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Research paper

The effect of polymer blends on release profiles of diclofenac sodium from matrices

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Abstract

The purpose of this study was to evaluate the effect of polymer blends on the in vitro release profile of diclofenac sodium. Several controlled release matrices of diclofenac sodium with different proportions of hydroxypropyl methylcellulose (HPMC; viscosity grade 60 and 500 mPa.s), carbopol 940 and lactose as a water soluble filler were prepared. The results showed that when HPMC (viscosity grade 60 mPa.s) alone was used as matrix former, diclofenac sodium was released fast but the release rate became slower with HPMC (viscosity grade 500 mPa.s) at higher polymer/drug ratios (more than 0.8:1). However in lower polymer/drug ratios (lower than 0.7:1) the release rate still was fast. The results showed that carbopol can extend the release time appreciably but the release profiles had considerable fluctuations, and drug release in first hours was slow but increased appreciably with time at the end of profiles. When an appropriate blend of HPMC (viscosity grade 60 or 500 mPa.s) and carbopol 940 was used, the drug release became more uniform and its kinetic approached to zero order and release fluctuations were diminished. The results with these polymer blends showed that it is possible to reduce the total amounts of polymer in each formulation. According to kinetic analysis data, drug release from these matrix tablets did not follow Fick's law of diffusion and the results were in agreement with the earlier reports.

Keywords: Diclofenac sodium; Matrices; Hydrophilic polymer; Carbopol; Hydroxylpropyl methylcellulose

1. Introduction

Diclofenac sodium is a potent nonsteroidal anti-inflammatory drug which has anti-inflammatory, analgesic and antipyretic properties. It is used for the treatment of degenerative joint diseases such as rheumatoid arthritis, osteoarteritis, and ankylosing spondilitis. Diclofenac sodium is rapidly dissolved in intestinal fluid and reaches its maximum blood concentration (C_{max}) within 30 min and is metabolized mainly by hepatic hydroxylation and subsequent conjugation [1]. In healthy human volunteers, mean plasma clearance of diclofenac sodium was 16 l/h and mean elimination half-life of the terminal phase was 1.2–1.8 h [2]. In order to diminish diclofenac sodium gastrointestinal irritation, which is a common problem with all nonsteroidal anti-inflammatory agents, effective enteric-coated dosage forms have been developed. However, it was previously reported that food effectively delays the absorption of the drug which causes a non-reproducible pharmacokinetic profile, and the drug has no immediate therapeutic effect [3]. The benefits of administering diclofenac sodium in a controlled release dosage form have been demonstrated by Fowler et al. [2]. In several investigations the feasibility of development of a sustained release form for diclofenac sodium was studied. The main activities in this regard were preformed around the designing of a matrix type formulation [4–8] which appear to be a very attractive approach from process development and scale up points of view. Different polymers such as hydroxypropyl methylcellulose (HPMC), sodium carboxy methylcellulose, and ethylcellulose were used in these studies. HPMC is the most important hydrophilic polymer used for the preparation of oral controlled release drug delivery systems [9–11]. One of the most important characteristics of HPMC is the high swellability, which has a considerable effect on the release kinetics of the incorporatrd drug [12–14]. In vitro drug release of water-soluble drugs, such as diclofenac sodium, is controlled by

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diffusing out of the gel layer, which is produced by hydration of polymer in the presence of biological fluids [14,15]. For soluble drugs, the most important factor in the selection of a polymer matrix is the medium infiltration rate. With a constant drug load, the medium infiltration rate can be controlled by changing the polymer content of matrix or introducing various polymers [14].

The aim of this study was to evaluate the effects of polymer blends in rate and kinetics of diclofenac release from matrix tablets. In this regard, blends of HPMC (60 mPa.s)- carbopol 940 and HPMC (500 mPa.s)- carbopol 940 were used to adjust the medium infiltration rate through the matrix tablets and controlled hydration, gelation or swelling process of matrix. The effects of various ratios of these polymers with lactose as a water-soluble excipent also were studied.

2. Materials and methods

2.1. Materials

Diclofenac sodium was obtained from Sobhan Pharm. Co. (Iran). Two viscosity grades of HPMC (60, 500 mPa.s) were supplied by Daroupakhsh Pharm. Co. (Iran). The carbopol 940 was from BF Goodrich. All other chemical and reagents were pharmaceutical grade.

2.2. Formulation of diclofenac sodium matrices using HPMC 60 or 500 mPa.s or carbopol

Diclofenac sodium matrices were produced by mixing diclofenac sodium with lactose, HPMC 60 or 500mPa.s or carbopol 940 and magnesium stearate and then passing the mixture through a No. 20 sieve. The granules were compressed to tablets with a 10 mm punch and die using a single punch Erweka machine (formulation A1–A11).

2.3. Formulation of diclofenac sodium matrices using HPMC and carbopol

These matrices were produced by mixing diclofenac sodium with lactose, HPMC (60 mPa.s) – carbopol 940 or HPMC (500 mPa.s) – carbopol 940 and magnesium stearate and then passing the mixture through a No. 20 sieve. Finally the granules were compressed to tablets as mentioned above (formulation A12–A19). The constituents of each formulation are presented in Table 1. The hardness of tablets in all formulations was adjusted in about 5–7 kgf.

2.4. Dissolution studies

Tablets of each formulation were subjected to dissolution testing using a USP XXIII paddle- type dissolution apparatus, in 900 ml buffer solution with pH of 1 and 6.8. The rate of stirring was 50 ± 1 rpm. The amount of diclofenac sodium was 100 ± 5 mg in all formulations. The dissolution medium temperature was maintained at 37 ± 1 °C. At each sampling interval, 5 ml of the dissolution medium was withdrawn and an equal volume of fresh buffer solution was replaced. Diclofenac sodium was determined at 275 nm using a double beam UV/VIS Spectrophotometer (Cecil CE). Experiments were performed for six tablets in each formulation and mean values were obtained.

2.5. Analysis of dissolution data

Numerous mathematical models describing drug release from HPMC-based controlled release formulation has been

Table 1
The ingredients of various formulations of diclofenac sodium matrices, each of these formulations contains 100 mg diclofenac sodium

Code of formulation	HPMC 60 mPa.s (mg)	HPMC 500 mPa.s (mg)	Carbopol 940 (mg)	Lactose (mg)	Magnesium stearate(mg)
A1	50	–	–	50	2
A2	60	–	–	50	2.1
A3	70	–	–	50	2.2
A4	–	50	–	40	2.2
A5	–	60	–	30	2.2
A6	–	70	–	50	2
A7	–	80	–	50	2.1
A8	–	90	–	50	2.2
A9	–	–	50	50	2
A10	–	–	70	50	2.2
A11	–	–	30	70	2
A12	–	–	40	60	2
A13	50	–	20	50	2.2
A14	60	–	10	50	2.2
A15	55	–	15	50	2.2
A16	–	60	10	50	2.2
A17	–	55	15	50	2.2
A18	–	50	20	50	2.2

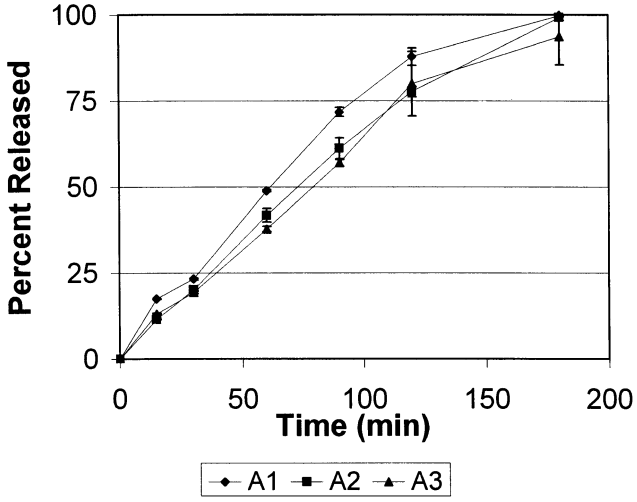

Fig. 1. The effect of various ratios of HPMC 60 mPa.s on the release profile of diclofenac sodium from matrices.

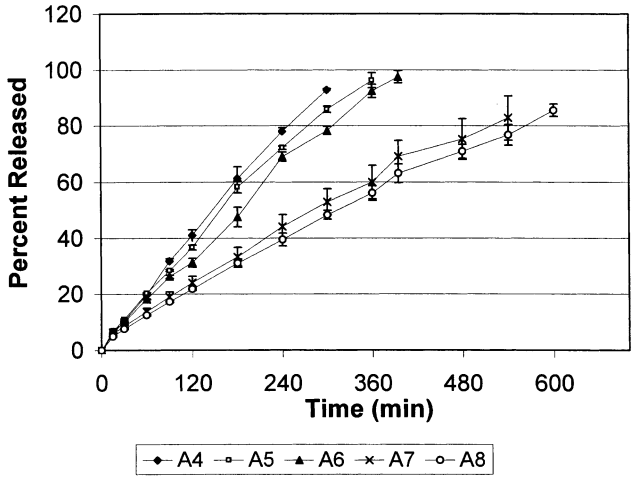

Fig. 2. The effect of various ratios of HPMC 500 mPa.s on the release profile of diclofenac sodium from matrices.

developed. But probably the most important aspect when developing new pharmaceutical products or evaluating drug release mechanisms is suitable predictive ability and accuracy of the model. In many cases, the use of simple empirical or semi-empirical models such as classical Higuchi equation and the so called power law is fully sufficient [9].

Dissolution data were analyzed using the equation proposed by Ritger and Peppas [16] to describe the mechanism of drug release from matrices.

$$\frac{M_t}{M_\infty} = Kt^n$$

Where M_t corresponds to the amount of drug released in time t, M_∞ is the total amount of drug that must be released at infinite time, K is a constant and 'n' is the release exponent indicating the type of drug release mechanism. If n approaches to 0.5 the release mechanism can be Fickean. If n approaches to 1 the release mechanism can be zero order and on the other hand if $0.5 < n < 1$ non- Fickean transport could be obtained [16].

The cumulative percentage of released drug versus time data was assessed for zero order release kinetic. The logarithm of the amounts of the remaining drug must be released versus time data were assessed for first order kinetic and the data of cumulative percentage drug release versus square root of time data were used to evaluate for Higuchi model kinetic.

Table 2
Correlation coefficients for release data of diclofenac sodium from different formulations after fitting to zero order, first order, Higuchi and Peppas Models

Code of formulation	Zero order model	Higuchi model	First order model	Peppas model	n[a]
A1	0.9983	0.9682	0.9617	0.9990	0.9389
A2	0.9958	0.9749	0.9537	0.9984	0.8641
A3	0.9973	0.9736	0.9381	0.9970	0.8551
A4	0.9942	0.9827	0.9889	0.9980	0.7696
A5	0.9975	0.9799	0.9141	0.9979	0.7768
A6	0.9708	0.9793	0.9244	0.9873	0.7721
A7	0.9881	0.9756	0.9248	0.9969	0.8944
A8	0.9854	0.9695	0.9777	0.9309	0.8482
A9	0.9638	0.8800	0.8950	0.9601	1.0803
A10	0.9435	0.8632	0.9154	0.9541	0.9188
A11	0.9935	0.9251	0.7916	0.9901	1.1478
A12	0.9975	0.9799	0.9141	0.9979	0.7768
A13	0.9942	0.9449	0.9622	0.9911	0.9222
A14	0.9936	0.9488	0.8726	0.9939	0.8612
A15	0.9936	0.9548	0.9523	0.9957	0.8764
A16	0.9943	0.9460	0.9445	0.9831	0.8235
A17	0.9981	0.9776	0.9932	0.9964	0.7151
A18	0.9957	0.9607	0.9853	0.9907	0.7679

[a] 'n' is release exponent in Peppas equation [9]

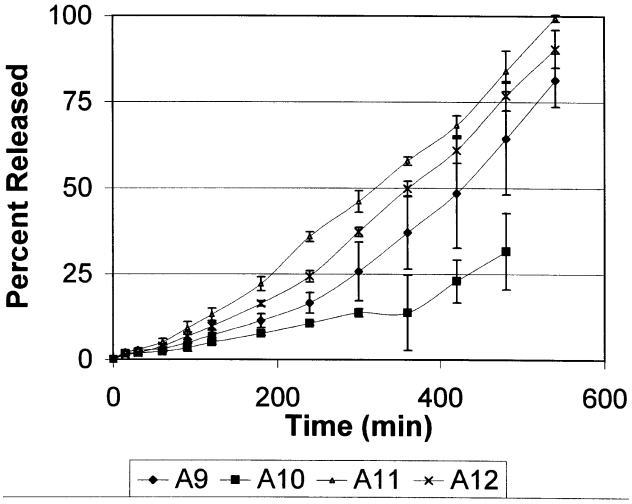

Fig. 3. The effect of various ratios of carbopol 940 on the release profile of diclofenac sodium from matrices.

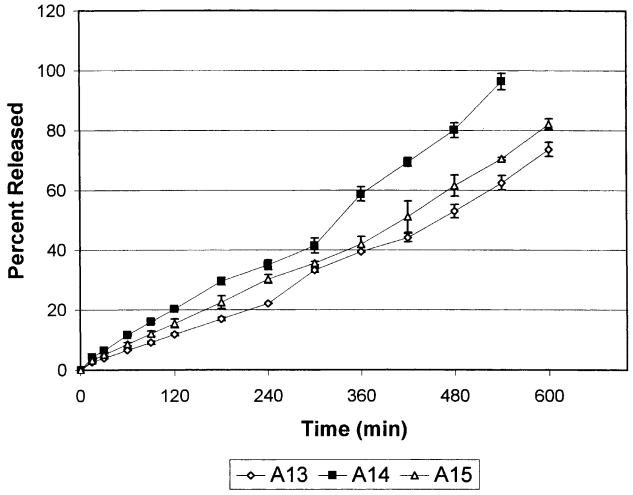

Fig. 4. The effect of various proportions of carbopol 940–HPMC 60 mPa.s on the release profile of diclofenac sodium from matrices.

3. Results and discussion

Early dissolution studies revealed that diclofenac sodium did not have appreciable solubility at pH 1 dissolution medium because of the weak acidic property of diclofenac sodium even after 2 h. In this regard dissolution profile of diclofenac sodium at this pH was not shown.

Figs. 1 and 2 show the effect of various HPMC (60 mPa.s)/drug and HPMC (500 mPa.s)/drug ratios on dissolution profiles respectively. With higher ratios, the rate of drug release were decreased. Also an increase in polymer viscosity grade had the same effect. From these figures it is apparent that these polymers can not separately produce an appropriate release rate. The results showed that only HPMC (500 mPa.s) in high polymer/drug ratio can extend the release time up to 10 h. In spite of prolonged release time, the correlation coefficient does not fit to zero order kinetic (Table 2).

Fig. 3 shows the effects of carbopol 940 alone on the release pattern of diclofenac sodium. It is apparent that this polymer in low polymer/drug ratio can sustain the drug release, but the pattern of release is not suitable. From this figure, it is obvious that the release of diclofenac sodium in early hours is very slow and after approximately 4 h the rate

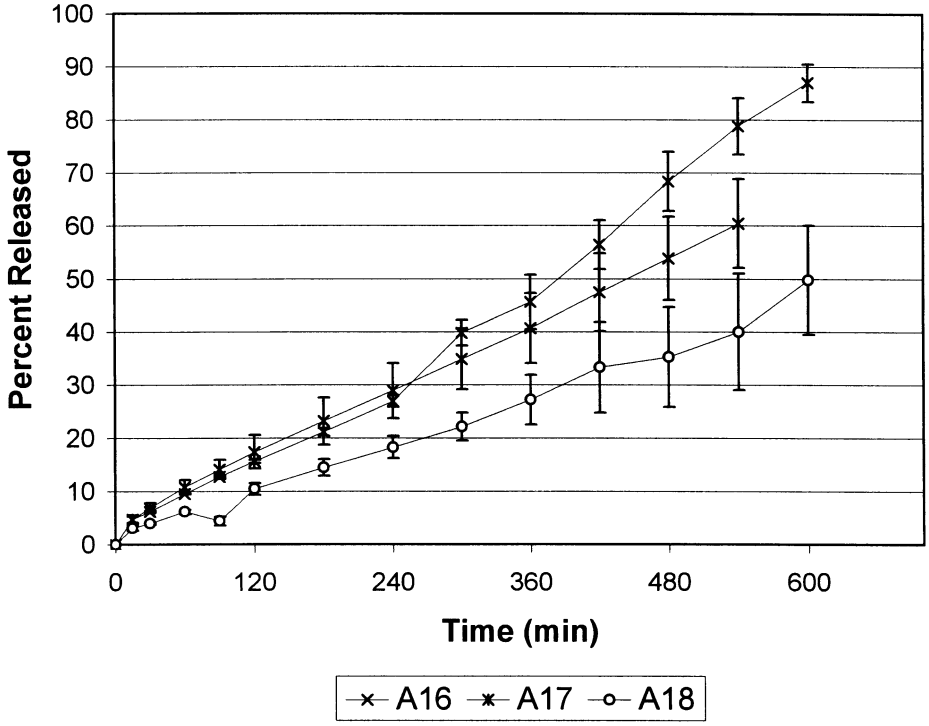

Fig. 5. The effect of various proportions of carbopol 940- HPMC 500 mPa.s on the release profile of diclofenac sodium from matrices.

of release appreciably increase. Therefore, these formulations can not be practically useful. To correct the release pattern of diclofenac sodium from matrices, blends of HPMC and carbopol 940 were used as a matrix former. The release profile of drug from these formulations are shown in Figs. 4 and 5. The release fluctuations in these formulations were decreased and the kinetic of diclofenac release approached to zero order kinetic (A17). These figures show that the blends of carbopol 940- HPMC (60 mPa.s) are better than carbopol 940- HPMC (500 mPa.s) and in these formulations the release fluctuations are minimum. These data showed that a combination of anionic polymer (carbopol 940) with nonionic HPMC produce a synergetic increase in viscosity. This is probably due to the stronger hydrogen bonding between the carboxyl groups of carbopol and hydroxy groups of HPMC, leading to stronger cross-linking between two polymers and diminish the release fluctuations [17]. Although in this study the ratio of HPMC/ Carbopol 940 is higher than the ratios used by Rao et al. [17]. The curve fitting data for zero order, first order, Higuchi model and Peppas model are presented in Table 2. According to Fig. 3 the release rate of diclofenac sodium increase with an increase in lactose/ carbopol ratio.

4. Conclusion

The results obtained in this study confirmed that carbopol 940 can be used as a matrix former, but according to Fig. 3 drug release from this matrices at the beginning is slow and increase appreciably with time. Also when carbopol 940 was used alone the release fluctuations were considerably high and the kinetics of release did not fit to zero order model. When carbopol 940 was used with HPMC (60 or 500 mPa.s) the release data became uniform and release of diclofenac sodium increased at the beginning (Figs. 4 and 5). This behavior of HPMC and carbopol blend has been reported by Rao et al. [17]. With blend of HPMC and carbopol, it is possible to reduce the total amount of polymers in matrix tablets and minimize the size and weight of these tablets (Table 1).

Acknowledgements

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