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Research Article

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# Characterization of Ethylcellulose and Hydroxypropyl Methylcellulose Microspheres for Controlled Release of Flurbiprofen

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## Abstract

The objective of this study was to design and optimize polymeric microspheres of flurbiprofen (FLB) with ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC) using response surface methodology. EC and HPMC were taken as independent variables whereas; the dependent variables were % drug release at pH 1.2, 4.5 and 7.4. FTIR spectra and TGA showed no significant difference between drug and polymers. DSC and XRD studies exhibited molecular dispersion of FLB within microspheres. Contour plots were drawn to predict the relationship between dependent and independent variables. Both polymers revealed their significant effects on drug release that followed the zero order which was further verified by the lowest values of Akaike information criterion. The mechanism of drug release followed super case II type of drug release. This study helped unraveling the influence of two factors on *in-vitro* drug release and thereby, proposed an appropriate sustained drug release formulation.

## Keywords

Microspheres; Response surface methodology; Ethyl Cellulose (EC); Hydroxypropyl Methylcellulose (HPMC); Flurbiprofen; Central composite design

## Introduction

From last decades, a considerable attention has been taken to employ the improvement of solubility of poorly water soluble drugs and their efficient delivery into the body. Introduction of microspheres as a sustained release drug delivery has attained a new breakthrough as a novel drug delivery system in the field of pharmaceutical technology. This methodology excludes number of complex manufacturing processes moreover, the rate of drug release from the dosage form is mainly controlled by the nature and concentration of polymer used. Therefore, it is crucial to optimize the formulation process for the successful development of a sustained release dosage form. Although, various statistical designs have been developed to optimize the process variables but among them, the response surface methodology (RSM) is one that has currently been used to develop a versatile relationship between investigational response and a set of contributing variables [1]. RSM is the set of mathematical and statistical technique that is used to analyze the problems that are influenced by several variables during manufacturing process. It is used only when few significant factors are involved in the optimization of process variables. It also reduces the number of experimentations and saves time, thus corroborating to be more effectual and cost-effective than traditional methods for the preparation of dosage forms [2].

Flurbiprofen (FLB) is non-steroidal anti-inflammatory (NSAID) drug that is effective for the treatment of fever, pain and inflammation in the body. The major untoward reactions that appear after FLB administration include gastrointestinal tract (GIT) including peptic ulcer, dyspepsia, cramping, gastric bleeding resulting in the treatment failure and patient incompliance [3]. FLB requires frequent administration round the clock to achieve its desired therapeutic effects due to its short biological half-life (2-6 hrs). Therefore, sustained release dosage form of FLB that may have a potential to keep therapeutic level of FLB in plasma for prolonged period may evade its toxic effects on GIT and will improve its area of application.

Oral Sustained release dosage forms are known to have many advantages over their immediate counterparts nevertheless; the drug must be dispersed adequately through well defined polymeric matrix system [4]. Biodegradable and non-biodegradable polymers have extensively been used for the release retarding efficacy [5,6]. Hydrophilic and lipophilic polymers are being widely used to control the release behavior of drug from matrix [7]. The ability of polymeric microspheres to encapsulate variety of drugs, high bioavailability and sustained release characteristics make them ideal vehicle for many control release applications [8].

Ethyl cellulose (EC) is a lipophilic polymer and has been widely used and broadly studied for both lipophilic hydrophilic drugs in the preparation of CR dosage system [9]. EC microspheres showed good extended drug release properties, especially for highly lipophilic drugs as this polymer has excellent membrane-forming ability, durability and low cost, however its flexibility is relatively inferior [10]. Extensive research is being carried out utilizing EC as a drug carrier to achieve the desirable drug release profile. Large doses of FLB can be incorporated in microspheres with EC because of its least chances of dose dumping which may result in severe gastric and mucosal irritation. Hydroxypropyl methylcellulose (HPMC) is another semi-synthetic ether derivative of cellulose used in this study. Due to its non-toxic nature, ease of compression and accommodation to high levels of drug loading, it has been a dominant hydrophilic vehicle used in controlled release dosage forms [11]. The hydration rate of HPMC increases with the increase of hydroxypropyl content and solubility which is pH independent.

The objective of this research work was to optimize the formulation of flurbiprofen loaded EC/HPMC microspheres by solvent evaporation method using RSM which showed a controlled release of flurbiprofen from these microspheres. Further we focused on the influence of each variable along with another variable on drug loading, entrapment efficiency, percent recovery of microspheres,

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interaction of flurbiprofen with EC and/or HPMC using RSM in combination with CCD. In order to optimize the flurbiprofen loaded EC/HPMC microspheres, computer simulation program Design-Expert® was applied. The present research proposes a rational basis for the development of sustained release dosage form of flurbiprofen using biodegradable and biocompatible polymers.

## Material and Method

### Materials

Flurbiprofen BP (Shrooq Pharmaceuticals Ltd., Lahore Pakistan) was received as a gift sample. Ethyl cellulose (Fluka AG, Switzerland), hydroxypropyl methylcellulose (K 15M, Colorcon India), dichloromethane (IR grade Fischer Scientific UK) and tween 80 (Sigma-Aldrich) were purchased and used as received. Hydrochloric acid, potassium dihydrogen phosphate, sodium hydroxide (Merck) and cellulose dialysis bag (MW 6491 Sigma–Aldrich) were used directly. All other chemicals and reagents used in this study were at least analytical grade.

### Preparation of microspheres

Flurbiprofen loaded EC/HPMC microspheres were prepared by solvent evaporation method using water as a continuous phase. Various concentrations of EC (0.2-2.0 gm) were first dissolved in 50 ml dichloromethane (DCM) at room temperature and 200 mg flurbiprofen was added to it. The mixture was sonicated for 20 minutes to form uniform dispersion of drug in polymers. This solution was poured into 400 ml of pure water previously containing various concentrations of dissolved HPMC (0.2-1.8 gm) and 0.5% tween 80. DCM was removed by stirring at 1,000 RPM at 20°C for 1 hour. After the removal of DCM, microspheres were collected on filter paper (Whatman filter paper NO 40) by filtration method. These collected microspheres were washed 3 times with pure water and dried in a vacuum silica desiccator at room temperature until a constant weight of microspheres was achieved. This ensured the removal of any trace solvent left in the formulated microspheres. All formulations were prepared at least 3 times and resulting batches were batches (Table 1) were analyzed for further characterization.

### Experimental design

Central composite design (CCD) was applied to perform this as described previously [1]. The amount of EC ($X_1$) and HPMC ($X_2$) was selected as the factors studied at 3 levels each. The central point (0,0) was studied in quintuplicate. All other processing variables were kept invariant throughout the study period. An account of total 13 experimental runs their factorial combination and translational of coded levels to each experimental unit employed during this study are summarized in table 2. The % of drug release at pH 1.2 ($Y_1$), at pH 4.5 ($Y_2$) and at pH 7.4 ($Y_3$) were taken as response variables.

### Evaluation of microspheres

**Determination of percentage yield:** The formed microspheres were recovered and weighed accurately. The yield of microspheres was determined by comparing the whole weight of formed microspheres against the combined weight of the copolymer and drug [12].

$$\%yield = \frac{mass\ of\ microspheres\ obtained}{total\ mass\ of\ drug\ and\ polymer\ used} \times 100 \quad (1)$$

**Measurement of microsphere hydration:** At the end of each microencapsulation process, microspheres were collected by filtration and weighed immediately ($M_1$) and after drying to a constant weight ($M_2$). The percentage of microsphere hydration was then calculated by following equation as it has been previously described [13].

$$Microsphere\ hydration\ (\%) = \frac{M_1}{M_2} \times 100 \quad (2)$$

**Determination of drug loading capacity of microspheres:** The capacity of microspheres to load the drug was determined. Accurately weighed amount of EC/HPMC microspheres were dissolved in DCM and then diluted this mixture with PBS (pH 7.4). This mixture was agitated up to 1 hour for the complete removal of DCM while, polymers were removed using 0.45 µm pore size Millipore® filters. The content of flurbiprofen was calculated by measuring its absorbance at 247 nm using UV-vis spectrophotometer (IRMECO U2020, Germany). The amount of flurbiprofen was calculated by converting measured absorbance using standard calibration curve and drug loading was calculated by following formula as previously described [14].

$$Drug\ loading\ (\%) = \frac{amount\ of\ drug\ in\ microspheres}{amount\ of\ microspheres} \times 100 \quad (3)$$

The percentage entrapment efficiency of microspheres was calculated by following formula [12].

$$Entrapment\ efficiency\ (\%) = \frac{actual\ drug\ loading}{theoretical\ drug\ loading} \times 100 \quad (4)$$

**Rheological studies of microspheres:**

**Bulk density:** An accurate amount of microspheres was introduced in 10 ml measuring cylinder and its volume was noted. After initial volume of cylinder was observed, the cylinder was allowed

**Table 1**: Composition of FLB loaded EC/HPMC microspheres.

| Ingredients | Amount to be used (mg) |
|---|---|
| Flurbiprofen | 200 |
| EC | 40-200 |
| PHMC | 20-180 |
| Tween 80 | 0.50% |

Abbreviations: FLB; flurbiprofen, EC; ethyl cellulose, HPMC; hydroxypropyl methylcellulose

**Table 2:** Factor combination of coded levels as per experimental design and their translation in actual units.

| Formulation Codes | Coded factor levels | | | | |
|---|---|---|---|---|---|
| | $X_1$ | | | | $X_2$ |
| F-1 | -2 | | | | 0 |
| F-2 | -1 | | | | -1 |
| F-3 | -1 | | | | 1 |
| F-4 | 0 | | | | -2 |
| F-5 | 0 | | | | 0 |
| F-6 | 0 | | | | 2 |
| F-7 | 1 | | | | -1 |
| F-8 | 1 | | | | 1 |
| F-9 | 2 | | | | 0 |
| F-10 | 0 | | | | 0 |
| F-11 | 0 | | | | 0 |
| F-12 | 0 | | | | 0 |
| F-13 | 0 | | | | 0 |
| **Coded level** | -2 | -1 | 0 | 1 | 2 |
| $X_1$: EC | 40 | 80 | 120 | 160 | 200 |
| $X_2$: HPMC | 20 | 60 | 100 | 140 | 180 |

to drop downward under its own weight on hard surface and every time, the volume of cylinder was noted. The tapping was stopped when no change of volume was observed. Loose bulk density (LBD) and tapped bulk density (TBD) were determined using following equations [15].

$$LBD = \frac{weight\ of\ microspheres}{volume\ of\ packing} \quad (5)$$

$$TBD = \frac{weight\ of\ microspheres}{tapped\ volume\ of\ packing} \quad (6)$$

**Carr's index:** It is used for indirect measurement of rheological properties of materials like bulk density, moisture content, size, shape surface area and cohesiveness of materials since all of them may influence the Carr's index. It is also called compressibility Index. It was calculated as follows:

$$C_i = \frac{initial\ volume - final\ volume}{initial\ volume} \times 100 \quad (7)$$

Whereas; the value of $C_i$ represented the flow characteristics of the materials. If $C_i$ < 15%, it reflects good flow characteristics and $C_i$ > 25% shows poor flow characteristics [16].

**Hausner's ratio:** Another index of calculating the flowability of the microspheres is known as Hausner's ratio which was calculated using following formula:

$$Hausner's\ ratio = \frac{volume\ before\ tapping}{volume\ after\ tapping} \quad (8)$$

**Angle of repose:** To calculate the angle of repose, microspheres were passed through the funnel on horizontal surface. The height of heap ($h$) formed after felled down microspheres and the radius of cone base ($r$) were determined. The angle of repose was calculated using following formula [16].

$$\tan\theta = \frac{h}{r} \quad (9)$$

**Fourier transform infrared spectroscopy (FTIR):** FTIR spectra of flurbiprofen and EC/HPMC microspheres were recorded using FTIR spectrophotometer (Perkin-Elmer-Spectrum RX-I, Lambda, USA) to investigate any interaction between flurbiprofen and polymers in formulated microspheres. The samples for FTIR spectroscopy were grounded with KBr to make the pellets by means of hydraulic pellet press by applying pressure of 600 kg/cm$^2$. The prepared pellets were scanned over the wave number range from 4000 to 400 cm$^{-1}$ with resolution of cm$^{-1}$.

**X-Ray diffractometry (XRD):** XRD of flurbiprofen and drug loaded EC/HPMC microspheres were recorded on powder X-Ray diffractometer (Philips APD15). Samples were irradiated with monochromatized X-rays (Cu-kα) and XRD patterns were recorded with scanning rate 2° min$^{-1}$ in the range of 4-40° of diffraction angle (2Θ).

**Scanning electron microscopy (SEM):** The surface morphology of the developed microspheres was examined using a scanning electron microscope (Hitachi S-6000) after gold coating using a sputter coater.

**Thermal analysis:** Differential scanning calorimetry (DSC) and thermogravimetric (TGA) studies were also performed on pure flurbiprofen and flurbiprofen loaded EC/HPMC microspheres. To perform these studies, samples were placed in aluminum pans and heated in nitrogen atmosphere at 10°C/min utilizing Perkin-Elmir DSC7and TGA7. The heating range of DSC7and TGA7 was 40-400°C and 50-450°C.

**Drug release study:** Flurbiprofen released from EC/HPMC microspheres was observed in phosphate buffer solutions (pH 1.2, 4.5 and 7.4) as a release medium at 37 ± 1°C using USP dissolution apparatus (Pharmatest). Approximately 100 mg microspheres were taken in dialysis bag containing 5 ml release medium and tied with paddle of dissolution apparatus. The rotation of paddle was adjusted at 100 RPM in 500 ml release medium. At predetermined time points, approximately 5 ml of aliquot of release medium was withdrawn and equivalent volume of fresh prewarmed (37 ± 1°C) release medium was replaced. The collected aliquot was centrifuged at 5000 RPM for 5 minutes and the supernatant was filtered through 0.45 µm pore size Millipore® filters. The content of flurbiprofen was analyzed directly at 247 nm using an UV-vis spectrophotometer (IRMECO U2020, Germany). The concentration of flurbiprofen in all formulated EC/HPMC microspheres was calculated using calibration curve. The in-vitro release experiments were performed in triplicate in an identical manner.

**Drug release kinetics:** The mechanism of drug release from controlled release matrix system can be reproduced by studying the drug release kinetic models. Therefore, we applied five kinetic models (Zero order, First order, Higuchi, Hixon-Crowell and Korsmeyer-Peppas) in order to calculate the drug release kinetics of flurbiprofen using newly developed software DDSolver [17]. We selected the best fitted release kinetic model on the basis of regression analysis. To validate goodness of best fit from above mentioned models, we also applied akaike information criterion (AIC) [18] using DDSolver. The mechanism of drug release from EC/HPMC microspheres was also studied by observing the value of "n" using Korsmeyer-Peppas equation [5]. If the value of n is equal to 0.45 then the mode of drug release usually follows fickian difusion (case I); whereas, the value of "n" greater than 0.45 but less than 0.89 would indicate that the mode of drug release is non-fickian (anomalous). While, if the value of "n" is more than 0.89 then the mode of drug release is supper case II type in which the erosion of polymers takes place to release the drug content from matrix whereas, anomalous exhibit the mechanism of drug release both by diffusion and erosion of polymer used.

**Optimization of data analysis:** Design Expert® software (State-Ease Inc., Min-neapolis, MN, USA) was applied to perform various RSM computations for current study. Polynomial models were created for all response variables by multiple regression analysis. Two dimensional contour plots were also drawn on the basis of polynomial model functions with the help of design Expert® software [19].

## Results and Discussion

### Recovery of microspheres

Flurbiprofen microspheres were prepared using solvent evaporation method using RSM in which the polymers were dissolved in water immiscible solvent (DCM) and FLB was dispersed in this polymeric solution. The resultant solution was then emulsified in an aqueous continuous phase to form droplets. After evaporation, the microspheres were obtained that were free-flowing, white in color and spherical in shape as confirmed by the SEM (Figure 1). The percentage recovery of microspheres was increased with the increase in the EC concentration was increased with fixed concentration of

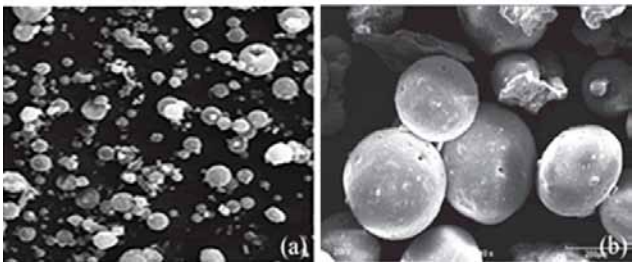


**Figure 1:** Morphology of microspheres for F-6 as revealed by SEM at (a) 100x and (b) 1000x magnification.

HPMC (F-1, F-5, F-9 in Table 3) whereas; the percentage recovery was decreased as the amount of HPMC was increased with fixed amount of EC (F-4, F-5, F-6 in Table 3).

In order to minimize the chance of aggregation and cake formation, Tween 80 (0.5%) was also used in the preparation of spherical shape microspheres. The total recovered weight of microspheres was observed to be less with higher concentrations of HPMC as compared to that of EC (Table 3). Less recovery of microspheres having increased concentration of HPMC was due to the loss of HPMC due to the evaporation of external phase. Stirring speed may also influence the recovery of microspheres, in our present study; we fixed the stirring speed at 1000 RPM. The recovery of microspheres at this speed was almost constant. By increasing the speed of stirrer more than 1000 RPM, the recovery of microspheres was decreased. This low recovery of microspheres was due to the formation of smaller microspheres which were lost during washing process. Whereas, stirring speed less than 1000 RPM caused the aggregation and adherence of materials to the walls of beakers which also resulted in low recovery of microspheres (data not shown).

## Degree of hydration

The degree of hydration of microspheres was measured. From Table 3, it was observed that the degree of hydration of microspheres was increased as the concentration of HPMC was increased with fixed concentration of EC (F-4, F-5, F-6) whereas, the degree of hydration of microspheres was decreased as the concentration of EC was increased with fixed concentration of HPMC (F-1, F-5, F-9). Miscibility of solvent and solubility of polymers in water may affect the degree of hydration of microspheres. EC is lipophilic polymer and it prevents the penetration of water into the microspheres [7] while HPMC is hydrophilic in nature and it allows the water to penetrate into the microspheres [20]. Due to hydrophilic nature, microspheres having more concentration of HPMC were more hydrated as compared to less concentration of HPMC having fixed amount of EC and this phenomenon was vise versa for increased concentration of EC with fixed amount HPMC (Table 3).

## Drug loading

Effect of EC and HPMC on drug loading and entrapment efficiency was investigated. Entrapment efficiency of microspheres was increased as the concentration of polymers was increased (Table 3). When compared, the entrapment efficiency and drug loading were observed to be higher with increase in EC/PHMC ratio. The increased concentration of HPMC increased the entrapment efficiency and drug loading when the concentration of EC was fixed and vise versa.

The entrapment efficiency and drug loading was increased when EC/HPMC concentration was increased but the microspheres containing higher HPMC concentration had higher values of entrapment efficiency and drug loading due to the reason that the loss of HPMC being hydrophilic in nature from dispersed phase into continuous phase was high. Results from table 3 indicate that the entrapment efficiency and drug loading were increased by decreasing EC/HPMC ratio.

## Rheological studies of microspheres

The rheological properties of all 13 formulations are expressed in terms of LBD, TBD, Carr's index, Hausner's ratio and angle of repose (Table 4). As given in table 4, there was a decrease in bulk density with increase in EC/HPMC concentration. The values of, Carr's index for all formulations was less than 15%, Hausner's ratio below 1.2 and angle of repose was less than 30°. The rheological properties of all 13 formulations indicated that microspheres were free-flowing in nature. Similar findings were also reported previously [11,21,22].

## FTIR spectroscopy

Figure 2 showed no significant difference in the FTIR spectra of pure FLB and FLB loaded EC/HPMC microspheres. FTIR spectra of FLB exhibited that the characteristic broad peak of FLB at the range of 2500-3500/cm were due to hydrogen bonding whereas

**Table 3**: Percentage recovery of EC/HPMC microspheres.

| Formulation Codes | Percent Recovery | Degree of Hydration | Entrapment Efficiency | Percent Drug Loading |
|---|---|---|---|---|
| F-1 | 33.35 | 151.95 | 62.65 | 7.95 |
| F-2 | 37.38 | 145.16 | 58.43 | 8.16 |
| F-3 | 24.26 | 162.13 | 65.26 | 8.48 |
| F-4 | 56.26 | 135.25 | 66.82 | 8.16 |
| F-5 | 46.66 | 146.25 | 71.66 | 8.38 |
| F-6 | 42.75 | 175.54 | 85.63 | 9.63 |
| F-7 | 40.15 | 145.65 | 75.46 | 8.56 |
| F-8 | 35.41 | 136.65 | 73.62 | 9.15 |
| F-9 | 60.95 | 145.75 | 77.25 | 9.16 |
| F-10 | 44.55 | 140.25 | 70.56 | 8.15 |
| F-11 | 47.25 | 148.95 | 71.75 | 8.45 |
| F-12 | 46.95 | 150.65 | 71.85 | 8.25 |
| F-13 | 45.65 | 146.85 | 72.15 | 8.15 |

**Table 4:** Rheological properties of EC/HPMC microspheres.

| Formulation Codes | LBD (gm/ml) | TBD (gm/ml) | Carr's Index (%) | Hausner's Ratio | Angle of Repose (º) |
|---|---|---|---|---|---|
| F-1 | 0.45 | 0.24 | 12.66 | 1.20 | 22.42 |
| F-2 | 0.17 | 0.21 | 14.54 | 1.18 | 20.54 |
| F-3 | 0.16 | 0.18 | 14.38 | 1.18 | 19.23 |
| F-4 | 0.28 | 0.34 | 14.75 | 1.23 | 24.25 |
| F-5 | 0.19 | 0.22 | 13.51 | 1.18 | 30.26 |
| F-6 | 0.12 | 0.24 | 10.66 | 1.11 | 30.74 |
| F-7 | 0.20 | 0.23 | 14.92 | 1.2 | 26.58 |
| F-8 | 0.19 | 0.22 | 14.18 | 1.22 | 26.56 |
| F-9 | 0.14 | 0.19 | 11.25 | 1.12 | 21.82 |
| F-10 | 0.19 | 0.21 | 12.55 | 1.19 | 30.65 |
| F-11 | 0.20 | 0.23 | 13.65 | 1.20 | 31.12 |
| F-12 | 0.19 | 0.22 | 13.60 | 1.16 | 29.85 |
| F-13 | 0.19 | 0.20 | 13.50 | 1.17 | 30.50 |

Abbreviations: LBD; loose bulk density, TBD: tapped bulk density

at 1698/cm and 2920/cm were because of carbonyl and hydroxyl group stretching respectively. No significant difference was observed in the characteristic peaks of pure FLB and FLB loaded EC/HPMC microspheres. The results of FTIR spectra were found to be in good agreement with already published reports [11,19,23] and suggests FLB stability in EC/HPMC microspheres.

## X-Ray diffractometry

XRD of pure FLB and FLB loaded EC/HPMC microspheres were carried out by using X-Ray diffractometer to find out any change in the crystallinity of FLB during microencapsulation. XRD pattern of FLB showed sharp peaks whereas; EC/HPMC microspheres decreased the sharpness of peak which exhibited that EC/HPMC dispersed the drug at molecular level blended EC/HPMC microspheres by decreasing the crystallinity of FLB (Figure 3). XRD patterns of FLB and FLB loaded EC/HPMC microspheres (Figures 3 and 2B) exhibited the change in crystalline nature of FLB might be due to the addition of EC/HPMC polymers and these polymers helped in spreading the drug completely at molecular level.

## Thermal analysis

Stability of FLB in EC/HPMC microspheres was investigated by thermal analysis using DSC (Figure 4A) and TGA (Figure 4B) thermograms. The melting point of FLB was revealed by endothermic peaks at 115°C. The same thermal behavior was also observed in FLB loaded EC/HPMC microspheres but the peak of FLB was less sharp which suggested that FLB encapsulated in microspheres was molecularly dispersed. Thermal analysis (DSC and TGA) was used to analyze the physical state of drug encapsulated in polymeric microspheres [24]. These results revealed that FLB encapsulated in EC/HPMC microspheres was in amorphous state. The results of thermal analysis proved the results of XRD in which it revealed that FLB was stable and encapsulated in microspheres was dispersed at molecular level.

## *In-vitro* drug release study

Drug release from EC/HPMC microspheres was investigated at pH 1.2 (Figure 5), 4.5 (Figure 6) and 7.4 (Figure 7). Dissolution studies were performed for 2 hrs at pH 1.2 and 4.5 whereas, 8 hrs at pH 7.4. Figure 5 represents the drug release profile of all formulations

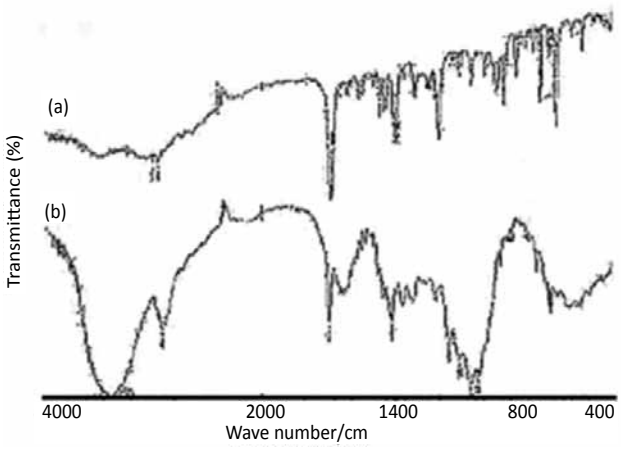


**Figure 2:** FTIR transmission spectra of (a) flurbiprofen and (b) F-6

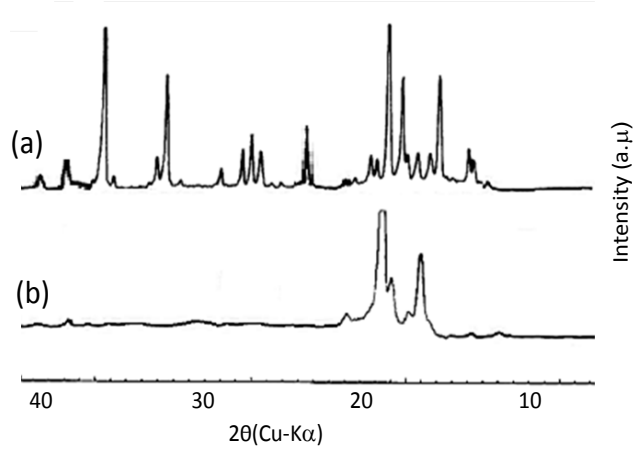


**Figure 3:** XRD patterns of (a) flurbiprofen and (b) F-6.

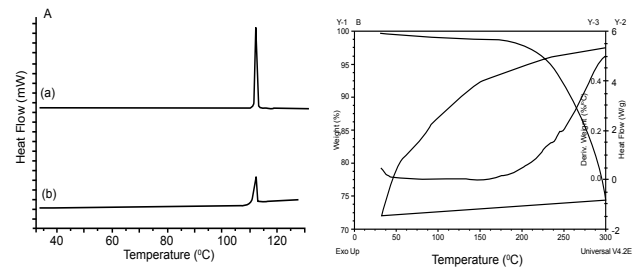


**Figure 4: A:** DSC thermograms of (a) flurbiprofen and (b) F-6, B: TGA thermograms of (a) flurbiprofen and (b) F-6.

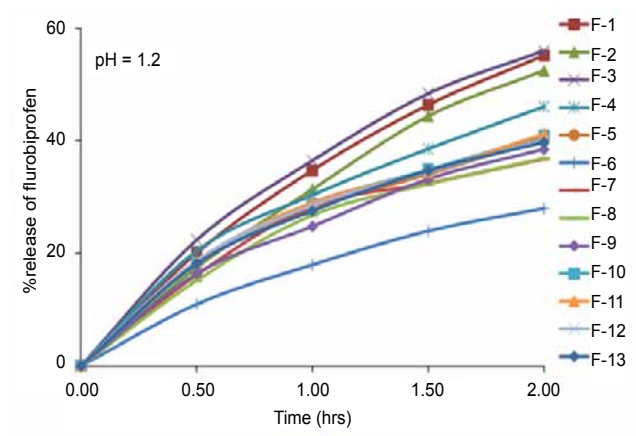


**Figure 5:** Release profiles of flurbiprofen from different formulations of microspheres of EC and HPMC at pH 1.2.

at pH 1.2. Formulations F-1, F-2 and F-3 showed abrupt release of FLB due to less concentration of EC/HPMC in microspheres. F-6 exhibited more prolonged drug release due to increased proportions of EC/HPMC. Such type of phenomenon was also observed when drug release study was performed at pH 4.5 (Figure 6). Whereas, at pH 7.4, the maximum drug release 58% (F-6) to 85% (F-1) revealing

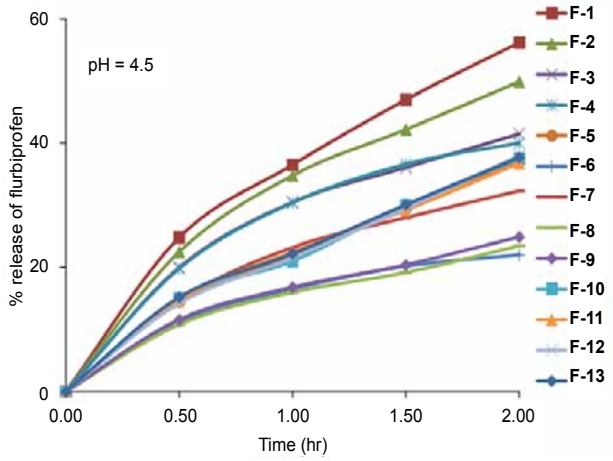


**Figure 6:** Release profiles of flurbiprofen from different formulations of microspheres of EC and HPMC at pH 4.5.

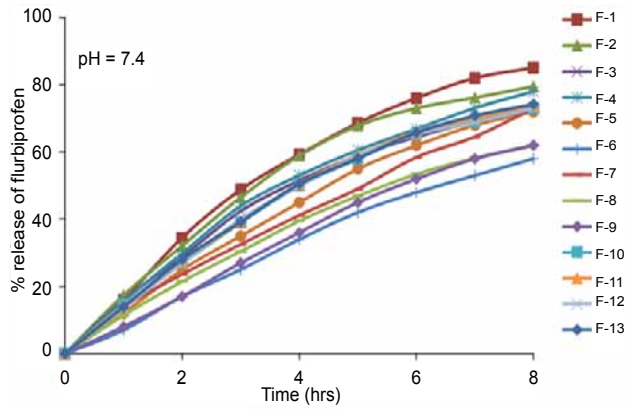


**Figure 7:** Release profiles of flurbiprofen from different formulations of microspheres of EC and HPMC at pH 7.4.

the sustained release pattern of drug from microspheres in PBS (Figure 7). Increasing the concentrations of EC/HPMC decreased the release of FLB from microspheres and vise versa.

Figures 8 and 9 represent the effect of both EC and HPMC on release rate of drug at pH 7.4. An efficient prolonged release was observed from F-1, F-5 and F-9 when the concentration of EC was increased with fixed amount of HPMC (Figure 8). Such type of phenomenon have never been shown before therefore, it is hypothesized that presence of HPMC acts as a barrier to the release retarding potential of EC. EC prevents the release of drug by swelling which is achieved by hydration. The concentration of HPMC in F-1 and F-5 is greater than that of EC, therefore, it prevented the hydration of EC that is essential for drug release whereas; in F-9, the concentration of EC is greater than HPMC that might be suitable hydration for the sustained release of drug. Such type of results have also been reported previously [25,26]. Figure 9 exhibits the effective release of FLB from F-4, F-5 and F-6 with fixed percentages of EC and increasing percentages of HPMC. Formulation F-4, F-5 and F-6 prolonged the release of FLB as the concentration of HPMC increased gradually with fixed amount of EC (Figure 9). Such results are in support with previously reported studies [20,27,28].

## Drug release kinetics

The dissolution data were analyzed according to various model dependent approaches (Zero order, First order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas) using DDSolver and the mode of drug release from microspheres was calculated plotting the curves. The kinetic model with highest value of coefficient of determination ($R^2$) was considered to be a more suitable model for all dissolution profiles. The results of kinetic analysis provided the evidence that Zero order was the best fit model for the dissolution data of all formulations at three different pH conditions (1.2, 4.5 and 7.4) as the plots showed the highest values of $R^2$ that indicated that the mode of drug release was independent of concentration of drug (Tables 5-7). All other models exhibited curvilinear plots having low values of $R^2$ when compared with that of zero order.

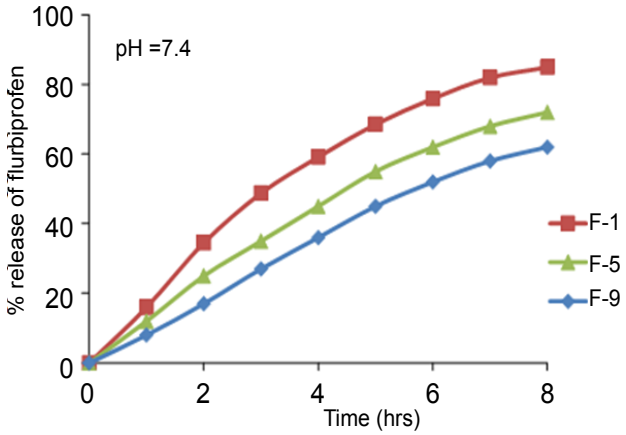


**Figure 8:** Release profile of three formulations flurbiprofen loaded EC/HPMC loaded microspheres (F-1, F-5, F-9) using fixed percentage of HPMC and various percentages of EC.

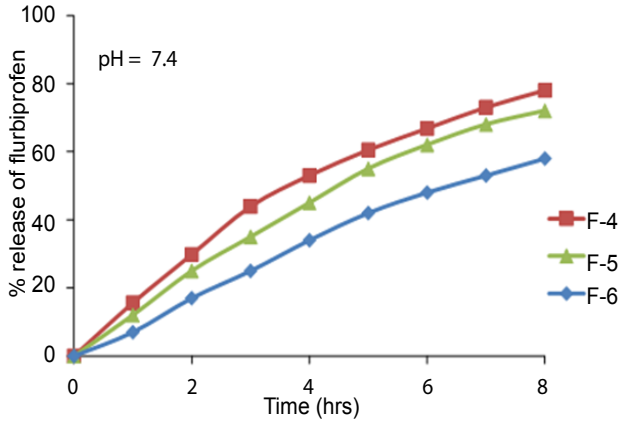


**Figure 9:** Release profile of three formulations flurbiprofen loaded EC/HPMC loaded microspheres (F-4, F-5, F-6) using fixed percentage of EC and various percentages of HPMC.

**Table 5:** $R^2$ values of FLB from EC/HPMC microspheres at pH 1.2.

| Formulation Codes | Zero-order $R^2$ | First-order $R^2$ | Higuchi $R^2$ | Hixson-Crowell $R^2$ | Korsmeyer-Peppas n |
|---|---|---|---|---|---|
| F-1 | 0.989 | 0.961 | 0.963 | 0.952 | 0.999 |
| F-2 | 0.989 | 0.977 | 0.957 | 0.946 | 1.02 |
| F-3 | 0.993 | 0.941 | 0.955 | 0.942 | 1.00 |
| F-4 | 0.995 | 0.971 | 0.965 | 0.956 | 1.08 |
| F-5 | 0.997 | 0.956 | 0.967 | 0.941 | 1.13 |
| F-6 | 0.998 | 0.925 | 0.968 | 0.913 | 1.18 |
| F-7 | 0.988 | 0.933 | 0.958 | 0.915 | 1.06 |
| F-8 | 0.988 | 0.957 | 0.968 | 0.943 | 1.07 |
| F-9 | 0.998 | 0.972 | 0.979 | 0.961 | 1.14 |
| F-10 | 0.906 | 0.955 | 0.966 | 0.942 | 1.12 |
| F-11 | 0.908 | 0.958 | 0.965 | 0.942 | 1.10 |
| F-12 | 0.912 | 0.962 | 0.964 | 0.943 | 1.14 |
| F-13 | 0.910 | 0.952 | 0.966 | 0.940 | 1.08 |

**Table 6:** $R^2$ values of FLB from EC/HPMC microspheres at pH 4.5.

| Formulation Codes | Zero-order $R^2$ | First-order $R^2$ | Higuchi $R^2$ | Hixson-Crowell $R^2$ | Korsmeyer-Peppas n |
|---|---|---|---|---|---|
| F-1 | 0.993 | 0.952 | 0.953 | 0.969 | 0.985 |
| F-2 | 0.997 | 0.957 | 0.967 | 0.950 | 0.899 |
| F-3 | 0.995 | 0.935 | 0.978 | 0.915 | 0.989 |
| F-4 | 0.993 | 0.922 | 0.976 | 0.900 | 1.08 |
| F-5 | 0.995 | 0.966 | 0.975 | 0.940 | 1.15 |
| F-6 | 0.998 | 0.891 | 0.977 | 0.868 | 1.13 |
| F-7 | 0.997 | 0.937 | 0.977 | 0.922 | 1.06 |
| F-8 | 0.996 | 0.928 | 0.976 | 0.919 | 1.08 |
| F-9 | 0.997 | 0.929 | 0.977 | 0.919 | 1.16 |
| F-10 | 0.956 | 0.962 | 0.9720 | 0.942 | 1.08 |
| F-11 | 0.955 | 0.954 | 0.9740 | 0.948 | 1.16 |
| F-12 | 0.945 | 0.941 | 0.9760 | 0.949 | 1.11 |
| F-13 | 0.967 | 0.945 | 0.9740 | 0.948 | 1.13 |

**Table 7:** $R^2$ values of FLB from EC/HPMC microspheres at pH 7.4.

| Formulation Codes | Zero-order $R^2$ | First-order $R^2$ | Higuchi $R^2$ | Hixson-Crowell $R^2$ | Korsmeyer-Peppas n |
|---|---|---|---|---|---|
| F-1 | 0.995 | 0.886 | 0.951 | 0.951 | 1.08 |
| F-2 | 0.996 | 0.889 | 0.964 | 0.969 | 0.895 |
| F-3 | 0.997 | 0.904 | 0.969 | 0.945 | 1.06 |
| F-4 | 0.996 | 0.907 | 0.967 | 0.959 | 1.12 |
| F-5 | 0.997 | 0.932 | 0.956 | 0.954 | 1.08 |
| F-6 | 0.999 | 0.967 | 0.945 | 0.934 | 1.20 |
| F-7 | 0.991 | 0.943 | 0.932 | 0.957 | 0.95 |
| F-8 | 0.999 | 0.942 | 0.944 | 0.966 | 0.98 |
| F-9 | 0.997 | 0.948 | 0.932 | 0.949 | 1.08 |
| F-10 | 0.997 | 0.930 | 0.955 | 0.945 | 0.988 |
| F-11 | 0.996 | 0.934 | 0.952 | 0.964 | 1.05 |
| F-12 | 0.998 | 0.933 | 0.958 | 0.955 | 1.08 |
| F-13 | 0.997 | 0.935 | 0.957 | 0.954 | 1.09 |

The choice of an appropriate model should be considered essential during the assessment of drug release from polymers via model-dependent approaches. Numerous professional statistical principles for selecting the best model have been provided by DDSolver, one of these is AIC. The model with lowest value of AIC as compared to other ones is considered best according to this criterion. AIC has been recognized as a finest criterion for analyzing the dissolution data of a drug [7]. We have utilized AIC to verify and elucidate the goodness of fit model among various models used in the present study. In order to verify the best fit model, dissolution data was also analyzed to calculate the AIC values. According to the values of AIC for all formulations (Tables 8-10), zero order was also found to be the best fit model to explain the mode of drug release from microspheres as the values of AIC for all other models were higher than the AIC values of zero order.

Drug release mechanism was also investigated from these microspheres using Korsmeyer-Peppas equation. The value of "n"

**Table 8:** AIC values for all formulations at pH 1.2.

| Formulation Codes | Akaeki information criterion | | | |
|---|---|---|---|---|
| | Zero-order | First-order | Higuchi | Hixson-Crowell |
| F-1 | 23.52 | 48.90 | 41.64 | 45.93 |
| F-2 | 20.62 | 64.12 | 43.62 | 31.40 |
| F-3 | 26.83 | 45.24 | 39.12 | 49.78 |
| F-4 | 25.42 | 50.16 | 31.56 | 32.12 |
| F-5 | 19.97 | 40.86 | 58.13 | 62.37 |
| F-6 | 11.39 | 59.28 | 34.38 | 40.01 |
| F-7 | 25.73 | 22.43 | 43.70 | 53.61 |
| F-8 | 24.05 | 20.14 | 43.95 | 61.56 |
| F-9 | 15.77 | 58.16 | 43.39 | 39.87 |
| F-10 | 19.97 | 40.86 | 58.13 | 62.37 |
| F-11 | 19.58 | 40.8 | 58.15 | 61.85 |
| F-12 | 19.85 | 40.78 | 58.25 | 62.52 |
| F-13 | 19.95 | 40.75 | 58.55 | 62.35 |

**Table 9:** AIC values for all formulations at pH 4.5.

| Formulation Codes | Akaeki information criterion | | | |
|---|---|---|---|---|
| | Zero-order | First-order | Higuchi | Hixson-Crowell |
| F-1 | 17.07 | 29.54 | 44.65 | 72.45 |
| F-2 | 27.24 | 21.54 | 49.92 | 73.70 |
| F-3 | 26.98 | 23.22 | 44.90 | 74.58 |
| F-4 | 20.47 | 23.96 | 49.55 | 75.22 |
| F-5 | 15.30 | 34.22 | 57.11 | 66.07 |
| F-6 | 12.63 | 20.07 | 42.03 | 70.61 |
| F-7 | 23.49 | 20.58 | 45.84 | 71.62 |
| F-8 | 19.60 | 37.77 | 42.71 | 78.41 |
| F-9 | 20.25 | 38.31 | 42.58 | 78.98 |
| F-10 | 13.30 | 34.22 | 57.11 | 66.07 |
| F-11 | 13.95 | 34.55 | 58.15 | 65.58 |
| F-12 | 13.55 | 34.35 | 57.85 | 66.85 |
| F-13 | 13.45 | 34.15 | 57.25 | 66.35 |

**Table 10:** AIC values for all formulations at pH 7.4.

| Formulations | Akaeki information criterion | | | |
|---|---|---|---|---|
| | Zero-order | First-order | Higuchi | Hixson-Crowell |
| F-1 | 16.54 | 22.17 | 49.21 | 38.51 |
| F-2 | 16.07 | 31.00 | 50.91 | 40.56 |
| F-3 | 17.77 | 25.75 | 47.53 | 40.75 |
| F-4 | 18.08 | 22.75 | 48.89 | 39.06 |
| F-5 | 14.98 | 52.05 | 51.12 | 43.62 |
| F-6 | 10.50 | 26.24 | 49.27 | 69.55 |
| F-7 | 21.66 | 25.21 | 53.99 | 65.79 |
| F-8 | 36.60 | 26.72 | 50.14 | 52.08 |
| F-9 | 14.31 | 36.26 | 52.44 | 55.09 |
| F-10 | 14.98 | 52.05 | 51.12 | 43.62 |
| F-11 | 14.56 | 51.85 | 51.32 | 43.58 |
| F-12 | 15.12 | 52.26 | 51.58 | 43.85 |
| F-13 | 14.85 | 52.38 | 50.85 | 42.98 |

was higher than 0.89 indicated that the mechanism of drug release from EC/HPMC microspheres followed super case II type of drug release (Tables 5-7) at three different pH conditions (1.2, 4.5 and 7.4) that indicated that multiple mechanisms (diffusion, erosion and chain relaxation) were involved to release the drug from microspheres. Our results are highly supported by already published reports [20,25,26]. Thus with the increase in polymer concentration, the surface pores for the escape of drug were found to decrease that may contribute in prolonging the release of drug from polymeric microspheres.

From literature [9,22], it has been evident that the initial drug release from EC containing EC usually follows anomalous mode but with the passage of time, microspheres begin to swell by increasing the uptake of water leading to form a front and decreased erosion that may prolong the release rate of drug. Here in our present study, the use of HPMC was used to control the balance between erosion and swelling of microspheres as HPMC is hydrophilic polymer and is highly susceptible to disintegration [27]. The addition of HPMC helped to maintain the zero order release kinetics throughout experimental runs exhibiting concentration and time-independent release profile of FLB that can be clearly described by figures 5-7. The ideal combination of both polymers through CCD may prolong the drug release with desired therapeutic effects and minimum chances of side effects.

## RMS optimization results

Central composite design involves 13 experimental runs. The values of independent factors with their responses are elaborated in table 11 in which $X_1$ (EC) and $X_2$ (HPMC) are independent factors whereas; $Y_1$ (cumulative drug release at pH 1.2) $Y_2$ (cumulative drug release at pH 4.5) and $Y_3$ (cumulative drug release at pH 7.4) are response variables.

## Response surface analysis

Two dimensional contour plots for studied response properties ($Y_1$, $Y_2$ and $Y_3$) are shown in figures 10-12 respectively. Figures 10 and 11 exhibit that the response $Y_1$ and $Y_3$ changes in nonlinear manner but in descending way with increase in the amount of polymers on the release of FLB at pH 1.2 and 4.5. It also exhibit that HPMC has comparatively greater impact on release of FLB than EC. When the results of response variables $Y_1$ and $Y_2$ were compared with that of $Y_3$ (at pH 7.4), it was revealed that $Y_3$ (Figure 12) varied in somewhat linear pattern with the increase of polymer's concentration but the effects of HPMC on the release of FLB was similar as in case of response variables $Y_1$ and $Y_2$. Our results are in agreement with already published reports [1,20,21,29,30] in which increased concentrations of EC/HPMC leads to decreased drug release up to greater extent by maintaining a balance between swelling and erosion in such a manner that sustained and prolonged release pattern of drug is achieved.

**Table 11:** Drug release parameters of various formulations prepared as per experimental design.

| Formulation Codes | $X_1$ (mg) | $X_2$ (mg) | $Y_1$ % | $Y_2$ % | $Y_3$ % |
|---|---|---|---|---|---|
| F-1 | 40.00 | 100.00 | 55.20 | 56.20 | 85.00 |
| F-2 | 80.00 | 60.00 | 52.50 | 49.90 | 79.50 |
| F-3 | 80.00 | 140.00 | 56.00 | 41.50 | 72.60 |
| F-4 | 120.00 | 20.00 | 46.10 | 40.00 | 78.00 |
| F-5 | 120.00 | 100.00 | 40.50 | 37.20 | 72.00 |
| F-6 | 120.00 | 180.00 | 28.00 | 22.00 | 58.00 |
| F-7 | 160.00 | 60.00 | 36.80 | 32.30 | 72.90 |
| F-8 | 160.00 | 160.00 | 36.90 | 23.50 | 62.00 |
| F-9 | 200.00 | 100.00 | 38.50 | 24.90 | 62.00 |
| F-10 | 120.00 | 100.00 | 40.95 | 37.50 | 73.00 |
| F-11 | 120.00 | 100.00 | 41.25 | 36.80 | 73.80 |
| F-12 | 120.00 | 100.00 | 40.15 | 38.00 | 72.90 |
| F-13 | 120.00 | 100.00 | 39.75 | 37.70 | 74.20 |

Abbreviations: $X_1$; ethyl cellulose, $X_2$; hydroxypropyl methylcellulose, $Y_1$; at pH 1.2, $Y_2$; at pH 4.5, $Y_3$; at pH 7.4.

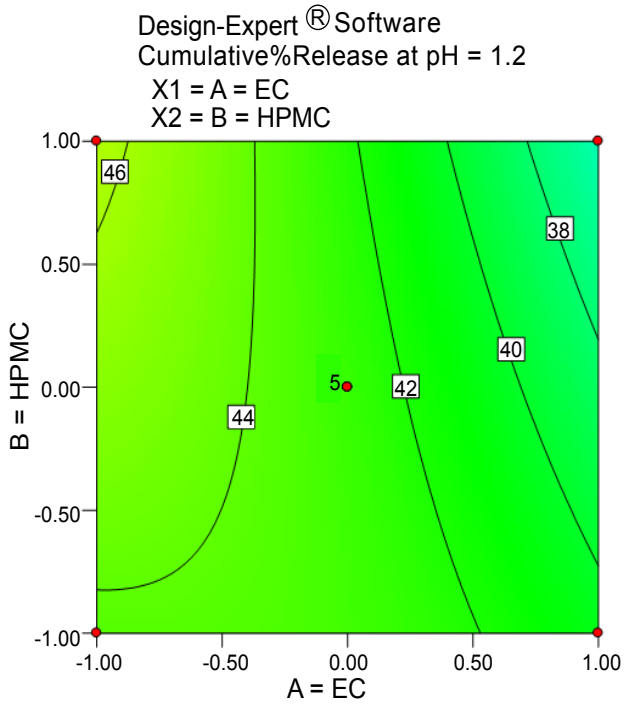


**Figure 10:** Contour plot showing the relationship between various levels of EC and HPMC on % release of flurbiprofen at pH 1.2.

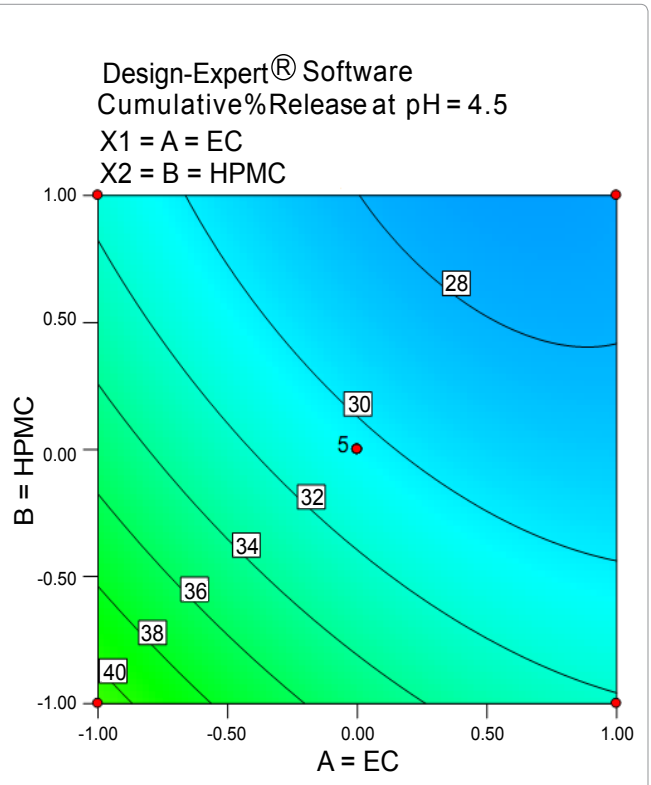


**Figure 11:** Contour plot showing the relationship between various levels of EC and HPMC on % release of flurbiprofen at pH 4.5

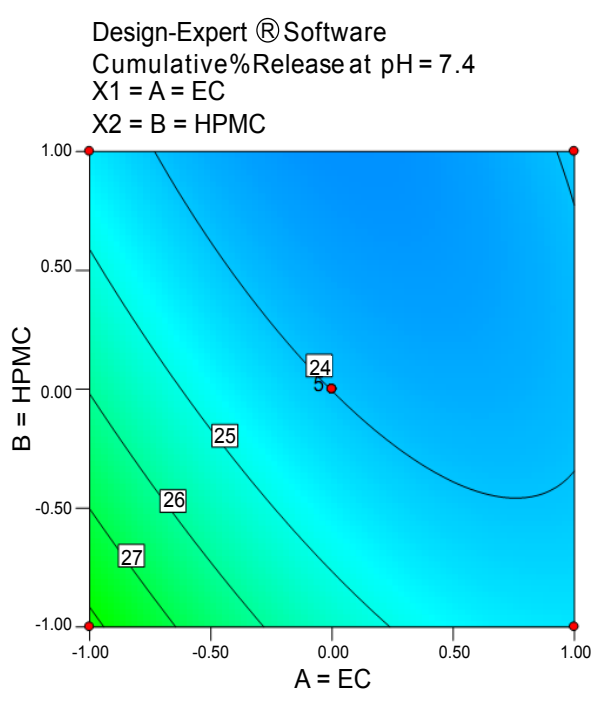


**Figure 12:** Contour plot showing the relationship between various levels of EC and HPMC on % release of flurbiprofen at pH 7.4

## Conclusion

EC/HPMC microspheres of FLB were successfully prepared using solvent evaporation technique and their release profiles were optimized by using CCD. Concentrations of EC/HPMC may influence the recovery, hydration, entrapment efficiency and drug loading of microspheres. Degree of hydration, entrapment efficiency and drug loading capability of microspheres increased with the increased concentrations of EC/HPMC. Rheological properties exhibited that all microspheres were free-flowing in nature. The results of FTIR, DSC, TGA and XRD revealed that experimental conditions allowed a uniform distribution of FLB within EC/HPMC microspheres having no significant effect on drug-polymer interaction. The RSM studied in this present work for *in-vitro* release of FLB from EC/HPMC microspheres proposes the understanding for the interaction between the combination and ratio of EC and HPMC. The release of drug from EC/HPMC microspheres followed zero order release kinetics which was further validated and verified by lowest values of AIC for zero order when compared with that of AIC values for all other kinetic models. The release kinetic results revealed that both polymers play their pivotal role for sustained release of FLB with a benefit of avoiding the harmful effects of FLB to GIT. However, appropriate balancing between these polymers may influence better results. High level of prognosis obtained using RSM verified that the 2-factor CCD can be competently utilized for the optimization of drug delivery system.

### Conflict of Interest

Authors declare that they do not have any conflict of interest for this article.

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