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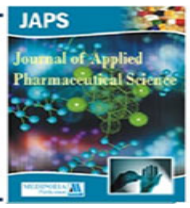

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Characterization and Evaluation of the Release Kinetics of a Model Poorly Water-Soluble and Low Dose Drug from Matrix Tablets Composed of Blends of Swellable and Erodible Polymers: Implications for Controlled and Complete Release

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ABSTRACT

The specific aim of this study was to prepare sustained release matrix tablets containing indapamide as a low dose and low water solubility model drug. The matrix formers were composed of blends of hydroxypropyl methylcellulose as a swellable polymer and methyl cellulose as an erodible polymer. The matrix tablets were prepared by the direct compression technique and they have shown robust and acceptable physical properties with a content uniformity within the acceptable limits. Lactose and microcrystalline cellulose were investigated as additives to these matrices in order to adjust and modulate the release of the drug from the matrices to achieve a release profile similar to that obtained from the reference commercial product, Natrilix®. All matrix tablets prepared with these two additives have gave a release profile that is close to zero order kinetics, however, the matrix tablets prepared with lactose gave a release profile with closer resemblance to that of the reference product with a similarity factor (F2) of 86. This is attributed to the rapid water solubility of lactose which enhanced higher erosion of the tablets, and thus, higher dissolution and diffusion of the drug. Microcrystalline cellulose is a swellable polymer where it has resulted in delayed release of the drug with time as compared to the reference product. Investigation of the mechanism of release of the drug from the matrices indicated that erosion is the dominant mechanism of drug release from these matrices.

Keywords: Indapamide, Hydroxypropyl methylcellulose, Methyl cellulose, Lactose, Microcrystalline cellulose, Sustained release.

INTRODUCTION

Controlled drug delivery systems are extensively studied mainly for the purpose of oral controlled drug delivery. The most commonly used method of modulating the drug release is to include it in a matrix system (Wise, 2000; Salsa *et al.*, 1997). Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance (Alderman, 1984).

The drug release for extended period of time, particularly for highly water-soluble drugs, using a hydrophilic matrix system is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. On the other hand, the release of poorly water-soluble drugs from such matrix systems is incomplete due to the poor water solubility and dissolution rate of the drug in the hydrophilic matrix system. The release of drugs from matrices is controlled by several factors in the formulation, and it varies depending on the properties of both drugs and the matrix forming agents (Leuner and Dressman, 2000; Mandal, 2000; Zuleger and Lippold, 2001; Michailova *et al*., 2001; Gendy et al., 2002). The phenomena involved in drug release from swellable matrices attract the attention of researchers. A detailed knowledge of the transport phenomena involved is the key pre-requisite towards the development of a reliable mathematical model useful for the prediction of the release kinetic as a function of the formulation parameters or the external conditions (Siepman and Peppas, 2001).

Various kinds of polymers have been used as matrix forming agents in controlled release preparations intended for oral administration. Hydrophilic cellulose derivatives, in particular hydroxypropyl methylcellulose (HPMC) and methyl cellulose (MC), are widely used because of their excellent properties in the manufacturing techniques of such preparation and in controlling the release of drugs (Rao *et al*., 1988; Sung *et al*., 1996). It is well known that HPMC is a swellable polymer and that MC is an erodible polymer. The physicochemical and pharmaceutical properties of HPMC and MC have been reported extensively and in details in the literature (Bonferoni *et al.*, 1995; Solinis *et al*., 1998). However, those of the mixtures or blends of these polymers have been scarcely presented (Jamzad *et al*., 2005; Chirico *et al*., 2007). The mixtures of HPMC and MC were of interest in connection with our work on controlled drug delivery systems and it is expected that the mixtures of these polymers will have some interesting properties as matrix forming agents regarding the release kinetics of poorly water-soluble drugs.

Among a lot of factors affected the release of drugs from matrices, it has been explained that swelling, erosion, and osmotic pressure were the main factors controlling the release of drugs from matrices. The release of drugs generally occurs according to two mechanisms; diffusion controlled mechanism due to swelling and solvent activated mechanism due to erosion. Usually, the release of drugs occurs by anomalous transport mechanism involving diffusion and erosion (United States Pharmacopoeia, 2000). However, the release of drugs from matrices could have some complicated patterns owing to the physicochemical properties of both the drug and the matrix forming agents.

The specific aim of this research project was to investigate the characteristics of matrices composed of blends of HPMC and MC using indapamide (IP) as a model of a low water-soluble and a low dose drug. Several formulations will be prepared and composed of IP, HPMC, and MC or from the polymers alone. The release profiles, swelling profiles, and erosion profiles form these formulations will be investigated in dissolution media and these profiles will be analyzed and characterized.

MATERIALS AND METHODS

Materials

Indapamide (IP) was a generous gift from Riyadh Pharma (Riyadh, Saudi Arabia) and its original supplier was Calao S. R. L (Italy). Hydroxypropyl methylcellulose, HPMC (K4M, K15M, and K100M) was obtained from Sigma Chemical Company (USA). Methyl cellulose (MC) was obtained from Fluka AG Chemicals (USA). Lactose and microcrystalline cellulose were obtained from FMC Corp., (USA). Magnesium stearate was obtained from Sigma Chemical Co. (USA). Natrilix® sustained release tablets were purchased from a local community pharmacy. Freshly distilled and de-ionized water was used in all experiments. All materials were of pharmaceutical grade and were used as supplied without any further treatment.

Preparation of matrix tablets

Several formulations were prepared from different blends in order to investigate different formulation variables and their effect on the release of the drug (IP) from the matrix tablets. The compaction of all blends was accomplished by direct compression. In general, the drug and the polymer blends were thoroughly mixed for 20 min using a tumbler mixer. Magnesium stearate was passed through a 0.25 mm sieve and then mixed with the initial mixture in the tumbler mixer for 10 min. All the formulations were prepared to produce matrix tablets with a target mass of 200 mg. The blends were compressed using a single station tablet press (TP60 CAPPLUS Technologies, USA) under a compression force of 2 ton ($2X10^3$ kg). The tooling and the settings of the machine were adjusted to produce similar tablets to the reference product (Natrilix®) regarding the mass, thickness, diameter, and mechanical strength or hardness. Several tablet formulations were prepared to investigate the following variables:

- The effect of various viscosity grades of HPMC. The formulations used to investigate this effect are coded F1 – F3 and are shown in Table 1.
- The effect of lactose as a release enhancer on the release of IP from the matrix tablets. The formulations used to investigate this effect are coded L1 – L4 and are shown in Table 2.
- The effect of microcrystalline cellulose as a release enhancer on the release of IP from the matrix tablets. The formulations used to investigate this effect are coded M1 – M4 and are shown in Table 3.

Table. 1: Formulations prepared with various HPMC viscosity grades.

Formulation [a]	F1	F2	F3
IP (mg)	1.5	1.5	1.5
Mg staerate (mg)	2	2	2
HPMC K4M (mg)	196.5	--	--
HPMC K15M (mg)	--	196.5	--
HPMC K100M (mg)	--	--	196.58

[a] Total tablet weight = 200 mg

Table. 2: Formulations prepared with HPMC K15M and lactose.

Formulation	IP (mg)	Mg stearate (mg)	HPMC K15M (mg)	Lactose (mg)
L1	1.5	2	196.5	--
L2	1.5	2	146.5	50
L3	1.5	2	96.5	100
L4	1.5	2	46.5	15.

Table. 3: Formulations prepared with HPMC K15M and microcrystalline cellulose.

Formulation	IP (mg)	Mg stearte (mg)	HPMC K15M (mg)	MCC*(mg)
M1	1.5	2	196.5	--
M2	1.5	2	146.5	50
M3	1.5	2	96.5	100
M4	1.5	2	46..5	150

* MCC = microcrystalline cellulose

After several preliminary studies and based on the investigations mentioned above, two final preparations were prepared and these were composed from blends of HPMC and MC in addition to lactose (formulation A) or microcrystalline cellulose (formulation B). These are formulations A and B and their compositions are shown in Table 4. These formulations were intended mainly to investigate the sustained release of the drug and to be compared to the reference commercial product (Natrilix®). The tablets produced from these formulations have been characterized for their physical properties and post-compression parameters according to the USP 24 methods [16]. Mass variations were performed on 20 tablets selected at random. Hardness of the tablets was evaluated by recording the force to fracture a tablet on a hardness tester for 6 tablets from each formulation (Coply Scientific). Friability was determined using an Erweka friability tester for 20 tablets at 100 rpm for 4 min. The thickness of the tablets was measured using a Vernier Calliper (Japan). For determination of drug content, a total of 10 tablets were weighed and powdered. A powder mass equivalent to 1.5 mg of IP was weighed, dissolved in methanol and filtered. The filtrate was collected, diluted suitably and analysed for the content of IP by using HPLC where the peak area of the samples was measured relative to an authentic standard.

Table. 4: Final tablet matrix formulations prepared from blends of HPMC K15M, MC, and lactose or microcrystalline cellulose. Total tablet weight is 200 mg.

Formulation(mg)	A	B
IP	1.5	1.5
Mg stearate	2	2
HPMC K15M	78	78
MC	26	26
Lactose	92.5	--
Microcrystalline cellulose	--	92.5

Drug release studies (in vitro dissolution studies)

Six matrix tablets from each formulation were subjected to drug dissolution test using a USP paddle type dissolution apparatus (Erweka Dissolution Tester, Germany). The dissolution medium was 900 ml of 0.05 M pH 6.8 phosphate buffer maintained at 37±0.5 °C and stirred at 50 rpm. At predetermined time intervals, samples were taken, filtered through a 0.45 µm membrane filter (Millipore, USA), and analysed for the content of IP using HPLC. After sampling, the same volume of the sample was immediately replaced by the dissolution medium. The average values of six measurements were used for the characterization of the release profiles of IP.

Swelling studies

Swelling or water uptake by the matrix tablets for each time point was studied under the same conditions as explained for the dissolution studies. Prior to the test, the tablets were weighed and then placed in the dissolution medium. At predetermined time intervals, the tablets were removed from the dissolution medium using a small manual basket, lightly patted with tissue paper, and weighed. The swelling index was calculated according to the following equation:

$$Q = (Ws / Wd) X 100$$

Where Ws is the intact weight of the swollen tablet and Wd is the dry weight of the tablet.

Erosion studies

Erosion studies were carried out on both IP containing and IP free matrix tablets. Prior to the study, the matrix tablets were weighed and then subjected to erosion test under the same conditions as explained for the dissolution studies. The matrix tablets were taken out from the dissolution medium at regular time intervals using a small manual basket, lightly patted with tissue paper, and dried in a hot air oven at 65 °C until a constant weight was achieved. The percentage of erosion was calculated according to the following equation:

$$R = (Wo – Wt / Wo) X 100$$

Where Wo is the initial tablet weight and Wt is the dry tablet weight after erosion test.

Analytical method

The drug content in the prepared tablets and the concentration of IP in the samples obtained from the release studies was determined according to the HPLC method presented by Pavdal and Bhargava with slight modification (Pavdal and Bhargava, 1993). This method has been described and validated for the chromatographic determination of IP and its degradation products. The HPLC system consisted of a Merck Hitachi L-7150 pump equipped with auto-sampler injector, a diode array detector, a solvent degasser, and an interface. The HPLC column used was 5 µm and 150 X 4.6 mm (Waters Spherisorb, VWR International Ltd., USA). The mobile phase (pH 3.1) consisted of water:acetonitrile (70:30), 0.1% triethyl amine and 0.08% phosphoric acid. The mobile phase was filtered through 0.45 µm membrane filter (Millipore, USA) and degassed by stirring under vacuum prior to use. The chromatographic conditions for the analysis were the following: the column temperature was ambient (23 – 25 °C), the detection wavelength was set at 242 nm, the injection volume was 20 µl, and the flow rate of the mobile phase was 1.5 ml/min.

RESULTS AND DISCUSSION

Figure 1 shows the influence of HPMC viscosity grade on the release of IP. A constant ratio of HPMC was used in the matrices except the viscosity grade was varied. The slowest drug release rate was observed from the formulation containing HPMC K100M. The K15M formulation exhibited higher release rate but less than the K4M formulation which showed the fastest release rate. The instantaneous release rate of the drug decreased over time for the viscosity grade series as observed from the results. This is reflected in the curvature of the percent of the drug release profile.

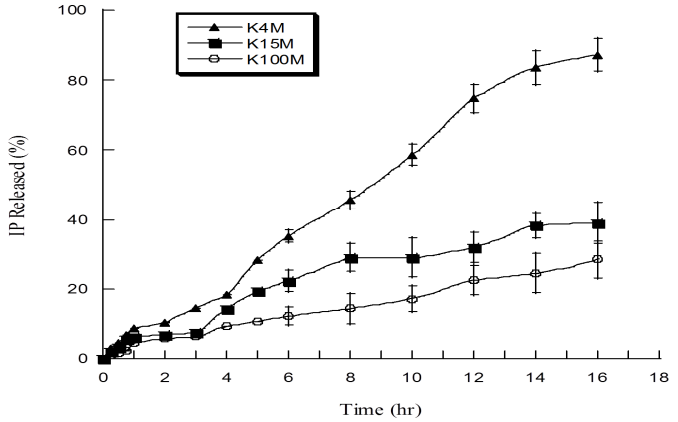

Fig. 1: Effect of using various HPMC viscosity grades on the release of IP from the matrices (pH = 6.8, n = 6).

The release mechanism from such matrices can be evaluated indirectly on the basis of the exponent 'n' in the equation proposed by Ritger and Peppas (1987). The equation is:

$M_t/M_\infty = Kt^n$

Where M_t is the amount of drug released at time t, M_∞ is the total amount of drug that is released at infinite time, K is a constant, and n is a characteristic exponent depending on the matrix geometry and the release mechanism in cases of coupling of diffusion and polymer relaxation or anomalous drug transport (Peppas and Sahlin, 1989; Siepmann and Peppas, 2001). Usually, the dissolution data up to 60% ($M_t/M_\infty < 0.6$) are analysed according to this equation in order to describe the mechanism of drug release from the matrices. According to this equation, the n value obtained for both of the matrices composed of HPMC K100M and K15M is 0.62 and 0.64, respectively. This indicates that the release of the drug is close to Fickian diffusion more than to erosion. It is expected that the dissolution of drug particles precedes matrix swelling and erosion. Then, the dissolved drug is transferred by diffusion through the water channels to the surface of the matrix and the surrounding liquid or dissolution medium. After swelling of the matrix, the release of the drug proceeds by diffusion through the gel layer or barrier formed by the cellulosic polymer. Based on these results and on several preliminary studies, it was decided to use HPMC K15M as the swellable polymer in our further experiments. The effect of lactose as a release enhancer on the release of IP from HPMC K15M matrix formulations is shown in Figure 2. Four formulations with varying ratios of HPMC K15M and lactose were prepared and evaluated for the effect of lactose on IP release. As shown in Figure 2, as the mass fraction of lactose increases in the matrix formulation, the release rate of the drug increases. The matrix formulation containing 150 mg of lactose (L4) has demonstrated rapid and complete release of the drug within almost less than 10 hours. Using lactose produces high initial release of the drug as well as higher release over time. This is expected due to the known rapid water solubility of lactose which will produce channels in the matrix that will allow the dissolution medium to penetrate the matrix and dissolve the drug more rapidly leading to enhanced diffusion of the drug out of the matrix (Jordan and Mandal, 1995; Obaidat and Obaidat, 2001).

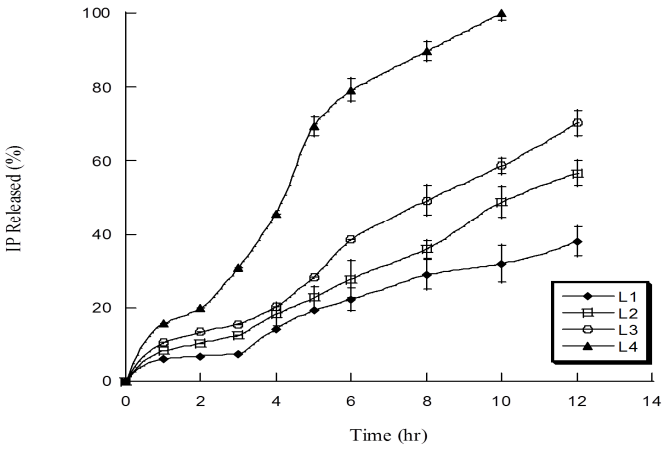

Fig. 2: Effect of lactose on the release of IP from HPMC K15M matrix formulations (pH = 6.8, n = 6).

To investigate the effect of microcrystalline cellulose as a release enhancer, four formulations containing various ratios of microcrystalline cellulose with HPMC K15M were prepared and evaluated for the release of the drug. The release of IP from these matrices is presented in Figure 3. The results indicated that none of the matrices has produced complete release of the drug over the time range of the experiment. As shown in Figure 3, the matrix formulation with the highest mass ratio of microcrystalline cellulose (M4) has demonstrated only about 60% release of the drug within 12 hours.

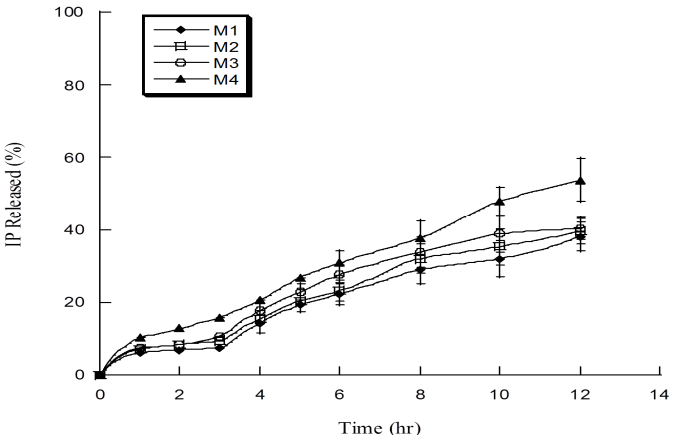

Fig. 3: Effect of microcrystalline cellulose on the release of IP from HPMC K15M matrix formulations (pH = 6.8, n = 6).

Microcrystalline cellulose produces its effect by swelling in water, and eventually, disintegration of the matrix. The presence of microcrystalline cellulose in addition to HPMC in the matrices (M2 – M4), where both of these polymers are of swellable type, has resulted in extensive swelling of the matrices. This extensive swelling is expected to produce prolonged path length for the drug through the gel layer, and consequently, significant delayed release of the drug from the matrices. Unlike microcrystalline cellulose, lactose produces its effect by the formation of pores in the matrices due to its high and rapid solubility in water compared with microcrystalline cellulose, and thus, higher extent and release rate of IP obtained from the matrices containing lactose. Based on these preliminary experiments and on comparison with the release of IP from the reference commercial product (Natrilix®), two final formulations have been prepared and their release of IP has been compared to the reference commercial product. These two final formulations were based on several preliminary experiments and have been prepared from polymer blends composed of HPMC K15M, MC, lactose, or microcrystalline cellulose. These two formulations have been coded as "A" and "B" and their components are shown in Table 4.

Prior to compression, the formulations' blends have shown good flow properties regarding the compressibility. The post-compression parameters such as hardness, friability, drug content, and tablet mass variations are shown in Table 5.

Table. 5: Post-compression parameters of the matrix tablets prepared from formulations A and B.

Formulation	A	B
Hardness (kg cm^{-2}) [a,b]	6.5 ± 0.1	7.7 ± 0.2
Friability (%) [a,c]	0.2 ± 0.1	0.4 ± 0.1
Diameter (mm) [a,b]	7.0 ± 0.0	7.0 ± 0.0
Thickness (mm) [a,b]	4.2 ± 0.03	4.3 ± 0.02
Drug content (%) [a,d]	99.94 ± 1.2	99.98 ± 1.1
Mass (mg) [a,c]	201.3 ± 1.5	202.5 ± 1.2

[a] mean ± SD, [b] n = 6, [c] n = 20, [d] n = 10

The hardness test indicated good mechanical strength of the tablets which also has been indicated by the friability test. The friability was less than 1% for all tablets. Therefore, robust physical properties have been obtained for all matrix tablets. Drug content was found to be consistent and almost uniform among the tablets (>99%) and no significant mass variability was observed in the produced tablets.

Figure 4 shows the release profiles of IP from matrices A and B containing HPMC, MC, and other components. Their release profiles were compared to that of the reference commercial product (Natrilix®) in the same figure. As it can be observed from Figure 4, the extent and release rate of IP from matrix formulation A was almost superimposed to that obtained from (Natrilix®) sustained release tablets. However, the release profile of IP from matrix formulation B was similar to that obtained from the reference product up to 10 hours of the experiment. Beyond that time, it was observed that there was a negative deviation of the release profile as compared to the reference product where the release rate seems to be somewhat slower. To clarify and to investigate the similarity between the release patterns, the release profiles of the drug were compared using the F2 metric test (FDA Guidance for Industry, 1997). According to this test, an F2 value between 50 and 100 usually indicates similarity between two dissolution profiles and a value below 50 indicates a significant difference. The release profile from formulation A was compared to the reference product and an F2 value of 86 was obtained which indicates similarity. Comparing the whole release profile obtained from formulation B to the reference product gave an F2 value of 48 indicating dissimilarity. However, comparing the release profile from formulation B to the reference product up to 10 hours of the release profile gave an F2 value of 70 indicating similarity between them until this time of release.

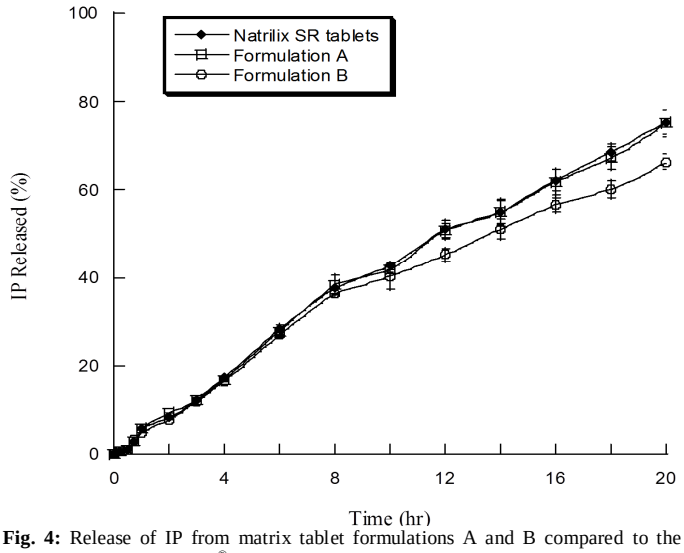

Fig. 4: Release of IP from matrix tablet formulations A and B compared to the reference product (Natrilix®) (pH = 6.8, n = 6).

The decrease in the extent and rate of release of the drug from formulation B after 10 hours could be explained by prolongation of the diffusion path length of the drug through the matrix. This formulation contains microcrystalline cellulose in addition to the other components and as indicated earlier this polymer produces its action by swelling. Before eventual erosion and disruption of the matrix, this cellulosic polymer forms a thick and a continuous gel layer with time due to its swelling. In this case, it is expected that the release of the drug will proceed in a slower fashion compared to the initial phase of the release process. It can be speculated that this phenomenon will result in less direct dissolution of the drug, and thus, less direct diffusion through the continuous gel layer or barrier.

Swelling and erosion studies have been carried out on matrix formulations A and B in an attempt to correlate the release profiles of the drug to the polymer compositions of these matrices. Figure 5 shows the swelling indices of matrix tablets A and B in phosphate buffer (pH 6.8) which is the same dissolution medium used in the drug release experiments. It can be observed from the swelling profiles in this figure that matrix tablets obtained from formulation B gave higher swelling indices compared to matrix tablets obtained from formulation A. Both formulations A and B contain the swellable polymer HPMC in their composition. The

higher swelling of matrix tablets from formulation B is contributed to the presence of microcrystalline cellulose which can enhance the swelling of the matrices. Unlike formulation B, formulation A contains lactose which is a rapidly water soluble polymer and can not significantly contribute to the swelling of the matrix. These results correlate well with the drug release results presented earlier where higher swelling of the matrix tablets obtained from formulation B with time has resulted in delayed and slower release of the drug. As explained before, the higher swelling is expected to prolong the diffusion path length of the drug through the thick gel layer that formed due to significant swelling, and hence, slower release of the drug.

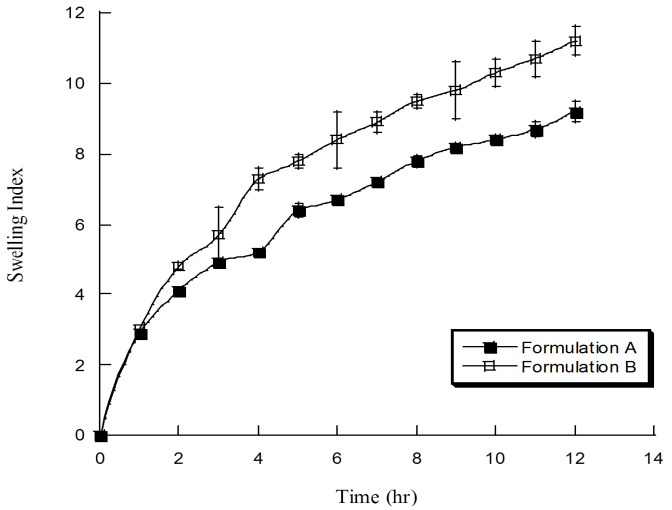

Fig. 5: Swelling profiles of matrix tablets A and B in phosphate buffer (pH 6.8, n = 3).

The results of erosion studies on matrix tablets A and B are presented in Figure 6. It can be observed from this figure that there was a rapid initial erosion of the two matrices within almost the first two hours of the experiment. This rapid initial erosion could be due to the rapid dissolution and release of the drug that is present on the surfaces of the matrices under investigation. Beyond that time, the erosion process proceeds in an almost slower rate with time, however, the percent erosion obtained from matrix tablets A was higher compared to that obtained from matrix tablets B. Although both of these matrices are composed of blends of swellable and erodible polymers but formulation A has shown a higher degree of erosion. This is attributed to the presence of lactose in this formulation which contributes more to the erosion process in addition to MC that is also present in the formulation. As mentioned earlier, lactose produces its effect by rapid dissolution in water and thus creating channels in the matrix that will eventually lead to significant erosion of the matrices. Since formulation B contains microcrystalline cellulose which is a swellable polymer, lower erosion was obtained compared to formulation A.

Other erosion experiments have been carried out on drug free matrices from both formulations A and B and containing the same ratios of the polymers as drug containing matrix tablets. The results of percent erosion obtained from these matrices where not significantly different from those obtained from the drug containing matrices. These results indicated that the presence of the drug in the matrix tablets does not significantly contribute to the stability against erosion of the gel structure of the polymers during the erosion studies. This could be attributed to the lower amount of the drug contained in the matrix tablets since it is a low dose drug.

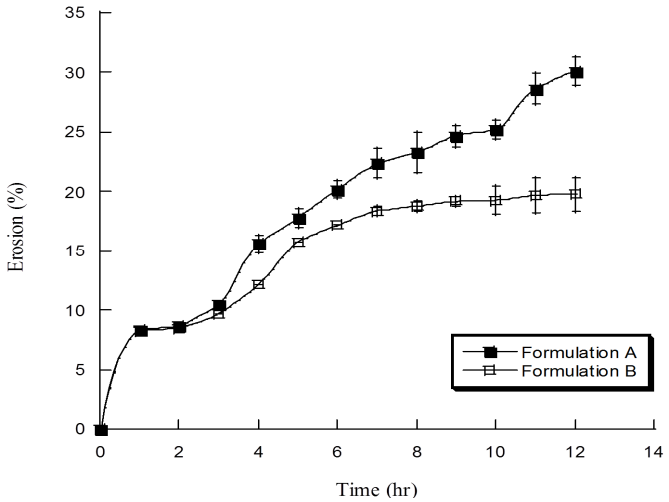

Fig. 6: Erosion profiles of matrix tablets A and B in phosphate buffer (pH 6.8, n = 3).

In order to determine the release mechanism of IP from matrix tablets A and B, the release profiles were analysed according to the power low model presented by Ritger and Peppas (1987):

$$M_t/M_\infty = Kt^n$$

According to this model, an n value of 0.5 usually indicates a diffusion mechanism for the release of the drug while a value of 1.0 indicates erosion control mechanism. The values obtained for n were 1.01, 0.92, and 0.75 for Natrilix® sustained release tablets, matrix tablets A and B, respectively. These values indicated anomalous release mechanism with erosion as the primary mechanism of drug release from all these formulations. However, the n value for the matrix tablets A was closer to 1, since as anticipated, in the presence of lactose in the matrix, water diffusion is enhanced and the drug is dissolved and diffused out of the matrix more rapidly. The characteristics of this polymer give the matrix a higher rate of gel erosion and a higher degree of erosion compared to matrix tablets B. In general, matrix erosion is attributed to the stress developed due to hydration and swelling of the cellulosic polymers contained in the matrix.

CONCLUSIONS

Sustained release matrix tablets containing the low dose and low water solubility drug, IP, have been successfully prepared by direct compression method. To correct the release pattern of the drug from the matrices, blends of HPMC K15M and MC were used as matrix formers in addition to lactose or microcrystalline cellulose. The fluctuations of drug release from these formulations decreased and the kinetics of drug release was close to zero order kinetics. The matrix tablet formulations containing lactose among

the components showed a release pattern of the drug that more closely resembles that of the reference product more than the formulations containing microcrystalline cellulose. This is due to the fact that lactose is a water soluble polymer and enhances matrix erosion more than microcrystalline cellulose. The use of low viscosity grade of HPMC polymer (K15M) was found to be desirable for drugs that are of low water solubility such as IP since the erosion rate of the matrix tablets is the dominant mechanism for drug release. This observation has also been confirmed in the literature for other poorly water soluble drug (Maghsoodi *et al*., 2008; Kiortsis *et al*., 2005). The prepared tablets have shown good post compression characteristics regarding hardness, friability, weight and content uniformity, and desired and reproducible drug release profiles as compared to the reference commercial product.

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