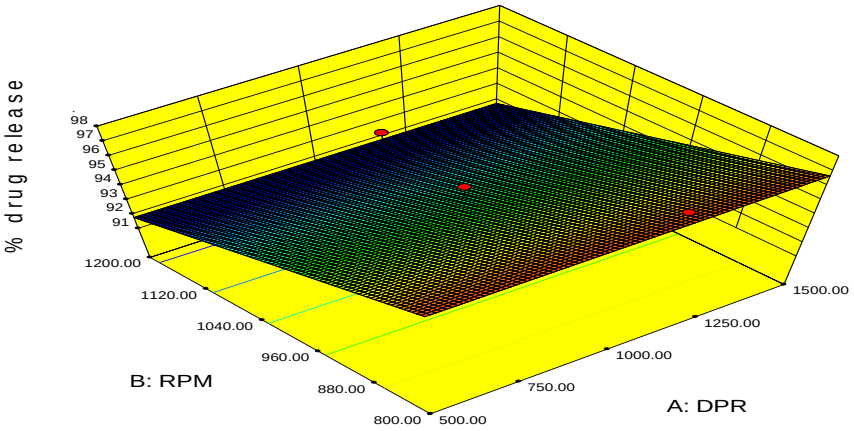
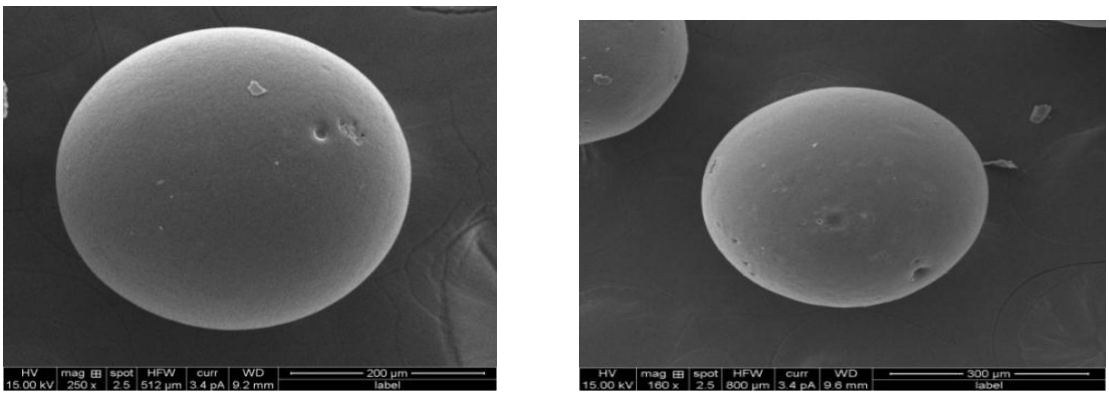


Figure 6:3D RSM Graph of KEC and KEA microspheres. Factor-Percentage Drug Release

The micromeritic properties of the optimized formulation of ethyl cellulose (KEC-OP) and egg albumin (KEA-OP) microspheres were also in the acceptable range. The SEM photographs of the optimized formulations showed that the microspheres were spherical in shape with pores on the surface (Figure 7). The floating behavior of the optimized formulation of both the polymers was shown in Figure 8. The results of optimized formulations of both the polymers were shown in Table 9 and 12, which confirmed the closeness of the predicted results with that of the observed results (Table 7 and 8). The *in-vitro* dissolution study of KEC-OP was extended up to 12 h and the rate of drug release was found to be 92.16 %. From the r^2 value (0.9900), *in-vitro* dissolution studies of the optimized formulation of ethyl cellulose (KEC-OP) demonstrated zero order kinetics and the mechanism of drug release was found to be Case II transport (Figure 9). From the r^2 value (0.9984) of KEA-OP, the *in-vitro* dissolution studies demonstrated peppas kinetics and Case II transport release mechanism (Figure 12).



KEC-OP **KEA-OP**

Figure 7: Scanning electron microphotographs of optimized formulations

KEC-OP **KEA-OP**

Figure 8: Floating behavior of coded optimized formulations

Table 7: Results of optimzed formulation of ketoprofen-ethyl cellulose microspheres (Predicted Vs Actual)

Observation	Amount of polymer (mg)	Rate of stirring (rpm)	Drug Entrapment Efficiency (%)	Drug Release at 10 h (%)
Predicted values	500	990.32	74.7069	80.0167
Practical values	500	1000	76.60	88.31

Table 8: Results of optimzed formulation of ketoprofen-egg albumin microspheres (Predicted Vs Actual)

Observation	Amount of polymer (mg)	Rate of stirring (rpm)	Drug Entrapment Efficiency (%)	Drug Release at 9 h (%)
Predicted values	1500	800.00	75.0684	96.7213
Practical values	1500	800.00	76.80	96.78

Table 9: Results of the coded optimized formulation of ketoprofen-ethyl cellulose microspheres (KEC-OP)

S.No	Parameters	Observed value
1	Percentage Yield (%)	66.24 ± 3.6
2	Bulk Density (g/cc)	0.1363 ± 0.004
3	Tapped Density (g/cc)	0.1631 ± 0.006
4	Bulkiness (cc/g)	7.3379 ± 0.23
5	Carr's Index (%)	14.446 ± 5.7
6	Hausner's Ratio	1.1725 ± 0.08
7	Angle of Repose	$24^{\circ}62^{'}$ ± 1.99
s8	Drug Entrapment (%)	76.6 ± 0.86
9	Buoyancy after 12 h (%)	92.16 ± 1.3
10	Drug Release after 10 h (%)	88.31 ± 3.5
11	Mean Particle Size (µm)	312.24 ± 3.1

All values are represented as mean ± standard deviation (n=3)

Table 12: Results of the coded optimized formulation of ketoprofen-egg albumin microspheres (KEA-OP)

S.No	Parameters	Observed value
1	% Yield	96.5 ± 3.8
2	Bulk Density (g/cc)	0.4866 ± 0.007
3	Tapped Density (g/cc)	0.5622 ± 0.009
4	Bulkiness (cc/g)	2.038 ± 0.029
5	Carr's Index (%)	12.7157 ± 0.19
6	Hausner's Ratio	1.1456 ± 0.002
7	Angle of Repose	$28^{\circ}17'$ ± 1.42
8	Drug Entrapment (%)	76.80 ± 0.93
9	Buoyancy after 12 h (%)	90.25 ± 1.6
10	Drug Release after 9 h (%)	96.78 ± 2.1
11	Mean Particle Size (µm)	411.24 ± 3.8

All values are represented as mean ± standard deviation (n=3)

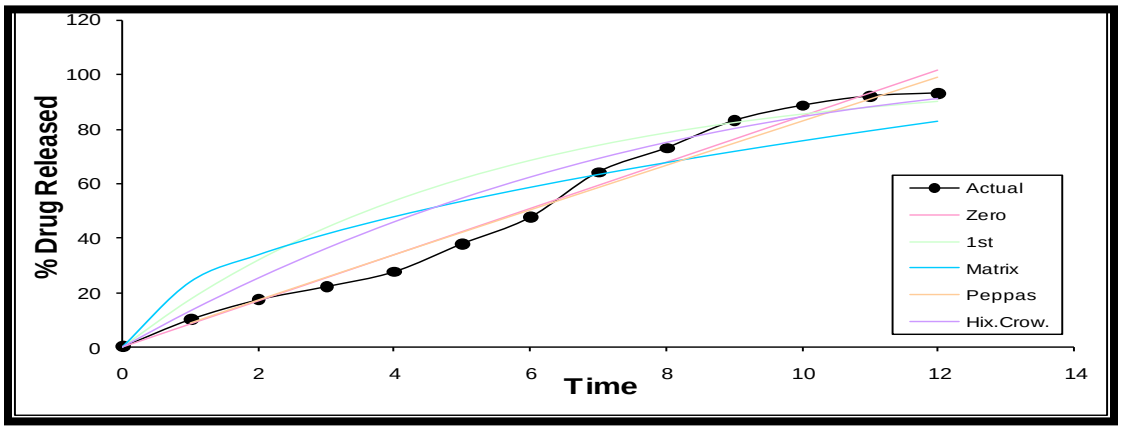


Figure 9: *In-vitro* release kinetics of optimized formulation (KEC-OP)

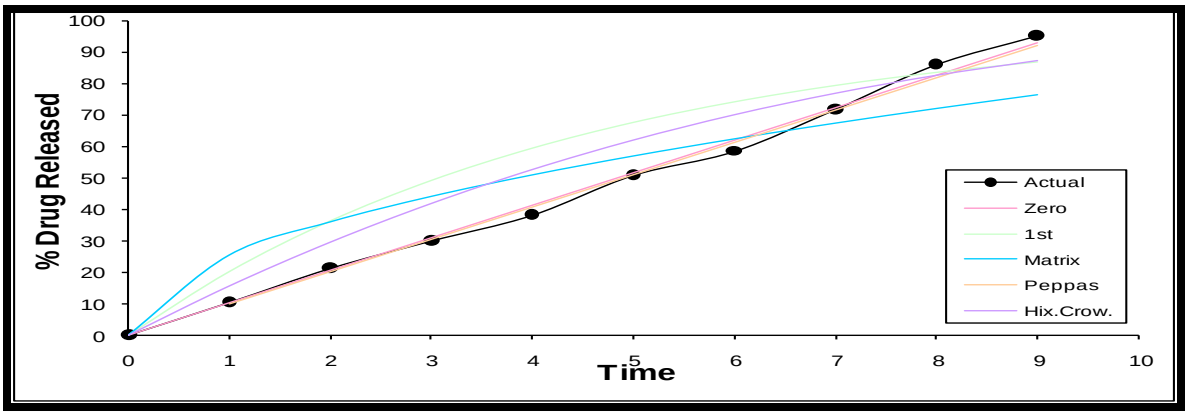


Figure 12: *In-vitro* release kinetics of optimized formulation (KEA-OP)

The amount of chloroform and dichloromethane in the KEC-OP formulation were found be within the limits as prescribed by the ICH guideline for impurities Q3C for the residual solvents. It can be inferred that the formulations were safe for oral administration (Table 10). The related chromatograms of the standard and KEC-OP were shown in Figure 10 and 11 respectively.

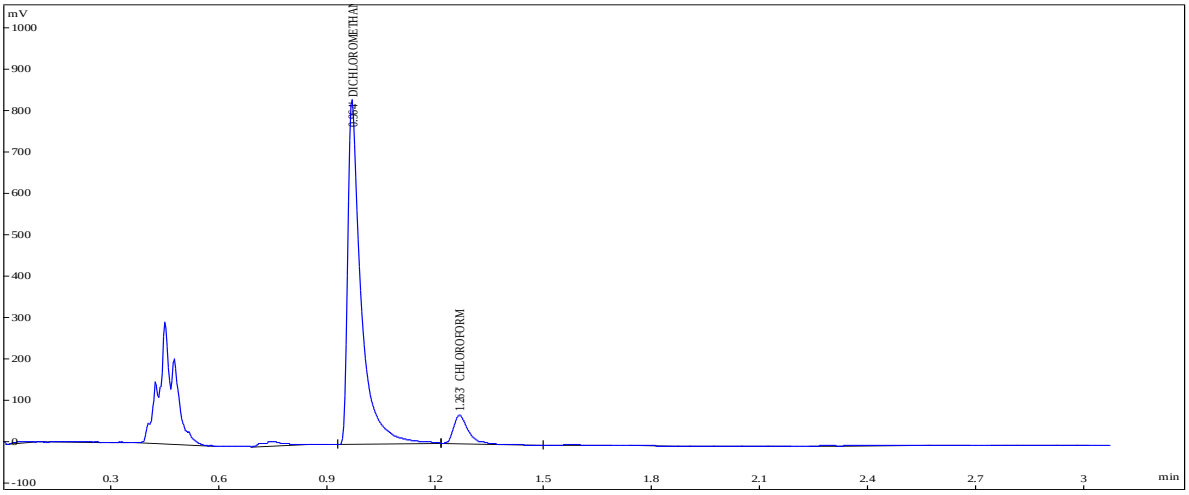


Figure 10: Gas chromatogram of standard (chloroform and dichloromethane)

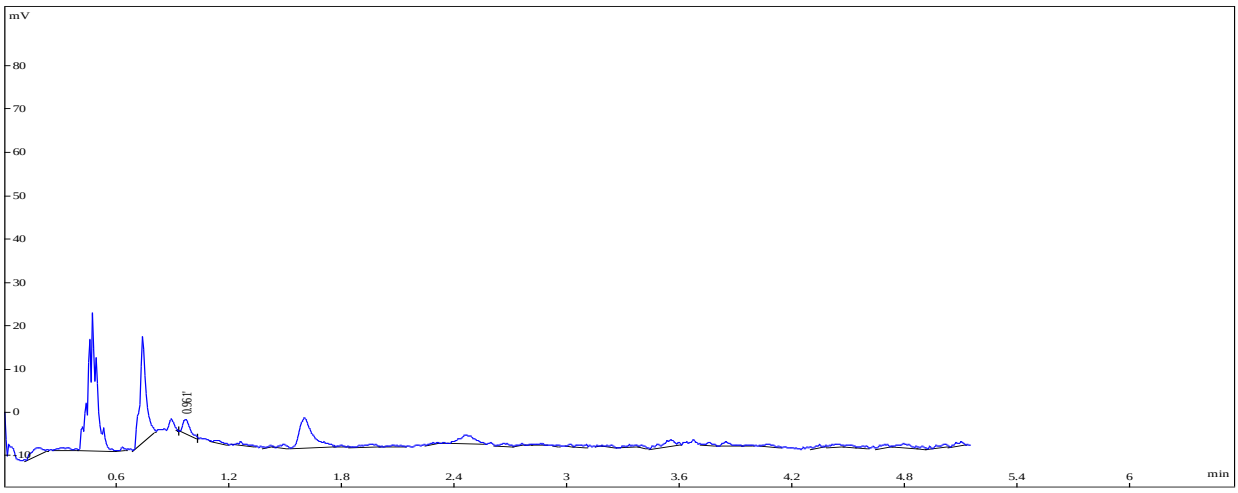


Figure 11: Gas chromatogram of KEC-OP (sample)

Table 10: Analytical residual solvent limits of KEC-OP

Sr.No	Test	Prescribed Limit (ppm)	Detected Limit (ppm)
1	Content of chloroform	60	Not detected
2	Content of dichloromethane	600	0.2 ppm/g

Stability studies of the coded optimized formulations of ketoprofen-ethyl cellulose microspheres and ketoprofen-egg albumin microspheres revealed maximum stability when stored at room temperature of 40 ± 2 ºC / 75 ± 5 % RH. The values of stability studies of ketoprofen-ethyl cellulose microspheres (KEC-OP) and ketoprofen-egg albumin microspheres (KEA-OP) were shown in Table 11 and 13 respectively. The results of percentage drug entrapment efficiency, percentage drug release and percentage buoyancy of both the optimized formulations were close to that of initial data with slight variations suggesting that it has an acceptable stability on storage.

Table 11: Stability studies for optimized formulation of KEC-OP

Characteristic parameters	Optimized formulation (KEC-OP) (40 ± 2 °C / 75 ± 5 % RH)			
	Initial day	2nd month	4th month	6th month
Physical appearance	++	++	++	++
Percentage Drug Entrapment (%)	76.6	78.25	77.50	78.10
In-vitro drug release at 10 h (%)	88.31	86.30	87.65	87.45
Percentage Buoyancy at 12 h (%)	92.16	91.56	93.26	92.35

Table 13: Stability studies for coded optimized formulation of KEA-OP

Characteristic parameters	Optimized formulation (KEC-OP) (40 ± 2 °C / 75 ± 5 % RH)			
	Initial day	2nd month	4th month	6th month
Physical appearance	++	++	++	++
Percentage Drug Entrapment (%)	76.80	78.56	77.80	76.55
In-vitro drug release at 10 h (%)	96.78	97.30	96.15	97.10
Percentage Buoyancy at 12 h (%)	90.25	91.56	88.28	91.35

CONCLUSION

Buoyant microspheres of ketoprofen using ethyl cellulose and egg albumin were prepared by emulsification solvent evaporation technique and heat denaturation technique respectively to improve the oral bioavailability with prolonged drug release for more than 9 h. The concentration of the polymer influenced the particle size, floating behavior and *in-vitro* drug release. The *in*-vitro drug release studies showed that the drug release was prolonged for more time up to 12 h in case of KEC formulations when compared to KEA formulations (9 h). Thus the prepared floating microspheres may prove to be potential candidate for multiple-unit delivery devices adaptable to any intragastric condition for sustained drug delivery.

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