ORIGINAL PAPERS

Adv Clin Exp Med 2011, **20**, 3, 343–349
ISSN 1230-025X

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Design and Evaluation of Modified Release Bilayer Tablets of Flurbiprofen

Projekt i ocena dwuwarstwowych tabletek flurbiprofenu o zmodyfikowanym uwalnianiu

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Abstract

Objectives. To design and evaluate modified release bilayer tablets of flurbiprofen.
Material and Methods. In this study, bilayer modified release (MR) tablets of flurbiprofen were formulated using ethylcellulose (EC) and polyvinylpyrrolidone (PVP) in different ratios as release retardant materials using a wet granulation method. *In vitro* release studies were done in dissolution media of varying pH i.e. pH 1.2, 4.5, 7.0 and 7.5.
Results. All tablets exhibited good physical quality with respect to appearance, content uniformity, hardness, weight variation and friability. *In vitro* dissolution data showed that increasing proportions of EC retarded whereas increasing PVP enhanced the drug release rate. The bilayer MR tablets showed an initial release of approximately 35% (i.e. 100 mg drug) in about 1 h, then sustaining the release for 12 h, ending up with 89.56% and 96.12% for formulation MR1 and MR2, respectively. The kinetic analysis of dissolution data showed that zero order release was observed in these tablets. When data was fitted to the Korsmeyer-Peppas model, a non-Fickian transport was observed with the MR tablets. A model independent approach showed that as the release rate increases, the MDT decreases, showing the retarding behavior of the non-biodegradable polymers employed in formulation development.
Conclusions. Bilayer modified release tablets of flurbiprofen can be successfully formulated using ethylcellulose and polyvinylpyrrolidone in different ratios as release retardant materials employing a wet granulation method (**Adv Clin Exp Med 2011, 20, 3, 343–349**).

Key words: ethylcellulose, polyvinylpyrrolidone, wet granulation method, non-Fickian release.

Streszczenie

Cel pracy. Zaprojektowanie i ocena dwuwarstwowych tabletek flurbiprofenu o zmodyfikowanym uwalnianiu.
Materiał i metody. W badaniu tym dwuwarstwowe tabletki flurbiprofenu o zmodyfikowanym uwalnianiu (MR) zostały stworzone z użyciem etylocelulozy (EC) i poliwinylopirolidonu (PVP) w różnych proporcjach jako środki opóźniające uwolnienie metodą mokrej granulacji. W badaniach uwalniania in vitro użyto środków rozpuszczających o różnym pH, tj. pH 1,2; 4,5; 7,0 i 7,5.
Wyniki. Wszystkie tabletki miały dobre fizyczne właściwości w odniesieniu do wyglądu, jednolitości zawartości, twardości, wahań wagi i kruszenia. W badaniach *in vitro* wykazano, że zwiększenie zawartości EC spowalniało, a zwiększenie zawartości PVP przyspieszało tempo uwalniania leku. Dwuwarstwowe tabletki MR wykazały początkowo uwalnianie ok. 35% (tj. 100 mg leku) w ciągu około 1 godz., a następnie utrzymanie rozpuszczenia przez 12 godz., kończąc na 89,56 i 96,12% dla preparatów MR1 i MR2. Analiza kinetyczna danych na temat rozpuszczania pokazała, że w tych tabletkach wystąpiło uwalnianie rzędu zerowego. Gdy dane dopasowano do modelu Korsmeyera-Peppasa, obserwowano transport masy tabletek MR niezgodny z prawem Ficka. Niezależne podejście wykazało, że w miarę wzrostu szybkości uwalniania, MDT zmniejsza się, co pokazuje opóźniające działanie nieulegających biodegradacji polimerów stosowanych w produkcji preparatu.
Wnioski. Dwuwarstwowe tabletki o zmodyfikowanym uwalnianiu flurbiprofenu z powodzeniem można produkować, stosując etylocelulozę i poliwinylopirolidon w różnych proporcjach jako środki opóźniające uwolnienie metodą mokrej granulacji (**Adv Clin Exp Med 2011, 20, 3, 343–349**).

Słowa kluczowe: etyloceluloza, poliwinylopirolidon, metoda mokrej granulacji, uwalnianie niezgodne z prawem Ficka.

Flurbiprofen is a propionic acid derivative that belongs to nonsteroidal anti-inflammatory drugs (NSAIDs). It is widely used and available as prescription medicine. The major adverse reactions with flurbiprofen are those affecting the gastrointestinal tract (GIT) including peptic and mucosal ulcer, dyspepsia, gastric bleeding resulting in treatment failures. Non compliance of patients and its short half life make it a strong candidate for sustained drug delivery [1].

Non-biodegradable polymers have been used successfully for their drug release retarding efficacy. Ethylcellulose (EC), being a water insoluble polymer, has been used previously for effectively controlling release rate of water soluble and insoluble drugs. Large doses of flurbiprofen can be incorporated in tablets with EC because of the least chances of dose dumping which may result in severe gastric and mucosal irritation. Polyvinylpyrrolidone (PVP) is a hydrophilic polymer which has been used previously alone [2] and in combination with other polymers such as PVAc [3]. EC, being an insoluble, erodable polymer, usually does not release all of the drug in the usual gastric transit time. Drug release from such a polymer can be maximized by using it in combination with other polymers or pore forming agents. PVP, being a hydrophilic polymer, swells and dissolves in dissolution media, making it a suitable candidate for combining with EC.

Varying pH conditions throughout the GIT is an important factor influencing the drug release from the dosage form. This affects the absorption of the drug from the gastrointestinal tract. Therefore it is necessary to study drug release under varying pH conditions. British Pharmacopoeia, 2007 (BP 2007) [4] gives insight into the various pH conditions at which the dissolution procedure should be conducted. Therefore dissolution studies were conducted according to BP 2007 at varying pH conditions in this study.

In this study, a model of a modified release (MR) design has been implemented. Different concentrations of EC and PVP were used to investigate their modulating effect. The MR flurbiprofen tablets were formulated by compressing the granules prepared by wet granulation. All these tablets were then evaluated in vitro by employing the usual quality control tests, especially dissolution in different simulated media.

Material and Methods

The flurbiprofen (FLB) was donated by Schazoo Laboratories, Lahore, Pakistan. Ethylcellulose (EC) and polyvinylpyrrolidone K30 (PVP K30) were purchased from Dow Chemicals-Pakistan and Fluka-Germany, respectively. All other analytical grade chemicals i.e. Avicel 101, potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid, magnesium stearate and talc were purchased from Merck, Germany. All the materials were used as such without further processing.

Preparation of Bilayer Modified Release Flurbiprofen Tablets

Bilayered matrix tablets were prepared by sandwiching a sustained release layer (core tablet), containing 200 mg flurbiprofen, between immediate release layers, containing 100 mg flurbiprofen. For the preparation of the sustained release part of the flurbiprofen MR tablets, all the ingredients were accurately weighed (Table 1). Flurbiprofen, EC and PVP were mixed together for 30 min using a mortar and pestle. A damp mass was prepared by using isopropyl alcohol (IPA) as a wetting agent to facilitate the adherence of powder particles [5]. The damp mass was pressed through a screen (mesh size 8) to prepare granules. The granules were dried in a thermostatically controlled oven at 80°C and passed through a screen of mesh size 18. After dry screening, magnesium stearate and talc were added to improve the flow of granules in the hopper to die cavity and to prevent the adhesion of the formulation to punches. Granules were compressed using a single punch tablet machine, using round shaped concave punches to produce sustained release core tablets (A_1, A_2, A_3).

Ethylcellulose retarded the release significantly so formulation A1 was further modified (FLB1-FLB5) by varying the amount of ethylcellulose and PVP in 5 different ratios (Table 2).

Table 1. Composition of different ingredients of flurbiprofen preliminary sustained release tablets

Tabela 1. Skład różnych składników tabletek flurbiprofenu o wstępnie przedłużonym uwalnianiu

Formulation No.	Flurbiprofen mg	Ethylcellulose mg	Poly Vinyl Pyrrolidone mg	Magnesium Stearate mg
A_1	200	50	5	5
A_2	200	50	10	5
A_3	200	50	15	5

Table 2. Composition of different ingredients of flurbiprofen final sustained release tablets (core tablets)

Tabela 2. Skład różnych składników tabletek flurbiprofenu o końcowo przedłużonym uwalnianiu (rdzeń tabletki)

Formulation No.	Flurbiprofen mg	Ethyl- cellulose mg	Poly Vinyl Pyrrolidone mg	Lactose mg	Magnesium Stearate mg	EC : PVP
FLB1	200	49.5	5.5	60	5	9 : 1
FLB2	200	38.5	16.5	60	5	7 : 3
FLB3	200	27.5	27.5	60	5	5 : 5
FLB4	200	16.5	38.5	60	5	3 : 7
FLB5	200	5.5	49.5	60	5	1 : 9

The immediate release part of the flurbiprofen MR tablets was also prepared by the wet granulation procedure using starch paste as binding agent. Flurbiprofen (100 mg) and starch (125 mg) were accurately weighed and mixed using a mortar and pestle. The damp mass was prepared using starch paste. The wet mass was pressed through a screen (mesh size 8) to prepare granules. The granules were dried in a thermostatically controlled oven at 80°C and then granules were passed through a screen (mesh size 18). Sodium starch glycolate (12.5 mg) was added extragranularly. After dry screening, magnesium stearate (5 mg) and talc (7.5 mg) were added [2]. These granules were compressed using a single punch tablet machine with round shaped concave punches by first making a floor bed of immediate granules then placing the core tablet and then spreading another layer of immediate granules over it. This process was done manually. Finally, the bi-layered MR flurbiprofen tablets (MR1 and MR2) were prepared by sandwiching a sustained release layer (FLB3 and FLB4 in MR1 and MR2, respectively) between immediate release layers. For final MR formulations MR1 and MR2, FLB3 and FLB4 were selected respectively based on their maximum sustaining effect on drug release.

Table 3. Various kinetic parameters of all formulations

Tabela 3. Różne wskaźniki kinetyczne wszystkich preparatów

Formulation Code	Zero Order Model	First Order Model	Higuchi Model	Korsmeyer-Peppas Model		MDT (h)
	R^2	R^2	R^2	R^2	N	
A1	0.971	0.9435	0.8944	0.9578	2.6036 (Super case II Transport)	18.48
A2	0.9922	0.8539	0.7811	0.9254	1.5443 (Super case II Transport)	16
A3	0.9632	0.941	0.8937	0.9529	1.4939 (Super case II Transport)	14.5
FLB1	0.986	0.9787	0.9533	0.9812	1.583 (Super case II Transport)	9.6
FLB2	0.9919	0.9778	0.957	0.9588	1.8645 (Super case II Transport)	8.61
FLB3	0.9844	0.9673	0.9606	0.9458	1.4529 (Super case II Transport)	6.77
FLB4	0.9637	0.9495	0.974	0.9679	1.5075 (Super case II Transport)	6.01
FLB5	0.971	0.9252	0.96	0.9739	1.6598 (Super case II Transport)	4.98
MR2	0.9747	0.9625	0.9734	0.9423	0.5079 (Non Fickian Transport)	4.83
MR1	0.9592	0.926	0.9741	0.9489	0.5472 (Non Fickian Transport)	4.12

Evaluation of Formulations

The flow characteristics (angle of repose) of formulated granules, weight variation, hardness, friability and dimensional measurements of prepared tablets were measured as directed previously [6]. Formulation assays, disintegration and dissolution tests were also performed for all formulations.

Dissolution Test

A dissolution test was carried out in apparatus II (Paddle apparatus) by the half change method, according to BP 2007, for studying the release of flurbiprofen for 12 h at different pH. This simulated the pH of almost the entire GIT. The temperature of the medium was kept constant at 37°C ± 0.5°C and rotation speed was 50 rpm. The study was carried out at increasing pH as follows:

0–2 h → pH 1.2
2–3.5 h → pH 4.5
3.5–5.5 h → pH 7.0
5.5–12 h → pH 7.5

The study was conducted for first 2 h in HCl buffer pH 1.2 (900 ml), then half the volume (450 ml) of this was replaced by phosphate buffer pH 7.5 to attain pH 4.5. After a further 1.5 h, half of the medium was replaced with phosphate buffer pH 7.5 and the pH was adjusted to 7.0. After a further 2 h, half of the medium was again replaced with phosphate buffer pH 7.5 and the pH was adjusted to 7.5. All pH adjustments were made with 2M HCl and 2M NaOH solutions [4].

At definite time intervals, a 3 ml sample was withdrawn, further diluting it to 20 ml and analyzed by a UV spectrophotometer (Shimadzu 1601, Japan) at 247 nm for flurbiprofen contents [4]. Each time, the sample withdrawn was replaced by fresh dissolution medium and the pH was rechecked. Dissolution of each formulation was done in triplicate and the mean of these values were taken.

Preparation of Calibration Curves for Estimation of Flurbiprofen During Dissolution

Since there was significant variation in pH conditions during dissolution, it was necessary to make separate calibration curves for each of these pH variations for accurate determination of flurbiprofen contents at a specific pH condition [7]. The values of linearity are given below:

In HCl buffer of pH 1.2, Slope = 0.0857, Intercept = 0.1202 and $R^2 = 0.9992$.

In pH 4.5 phosphate buffer solution, Slope = = 0.0865, Intercept = 0.1200 and $R^2 = 0.9990$.

In pH 7.0 phosphate buffer solution, Slope = = 0.0865, Intercept = 0.1245 and $R^2 = 0.9991$.

In pH 7.5 phosphate buffer solution, Slope = = 0.0876, Intercept = 0.1336 and $R^2 = 0.9995$.

Kinetic and Mechanistic Analysis of Drug Release Pattern

The kinetic and mechanistic analysis of the drug release pattern was conducted using various model dependent (Zero order, First order, Higuchi and Korsmeyer-Peppas Model) and model independent [mean dissolution time (MDT) determination] approaches as mentioned previously [8].

Statistical Analysis

Analysis of variance (ANOVA) was used to determine the differences between the calculated parameters using SPSS, version 12.0. The level of significance was set at 0.05.

Results and Discussion

The granules prepared for MR tablets showed good flow characteristics because their respective angle of repose lies within the pre-determined acceptable range. The MR tablets showed acceptable hardness and friability (< 1%) which is in accordance with the limits specified by BP 2007. The MR tablets showed weight variation within allowed limits (5%) and none of the tablets deviated more than 5% as specified by BP 2007. While the thickness and width of all tablets was approximately 5.90 ± 0.13 mm and 13 ± 0.13 mm, respectively. The drug content assay of the MR tablets was 300 ± 0.95 mg.

The *in vitro* sustained release of flurbiprofen from the tablets prepared as above was examined by performing dissolution tests under the following conditions: paddle method, pH 1.2, 4.5, 7.0, 7.5, dissolution medium volume 900 ml and then different models were applied to analyze the dissolution data.

Ethylcellulose is an inert hydrophobic polymer. Its diverse properties, like nontoxic, good compression and stability during storage, make it suitable for designing sustained release devices [9]. It is widely used to control dissolution rate from sustained release preparations [10]. It has been used as a matrix former for both water soluble and sparingly soluble drugs [11]. The MR tablets prepared with EC as a matrix former remained intact during and after dissolution which is in agreement with previous work [12].

All the preparations i.e. A1, A2, A3, FLB1 to FLB5, MR1 and MR2 were subjected to a dissolution test at varying pH. It is evident from the dissolution data that the total amount of the drug released after 12 h is 29.06, 34.33 and 37.78% from formulations A1, A2 and A3, respectively, which exhibit significantly ($p < 0.05$) different release behavior among these formulations. Overall drug release is slow due to the effect of EC but with the increasing concentration of PVP, the amount of the drug released increases (Fig. 1) which is attributed to the swelling and then dissolving of the PVP leading to the formation of pores and ultimately enhancing release of the drug. The initial slow release of the drug at a low concentration of EC is due to the slightly acidic nature of the drug i.e. flurbiprofen has a lower pKa value so it is less soluble in acidic pH, i.e. 1.2 later, however with the increasing pH, drug release also increases [9]. Also, the MDT (Table 3) for these three formulations validates the result that as the amount of PVP is increased, MDT decreases i.e. the retarding effect of EC is decreased, thus confirming these findings.

If the concentration of EC is decreased, keeping the total amount of polymer at a constant level (increasing PVP level), faster release of flurbiprofen occurs because of the lesser amount of EC, which exhibits a more pronounced effect of PVP (Fig. 2). It is evident from dissolution data that with the increase of PVP in the formulations, the rate of drug release is significantly ($p < 0.05$) increased attributing to the effect of PVP i.e. first swelling and then dissolving leading to the formation of pores and enhancing the release of the drug (53.89, 63.85, 82.85, 93.84% in 12 h for FLB1 to FLB4 and 99.99% in 10 h for FLB5). The results are in accordance with the MDT values (Table 3) of 9.6, 8.61, 6.77, 6.01 and 4.98 h for FLB1 to FLB5 respectively, clearly reflecting the release retarding behavior of the polymer combinations used.

The dissolution test of bilayer flurbiprofen MR tablets with a sustained release core and the immediate release coat shows that there is an initial rapid release of the drug attributed to the dissolution of the immediate release portion of the novel dosage form resulting in a release of 35% of the drug (approximately) in 2 h, which is equivalent to the dose of the immediate release part i.e. 100 mg (Fig. 3). After this, the sustained portion of the novel dosage form starts to release the drug in a controlled manner ending up with 89.56 and 96.12% release from MR1 and MR2 respectively, in 12 h, fulfilling the objective of the MR dosage form. The results are in accordance with the MDT values (Table 3) of 4.83 and 4.12 h for MR1 and MR2 respectively, clearly reflecting the retarding behavior of the polymer combinations, that is, the release increases with the decrease in retarding behavior.

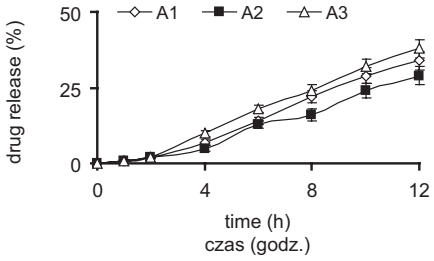

Fig. 1. Effect of the increased concentration of PVP with a constant amount of EC on dissolution profiles of different sustained release formulations A1, A2, A3

Ryc. 1. Wpływ zwiększonej zawartości PVP ze stałą zawartością EC na profil uwalniania różnych preparatów o przedłużonym uwalnianiu A1, A2, A3

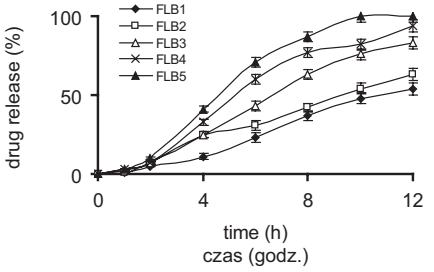

Fig. 2. Effect of increased concentration of PVP with decreased amount of EC on dissolution profiles of different sustained release formulations FLB1 to FLB5

Ryc. 2. Wpływ zwiększonej zawartości PVP ze zwiększoną zawartością EC na profil uwalniania różnych preparatów o przedłużonym uwalnianiu FLB1 do FLB5

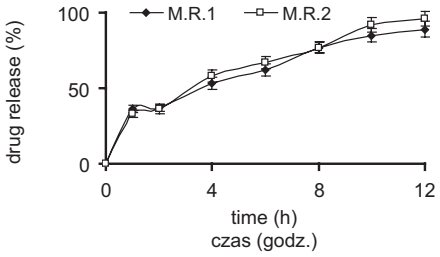

Fig. 3. Dissolution profiles of modified release tablets M.R.1 and M.R.2

Ryc. 3. Profil rozpuszczanie tabletek o zmodyfikowanym uwalnianiu MR1 i MR2

EC possesses a plastic and hydrophobic property which allows the release of the drug into the dissolution media through pores and cracks formed in the EC matrix. Flurbiprofen is a weakly acidic drug with a lower pKa, so the initial burst effect of the drug is minimized because of its less solubility in acidic media but with the increasing pH the release increases. This same effect has been observed by others [13].

The mechanism of release patterns of modified release flurbiprofen tablets as described earlier were then analyzed by employing Zero order, First

order, Higuchi and Korsemeyer-Peppas model (Table 3). Formulation A_1, A_2 and A_3 showed a zero order release profile with R^2 values in a range of 0.9632–0.9922 with almost linear curves; while for FLB1–FLB5, R^2 values ranged between 0.9637–0.9919. When the data was fitted to a Korsemeyer-Peppas equation, super case II transport was observed for FLB1–FLB5, showing that release is dependent on diffusion, relaxation and erosion of the polymer, with "n" value greater than 0.95 in all formulations. The MR1 and MR2 tablets showed the typical behavior of a controlled release dosage form by giving immediate release (approximately 35%) immediately which is an initial dose for the theoretical achievement of peak plasma concentration and then controlling the release and sustaining the effect of flurbiprofen for 12 h, giving R^2 values of 0.9872 and 0.9793 respectively, showing that bilayer MR tablets follow zero order release.

Since MDT shows the drug release retarding efficiency of polymers used in a formulation, it was therefore used for the comparison of release profiles of different formulations [3]. The values of MDT changed with the change in polymer ratio (EC to PVP) but with constant total polymer contents (Table 3). In this study, it was also found that increasing the level of EC at the same EC to PVP ratio resulted in increasing MDT values whereas increasing the amount and ratio of PVP in the formulations resulted in decreasing MDT. This finding suggested that higher levels of EC in the formulations resulted in increased retarding efficacy and higher levels of PVP led to decreased release retarding efficacy. This finding is in accordance to the previous finding [14].

On the basis of this study, it is concluded that a model of sustained zero order release formulation with a loading dose and later maintenance dose to sustain drug plasma concentration was successfully implemented on the modified release flurbiprofen tablets. Different combinations of the polymers EC and PVP at different ratios showed a significant release retarding behavior. The investigations showed that all the combinations of EC and PVP were able to retard the release of the flubiprofen for a prolonged period of time of almost 12 h, except flurbiprofen 5 which released the entire drug in 10 h.

In-vivo study of modified release tablets of flurbiprofen should be done to evaluate various pharmacokinetic parameters and to develop IVIV correlations. The pH independent release study of flurbiprofen can also be done using different weak basic salts to minimize the effect of the varying pH of the GIT. Low solubility and high absorption of flurbiprofen in the stomach offers a promising opportunity to prepare floating tablets of flurbiprofen and development of IVIV correlations.

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Conflict of interest: None declared

Received: 26.11.2010
Revised: 20.04.2011
Accepted: 2.06.2011