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# The Formulation of Flurbiprofen Loaded Microspheres Using Hydroxypropylmethycellulose and Ethylcellulose

## Opracowanie mikrosfer wypełnionych flurbiprofenem za pomocą hydroksypropylmetycelulozy i etylocelulozy

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**A** – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

## Abstract

**Objectives.** The aim of the present work was to formulate flurbiprofen (FLB) loaded microspheres of hydroxypropylmethycellulose and ethylcellulose polymers to study the effect of different proportions of the polymer mixture on the release behavior of the drug.
**Material and Methods.** A series of microspheres were prepared using tween-80 as a surfactant. The prepared microspheres were evaluated for entrapment efficiency (%) and percentage recovery. Drug release was performed in USP phosphate buffers of pH 1.2 and 6.8. Drug release data were plotted in various kinetic models, including zero-order, first-order, Higuchi and Korsmeyer-Peppas models to investigate the optimum composition suitable for sustained drug delivery.
**Results.** A significant difference in drug release kinetics was observed by varying the composition of hydroxypropylmethycellulose/ethylcellulose. As the ratio of EC/HPMC was increased, the release rate of flurbiprofen decreased.
**Conclusions.** This study demonstrated the potential of polymer combinations in the formulation of microspheres for water-insoluble drugs utilizing HPMC and EC as release retardant materials, using a simple solvent evaporation microencapsulation technique. It was observed that various physico-chemical properties of the microspheres varied according to the change in polymer concentrations used in the formulations (**Adv Clin Exp Med 2013, 22, 2, 177–183**).

**Key words:** flurbiprofen, microspheres, HPMC, ethylcellulose.

## Streszczenie

**Cel pracy.** Opracowanie mikrosfer wypełnionych flurbiprofenem (FLB) za pomocą polimerów hydroksypropylmetycelulozy i etylocelulozy w celu zbadania wpływu różnych proporcji mieszaniny polimerów na uwalnianie leku.
**Materiał i metody.** Wytworzono zestaw mikrosfer z użyciem tween-80 jako środka powierzchniowo czynnego. Przygotowane mikrosfery oceniono pod względem wydajności uwięzienia (%) i odsetka odzyskania. Uwalnianie leku prowadzono w buforach fosforanowych o USP pH 1,2 i 6,8. Dane uwalniania leku wykreślono w różnych modelach kinetycznych, w tym rzędu zerowego, pierwszego rzędu, modelach Higuchi i Korsmeyer-Peppas badających optymalną kompozycję odpowiednią do przedłużonego uwalniania leku.
**Wyniki.** Zaobserwowano znaczącą różnicę kinetyki uwalniania leku w zależności od proporcji hydroksypropylmetycelulozy i etylocelulozy. Im większy stosunek EC / HPMC, tym mniejsza szybkość uwalniania flurbiprofenu.
**Wnioski.** Badanie to wykazało możliwości kombinacji polimerów w preparacie zawierającym mikrosfery jako nośnik leków nierozpuszczalnych w wodzie z wykorzystaniem HPMC EC jako materiałów opóźniających uwalnianie, za pomocą prostego odparowania rozpuszczalnika techniką mikrokapsułkowania. Stwierdzono, że właściwości fizykochemiczne mikrosfer zależą od zmian w stężeniu polimeru stosowanego w preparatach (**Adv Clin Exp Med 2013, 22, 2, 177–183**).

**Słowa kluczowe:** flurbiprofen, mikrosfery, HPMC, etyloceluloza.

Flurbiprofen (FLB) is a non-steroidal anti-inflammatory (NSAID) drug that is widely used for the treatment of fever, pain and inflammation. It is available as a prescription medicine and its use is increasing every day. The major adverse reactions to FLB are related to the gastro-intestinal tract (GIT), i.e. dyspepsia, cramping, gastric bleeding and peptic ulcer, causing non-compliance among patients, which ultimately results in treatment failure. The plasma half life of FLB is short (3–6 h), so its administration is frequent; making it a suitable candidate for the formulation of a controlled release (CR) dosage form [1, 2].

Although the CR oral dosage form has many advantages over immediate-release dosage, the drug must be dispersed adequately throughout the defined polymer matrix and GIT [3]. Microspheres have been reported to disperse drugs uniformly, and are used in treating many diseases that require a constant drug level in the blood or targeting of specific cells or tissues [4]. Various synthetic and natural polymers are available for the development of microspheres [5]. Microsphere-based drug delivery systems may increase the life span of the active substance. Due to their small size, microspheres have a large exposed surface area and thus can be used for the controlled release of drugs [6].

Non-biodegradable polymers are being used successfully to retard drug release efficiently. Hydrophilic and lipophilic polymers are also used as excipients to control the release rate of drugs from matrices [7]. The ability of polymeric microspheres to encapsulate a variety of drugs, their biocompatibility and their sustained release action make them an ideal vehicle for the delivery of drugs [8]. Ethylcellulose (EC) is a lipophilic polymer that is widely used and studied for the preparation of CR formulations of both lipophilic and hydrophilic drugs [9]. Ethylcellulose microspheres show good extended drug release properties, especially for highly lipophilic drugs. This polymer has excellent membrane- forming ability and durability; however, its flexibility is relatively inferior [10]. Extensive research has been carried out to investigate the utilization of EC as a vehicle to achieve the desired drug release profile. Larger doses of FLB can be incorporated in microspheres of EC because there is very little chance of dose dumping, which may result in severe gastric irritation.

Hydroxypropylmethylcellulose (HPMC) is another polymer used in this study. It is a semi-synthetic ether derivative of cellulose. Due to its non-toxic nature and ability to accommodate high levels of drug loading, it has become the dominant hydrophilic vehicle for CR formulations [11]. The hydration rate of HPMC increases along with increases in hydroxypropyl content and solubility, which is a pH-independent process [12].

The objective of this study was to develop and characterize an oral microparticulate dosage form of FLB to improve the release of the therapeutic agent.

# Material and Methods

Hydroxypropylmethycellulose (HPMC) and ethylcellulose (EC) were purchased from Flucka (Buchs, Switzerland). Tween-80 was purchased from Merck (Darmstadt, Germany). All the chemicals were of analytical grade and were used without further purification.

## Synthesis of HPMC/EC Microspheres

HPMC/EC microspheres of FLB were prepared by the solvent evaporation method using distilled water as the continuous phase. The drug (FLB) and polymers (EC/HPMC) were precisely weighed in different proportions (Table 1). Various quantities of EC were first dissolved in 50 ml of dichloromethane at room temperature and then 0.2 g of the drug (FLB) was added to it. The mixture was sonicated for 20 minutes to form a uniform drug polymer dispersion. This organic phase was slowly added to 400 ml distilled water containing various previously dissolved concentrations (Table 1) of HPMC and 0.5% tween-80, while maintaining the temperature at 20°C for 1 hour. The stirring speed was increased from 500 to 1000 rpm and optimized at 700 rpm, in order to obtain a sufficient yield of microspheres with the appropriate size distribution. The microspheres formed were filtered using Whatman filter paper no. 40, washed three times with distilled water and dried overnight at room temperature.

## Recovery of the Microspheres

The obtained microspheres were weighed accurately. The yield of microspheres was determined by comparing the whole weight of the formed microspheres against the cumulative weight of the polymers and drug [14].

$$\text{Percent yield} = \frac{\text{weight of microspheres obtained (g)}}{\text{weight of all species charged (g)}} \times 100$$

## Entrapment Efficiency

Percentage entrapment efficiency is the percentage of drug entrapped in the microspheres in relation to the initial quantity of drug used. An

**Table 1.** Different formulations of FLB loaded EC/HPMC microspheres

**Tabela 1.** Różne składy mikrosfer wypełnionych FLB EC/HPMC

| Formulation (Preparat) | HPMC (g) | EC (g) | Concentration of tween-80 (% w/v) | Percentage recovery (Mean ± SD) | Entrapment efficiency (Mean ± SD) |
|---|---|---|---|---|---|
| F1 | 1.0 | 0.2 | 0.5 | 37.5±4.8 | 76.8±3.3 |
| F2 | 1.0 | 0.4 | 0.5 | 43.3±3.6 | 86.6±4.5 |
| F3 | 1.0 | 0.6 | 0.5 | 51.2±5.4 | 88.6±2.7 |
| F4 | 0.2 | 1.0 | 0.5 | 76.2±4.1 | 63.6±5.8 |
| F5 | 0.4 | 1.0 | 0.5 | 68.6±6.9 | 65.9±3.2 |
| F6 | 0.6 | 1.0 | 0.5 | 53.7±3.8 | 66.7±6.6 |
| F7 | 1.0 | 0 | 0.5 | 35.2±5.5 | 73.3±5.8 |
| F8 | 0 | 1.0 | 0.5 | 87.9±4.2 | 61.6±4.4 |

appropriate amount of microspheres in 100 ml of phosphate buffer (pH 6.8) was placed in an ultrasonic bath at 70°C for 20 minutes to completely remove the FLB from the polymers. After it had cooled to room temperature, it was filtered through a 0.45 µ nylon disc filter. Next, 0.5 ml of supernatant was taken and diluted to 5 ml with the phosphate buffer solution (pH 6.8). The absorbance of FLB at 247 nm was measured using a UV/Vis spectrophotometer (IRMECO U2020, Germany) to calculate the concentration of the drug. The experiments were carried out in triplicate to obtain the mean values. Entrapment efficiency was determined by the following formula [15]:

$$\text{Percentage entrapment efficiency} = \frac{\text{actual drug loading (\%)}}{\text{teoretical loading (\%)}} \times 100$$

## *In vitro* Drug Release, Release Kinetics and Statistics

*In vitro* release study of FLB from the microspheres was performed using USP dissolution apparatus (Pharmatest, Germany). Phosphate buffer solutions (pH 1.2 and 6.8) were used as the dissolution medium. 100 mg of microspheres were taken in a sieve and put into the dissolution medium. *In vitro* FLB release studies were performed at a paddle rotation speed of 100 rpm in 500 mL of dissolution medium at 37 ± 0.5°C. Aliquots of the dissolution medium (5 mL) were withdrawn at predetermined time intervals and replaced with equal volumes of fresh phosphate buffer to maintain a constant volume in dissolution flask. The collected samples were suitably diluted and filtered through a 0.45 µ nylon disc filter. Then these samples were analyzed spectrophotometrically at 247 nm using an UV/Vis spectrophotometer (IRMECO U2020, Germany) to determine the FLB contents. All the experiments were carried out in triplicate to obtain mean values.

Drug release kinetics is assumed to reflect different release mechanisms of controlled release matrix systems. Therefore, four kinetic models were applied to analyze the *in vitro* dissolution data to find the best-fitting model. To ascertain the mode of drug release from these formulations, dissolution data were fitted to a zero-order model (the cumulative percentage of drug released versus time) [13, 14], a first-order model (Ln of the cumulative percentage of drug released versus time) [15], the Higuchi model (the cumulative percentage of drug released versus the square root of time) [16] and the Korsmeyer-Peppas model (Ln of the cumulative percentage of drug released versus the Ln of time) [17]. The Korsmeyer-Peppas model gives the value of the release exponent (n) which represents the mode of drug release, i.e. if $n \leq 0.45$, the release of the drug is diffusion controlled (Fickian); if $0.45 < n > 0.89$, the release of the drug is diffusion and erosion controlled (anomalous or non-Fickian); and if $n \geq 0.89$, the release of the drug is zero-order or case II transport.

In all cases, data analysis was performed by applying a one-way ANOVA with a probability of $p < 0.05$ set as statistically significant [13].

# Results and Discussion

## Recovery of Microspheres

The flurbiprofen microspheres were prepared by the solvent evaporation method. The microspheres were off-white in color and spherical in shape. The method used for the preparation of the

microspheres was advantageous for the entrapment of water-insoluble drugs.

The recovery of the microspheres was found to be related to the stirring speed, the concentration of surfactant and the HPMC concentration in the external water phase. Stirring speed proved to be a dominating factor, as it provided the energy to disperse the organic phase in external water phase. In the experiment, stirring speed was increased from 500 to 1000 rpm. The experimental results demonstrate that a high stirring speed yields smaller microspheres because the emulsion can break up into smaller droplets at a higher input power. Hence, the stirring speed had to be optimized in order to obtain a high yield of microspheres. All of the emulsions were produced at 500 rpm. Similar results have also been found in the literature [18] which demonstrated that a high stirring speed yielded smaller microspheres due to the emulsion breaking up.

The surfactant (tween-80) at a concentration of 0.5% w/v made the hydrophobic material wettable and formed microspheres of the appropriate shape. An attempt was made to prepare microspheres without a surfactant, but failed: An aggregated cake formed during the process. This caking was due to a high interfacial tension between the hydrophobic material and the aqueous external phase. This tendency to aggregate was reduced by using adequate quantities of surfactant in the external phase [20].

The percentage recovery of FLB in the microspheres varied from 35.2±5.5% to 87.9±4.2% (Table 1). The recovered weight of the microspheres significantly decreased ($p < 0.05$) with the increase in HPMC concentration, and significantly increased ($p < 0.05$) with the increase in EC quantity (Table 1). The low recovery with HPMC could be due to the loss of the drug to the external aqueous phase during emulsion development, as in a previous investigation [19].

## Entrapment Efficiency

The entrapment efficiency (%) of FLB in the microspheres varied from 61.6±4.4% to 88.6±2.7% (Table 1). The HPMC concentration in the external water phase is known to be a key factor influencing the entrapment efficacy of FLB [20]. The formulations containing larger concentrations of HPMC (F1–F3) have significantly higher drug entrapment efficiency ($p < 0.05$), while the other three formulations (F4–F6) have lower efficiency. Furthermore, the gradual increase in the HPMC concentration from formulation F4 to F6 resulted in increased entrapment efficiency. The reason behind this might be the high concentration of HPMC in the aqueous phase, which retards drug loss: The results of microsphere recovery show that HPMC loss during the process of encapsulation is greater than EC loss due to the aqueous solubility of HPMC [21]. The concentration of EC has little effect on entrapment efficiency: Only a non-significant increase in entrapment efficiency ($p > 0.05$) is observed when the EC concentration is increased.

## *In vitro* Drug Release Study

*In vitro* drug release studies of all the formulations were carried out in two different pH conditions: pH 1.2 and 6.8. Although FLB is weakly acidic in nature [1], it was found that the cumulative drug release from the microsphere was retarded as the pH of the medium increased from 1.2 to 6.8. This shows that HPMC-EC combination provides better control of FLB release in basic medium than in an acidic one.

Formulations F1, F2 and F3 offered better controlled release of the drug in both acidic and basic media than other formulations. These formulations have a higher content of HPMC than EC. HPMC is a water soluble polymer, and its aqueous solubility plays a key role in the initial burst release of the drug from formulation F1, F2 and F3 [12]. HPMC, being a hydrophilic matrix former, undergoes swelling in a liquid solvent as a result of the relaxation of polymeric chains, and a jelly-like network forms around the system. This mechanical feature – a surface-hydrated viscous barricade – plays a crucial role in the whole drug release rate. Although it is desireable for a controlled release system to release the drug in zero-order kinetics, it is tremendously tricky to attain such a model, since the kinetics of release are influenced by the physico-chemical nature of the surrounding medium and by the processing factors [20]. According to a previous study [22], the drug-to-polymer ratio is one of the most important factors that affect the drug release rate from a HPMC matrix system. An enhancement of the viscosity of the HPMC gel is observed with increases in its concentration. This could be responsible for a reduction in the valuable diffusion coefficient of drug, and ultimately for a reduction in the release of drug. In the current study it was also observed that the release rate of the drug diminished with the increase in the drug-to-polymer ratio. It is postulated that upon coming into contact with water, a hydrophilic polymeric matrix like HPMC absorbs water, which causes swelling and the formation of a jelly-like layer that creates an obstacle to drug diffusion. The important processes that take place during the release of the drug from a polymeric matrix are

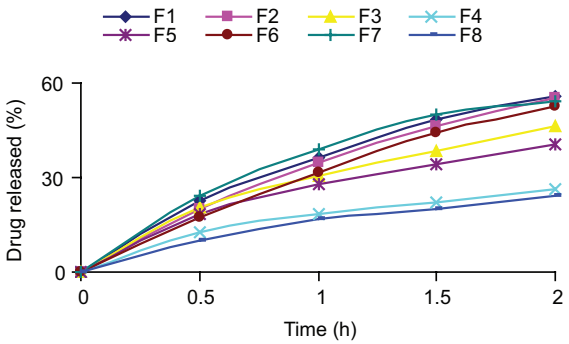


**Fig. 1.** Percentage of flurbiprofen release of all formulations at pH 1.2

**Ryc. 1.** Odsetek uwolnienia flurbiprofenu z wszystkich preparatów dla pH 1,2

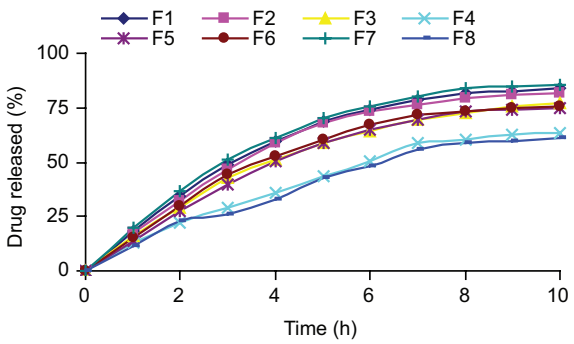


**Fig. 2.** Percentage of flurbiprofen release of all formulations at pH 6.8

**Ryc. 2.** Odsetek uwolnienia flurbiprofenu z wszystkich preparatów dla pH 6,8

**Table 2.** Release kinetics of the microspheres

**Tabela 2.** Kinetyka uwalniania mikrosfer

| Formulation (Preparat) | Dissolution Media | Zero Order Kinetics | | First Order Kinetics | | Higuchi Kinetics | | Korsemeyer-Peppas Kinetics | |
|---|---|---|---|---|---|---|---|---|---|
| | | $R^2$ | $K_o$ | $R^2$ | $K_1$ | $R^2$ | $K_H$ | $R^2$ | n |
| F1 | pH 1.2 | 0.962 | 27.6 | 0.697 | 1.764 | 0.987 | 39.98 | 0.730 | 0.295 |
| | pH 6.8 | 0.882 | 8.104 | 0.541 | 0.290 | 0.972 | 29.57 | 0.607 | 0.305 |
| F2 | pH 1.2 | 0.975 | 27.34 | 0.716 | 1.771 | 0.978 | 39.16 | 0.748 | 0.397 |
| | pH 6.8 | 0.878 | 7.965 | 0.548 | 0.291 | 0.967 | 29.04 | 0.612 | 0.304 |
| F3 | pH 1.2 | 0.948 | 22.06 | 0.684 | 1.658 | 0.995 | 32.31 | 0.708 | 0.462 |
| | pH 6.8 | 0.914 | 7.472 | 0.567 | 0.290 | 0.976 | 22.53 | 0.630 | 0.399 |
| F4 | pH 1.2 | 0.930 | 12.56 | 0.698 | 1.427 | 0.998 | 18.60 | 0.692 | 0.791 |
| | pH 6.8 | 0.953 | 6.417 | 0.623 | 0.289 | 0.972 | 22.52 | 0.675 | 0.589 |
| F5 | pH 1.2 | 0.939 | 19.38 | 0.684 | 1.606 | 0.997 | 28.55 | 0.701 | 0.596 |
| | pH 6.8 | 0.909 | 7.511 | 0.769 | 0.158 | 0.971 | 26.98 | 0.643 | 0.504 |
| F6 | pH 1.2 | 0.983 | 26.38 | 0.739 | 1.77 | 0.964 | 37.36 | 0.767 | 0.686 |
| | pH 6.8 | 0.890 | 7.42 | 0.558 | 0.289 | 0.972 | 26.94 | 0.618 | 0.798 |
| F7 | pH 1.2 | 0.962 | 27.6 | 0.697 | 1.764 | 0.987 | 39.98 | 0.730 | 0.295 |
| | pH 6.8 | 0.882 | 8.104 | 0.541 | 0.290 | 0.972 | 29.57 | 0.607 | 0.305 |
| F8 | pH 1.2 | 0.930 | 12.56 | 0.698 | 1.427 | 0.998 | 18.60 | 0.692 | 0.791 |
| | pH 6.8 | 0.953 | 6.417 | 0.623 | 0.289 | 0.972 | 22.52 | 0.675 | 0.689 |

water infiltration into the dry matrix, hydration of the system, gel formation of the polymer material, dissolution of the drug substance and eventually the diffusion of the dissolved drug via the resultant gel membrane. Since the transport of the drug via a polymeric matrix system is largely diffusion controlled, the Strokes-Einstein equation can be cited here, which states that the diffusion process will be slower in a more gelatinous layer.

At pH 1.2, increases in the release-retarding capacity of the polymer combination were observed with increases in the ratio of EC/HPMC (Figure 1). At pH 6.8, almost the same pattern of drug release is found. Formulations containing higher amounts of EC retarded drug release more than those with relatively lower amounts of EC, whereas those formulations with higher amounts of HPMC rapidly released the drug in basic media

(Figure 2). These results show that EC has better binding capability than HPMC. In all the formulations, the *in vitro* drug release at pH 1.2 and 6.8 is best explained by the Higuchi model release pattern, as the highest linearity is shown by the plot (Table 1, Figures 1 and 2). This means that the release of a drug from an insoluble matrix could be described as the square root of time based on Fickian diffusion [11], which represents the Higuchian kinetics. It is also evident from the results (Table 2) that the release of FLB from microspheres prepared using high quantities of HPMC occurred via Fickian diffusion ($n < 0.45$), while non-Fickian diffusion mode ($0.45 < n < 0.89$) was observed from the microspheres made using larger amounts of EC. The non-Fickian mode of transport represents two processes: diffusion and erosion, occurring simultaneously. This means that specific narrow channels are produced in the matrix due to its erosion, through which the release of the drug takes place.

The authors concluded that this study demonstrated the potential of polymers combinations in the formulation of microspheres for water insoluble drugs utilizing HPMC and EC as release-retardant materials using a simple solvent evaporation microencapsulation technique. It was observed that various physico-chemical properties of the microspheres varied in relation to changes in polymer concentrations used in the formulations. As the ratio of EC/HPMC was increased, the release rate of flurbiprofen decreased. This study shows that flurbiprofen loaded microspheres of HPMC and EC can be used for drug delivery at a constant rate.

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