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EVALUATION OF THE SWELLING, EROSION AND DRUG RELEASE FROM POLYSACCHARIDE MATRIX TABLETS BASED ON PECTIN AND INULIN

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Abstract

The aim of this study was to investigate swelling, erosion and drug release behavior of tablets containing pectin and inulin (polysaccharide) compared with different grades of hydroxy propyl methyl cellulose (HMPC) in the preparation of slow-release tablets. In this study, theophylline was used as a drug model. HPMC K100 and HPMC K4M and high methoxylated pectin were selected as extended release matrix formers. Tablets were prepared by using direct compression. After determination of mechanical properties, swelling, erosion and drug release studies of matrix tablets were carried out in simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and distilled water. The results of study showed a pH-dependent formation of hydrogel for the pectin tablets so that swelling of tablets in SIF was much more compared to SGF. Tablets made of HPMC K100 released the total drug in 12 h while drug release from pectin-based tablets at the same time was only 65%. Other formulations released their drug less than 12 h. Among the formulations, tablets containing pectin and HPMC K100 had high swelling, low erosion and slow drug release and therefore they were suitable as extended release systems.

Keywords:

Pectin, Inulin, HPMC, Swelling, Erosion.

Introduction

Hydrophilic matrices are commonly used as oral drug delivery systems and being increasingly investigated for controlled-release applications because of their good compatibility (1). They are usually easy and economical to formulate. Drug release from hydrophilic matrix tablets is controlled by the formation of a hydrated viscous layer around the tablet which acts as a barrier to drug release by opposing penetration of water into the tablet and also movement of dissolved solutes out of the matrix tablet (2). The hydration characteristics of the polymer and the subsequent physical properties of the hydrated gel layer may critically influence drug release (3). The device may be a swellable, hydrophilic monolithic system, an erosion-controlled monolithic system or a non-erodible system. Recently, many controlled-release formulations based on hydrophilic matrices have been developed. From polysaccharides, pectin has been the successful choice for this purpose (4-10). The non-toxicity and the low production costs of pectin make it of great interest for the formulation of controlled-release dosage forms. Pectin, a structural

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component of plant cell walls, is an important water-soluble polysaccharide of plant origin and is of considerable interest for food industry as a gelling agent and a stabilizer in foods. Industrial pectins are devided into two categories: Low methoxylted and High methoxylated. In the Low methoxyl group the esterification of acidic groups is less than 50% while it is more than 50% in high methoxylated form. Inulin is a natural linear polysaccharide of fructose which is used as a sweetener and coupler in medical products and as stabilizers in the protein products. Penetration of inulin to water is fast (dissolution time of less than 1.2 hr) but when it comes to hydrogel an unusual behavior shows which can be influenced by the type of branches, initial concentration, ionic strength and pH of dissolution medium (11-13).

The majority of investigations on polysaccharides as matrix forming agent have been carried out on their own and no similar acting polymer has been compared with them. Therefore, regarding the safety, low cost and natural characteristics of polysaccharides the aim of our study was to evaluate the utility of pectin and inulin in hydrophilic matrices as extended release matrices and to compare swelling, erosion and drug release of the resulted matrices with those of tablets containing different grades of HPMC.

Materials and methods

HPMC K100 and HPMC K4M (Colorcon,UK), Pectin (high methoxylated from citrus, Sigma & Aldrich, Germany), Inulin (Orafti, France) and theophylline (Darupakhsh, Iran) were purchased from indicated sources. All chemicals were of analytical grade.

Tablet preparation

Six formulations were used for preparation of theophylline tablets. All of the formulations contained 33% of theophylline and 1% of magnesium stearate as lubricant. Pectin, inulin, HPMC K100, HPMC K4M, HPMC K100:HPMC K4M (in the ratio of 1:1) and HPMC K100:inuln (in the ratio of 1:1) up to 66% of the weight of the tablet were separately added to the mixture of drug and lubricant. Two hundred tablets were prepared from each formulation using single punch tablet press machine (Erweka, Germany). Tablet formulas prepared with weight of 330 grams, 13 mm in diameter and hardness of 5 kg.

Swelling or water uptake studies

Tablets were accurately weighed (W_0) and placed in the basket of apparatus 1 USP dissolution tester (Erweka DT800). Baskets were then immersed in 500 mL of dissolution medium with rotating at 100 rpm. Samples were separately analyzed in simulated gastric fluid (SGF) without pepsin (pH 1.2), simulated intestinal fluid (SIF) without pancreatin (pH 6.8), and purified water at 37 ± 0.5 ˚C. After 2, 5, 10, 20, 60, 120, 180 and 240 min, tablet was removed from the basket, lightly blotted with tissue paper to remove excess test liquid and then reweighed (W_1). The experiments were performed in triplicate. The percentage increase in weight due to absorbed liquid or water uptake was estimated at each time point from the following equation (14):

$$\% \text{ weight change} = W_1 - W_0/W_0 \times 100$$

Matrix erosion studies

The standard USP/NF dissolution apparatus I (ERWEKA DT800) was used for this purpose. The dry matrices were weighed (W_i), placed in dissolution baskets, and subjected to dissolution media containing 500 ml of different media (SGF, SIF and purified water) maintained at 37±0.5 °C with the baskets rotating at 100 rpm. At regular intervals (2, 5, 10, 20, 60, 120 and 180 min) basket–matrix assemblies were removed from the dissolution vessels, tablets were dried to a constant weight in a hot-air

oven at 50 ˚C and reweighed (W_t). The separated samples were used for each interval. The experiments were carried out in triplicate. The percentage matrix erosion (E) at time, t, was estimated from the following equation (15):

$$\text{Matrix erosion (\%)} = W_i - W_t/W_t \times 100$$

In vitro drug release studies

In vitro drug release studies were performed using the USP/NF dissolution apparatus I (ERWEKA DT800). A 500-ml volume of SGF, SIF and purified water maintained at 37±0.5 ˚C, were used as dissolution medium. Rotational speed of the baskets was 100 rpm. Aliquots of 5 ml of dissolution medium were withdrawn at determined intervals and replaced with an equal volume of fresh dissolution medium. The dissolution samples were then analyzed at 272 nm for the drug content using a UV spectrophotometer (CECIL CE2501). Each experiment was carried out for 12 h. The dissolution data represented an average of three determinations.

Morphology of swollen tablets

Morphological examination of the swollen tablets was carried out using a digital camera (Canon) equipped with lens 6.2-18.6mm 1:2.8-4. Photo imaging was performed on each tablet formulation after hydrating in different media (i.e., purified water, SGF, or SIF) for 0.5, 1, 3 hours. The tablets were taken out from the medium and were photographed by a digital camera. Under the same optical conditions, an image of a linear scale was used to calibrate (16).

Statistical analysis of data

Swelling data of different formulations at various times were statistically compared by general linear model (repeated measure design) and Tukey test. Matrix erosion data of different formulations at various intervals were statistically compared by general linear model (repeated measure design) and Tukey test. Dissolution profiles were analyzed using model independent approach (multivariate analysis of variance followed by Tukey test).

Results and discussion

Evaluation of tablet properties showed that all formulations resulted in acceptable tablets including hardness between 4.23-6.33 kg, friability less than 1% and content uniformity of 100±2%.

The results of tablet swelling tests in distilled water, SGF and SIF are shown in Fig. 1. Inulin tablets could not produce a stable gel layer after inserting in dissolution media and eroded completely within 10 min, so they are not included in further evaluations. As shown in the figures, tablets containing pectin had the highest swelling rate in 3 media, with the maximum swelling rate of 1600% in distilled water. It has been proved that the swelling of high methoxylated pectin was related to the formation of hydrogen bonds between the hydrophobic groups of polysaccharide chains (14), so the highest swelling rate in distilled water could be attributed to the absence of agents that rupture the hydrogen bonds, such as salts and ionic strength. The results also showed that the swelling of pectin in SIF is greater than in SGF (p-value<0.05). Pectin has a pH of 3-4, it means that in acidic medium and it can be converted to pectinic acid which has lower swelling capacity compare to pectin (17). Tablets containing HPMC K100 also had higher swelling than HPMC K4M (p-value<0.05), which could be related to higher viscosity and stability and lower erosion of HPMC K100 gel layer compare to HPMC K4M. The results revealed that swelling rate of both HPMC grades in different media did not differ significantly, indicating that the ionic strength or pH variations have no effect on swelling of HPMC (16). Addition of inulin to HPMC 100K decreased its

swelling in all three media, due to high solubility and erosion of inulin in water.
Fig. 2 shows the results of erosion tests. As shown in the figures the highest erosion rate belongs to HPMC 4M, which could be related to low viscosity and weakness of its gel layer. Tablets containing pectin had the lowest erosion in SGF, SIF and distilled water. Pectin tablets in SIF had the lower erosion rate than SGF (p-value<0.05) that is accordant with the swelling results. Comparing matrix erosion of tablets containing HPMC K100-HPMC K4M and tablets with HPMC K100-inulin showed no significant difference between two formulations.

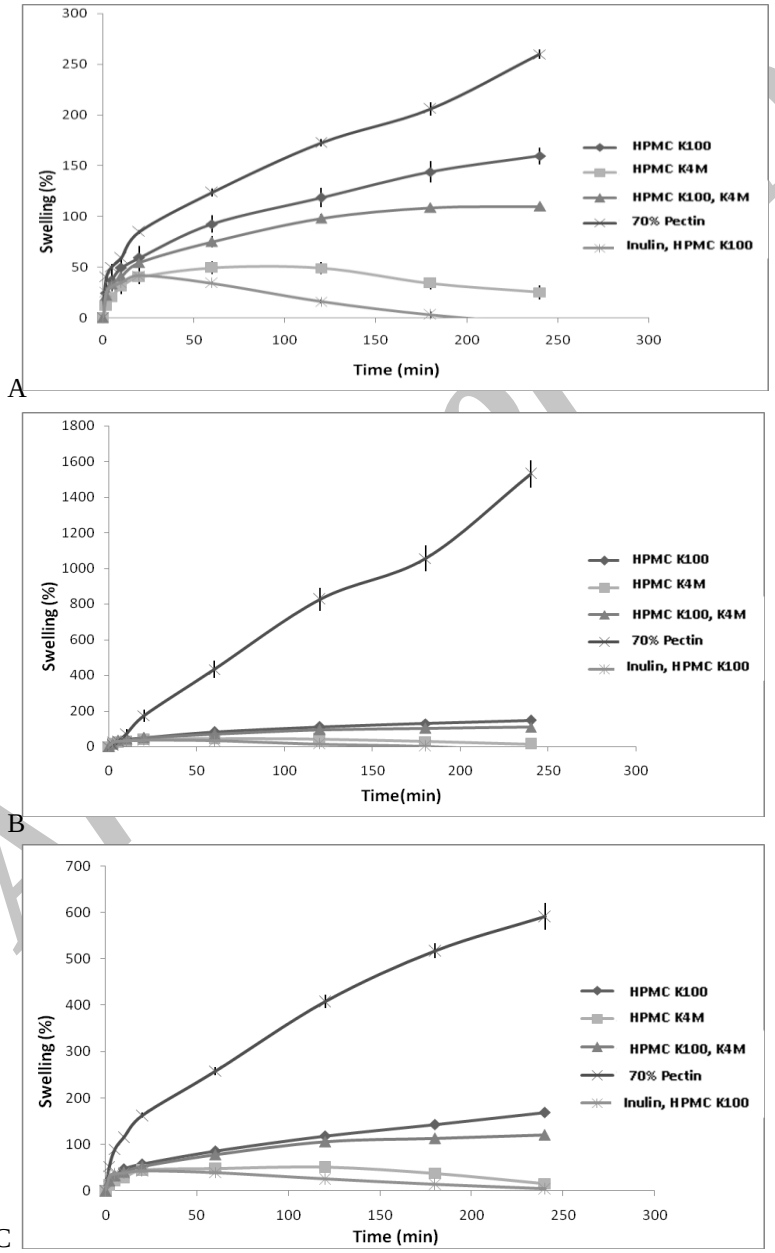

Fig. 1: Swelling or water uptake by different matrix tablets as a function of time in: A) SGF, B) Distilled water, C) SIF.

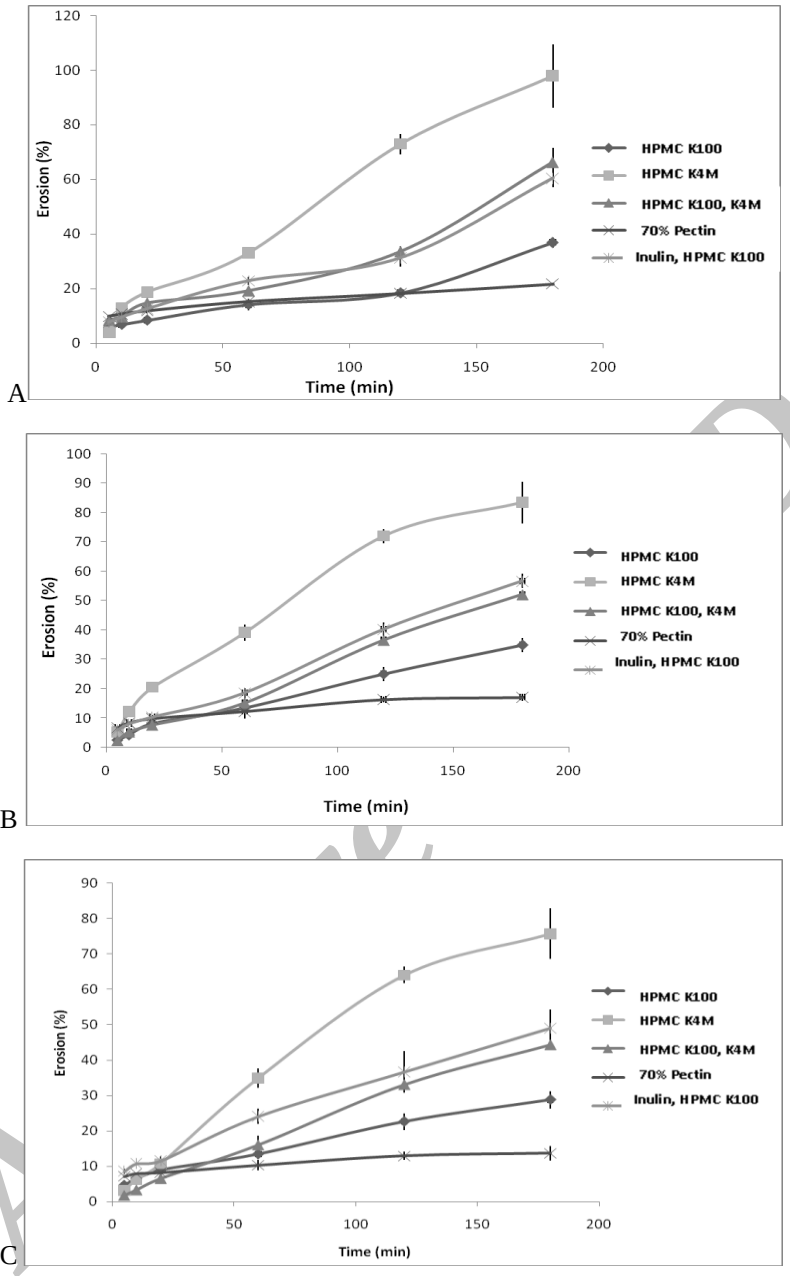

Fig. 2: Plots of percent erosion of different matrix tablets as a function of time in: A) SGF, B) Distilled water, C) SIF.

The results of in-vitro dissolution tests are indicated in Fig. 3. Since the drug release occurs through the hydrophilic gel barrier around the tablets, drug release rate from matrix tablets is dependent on the formation and viscosity of gel layer and its swelling or erosion rate. As shown in Fig. 3, tablets containing pectin have slow release rate, because of the fast formation of a high viscosity gel layer around the tablet which is more stable and has the lowest erosion rate. The drug release rate of pectin tablets increased in SGF compared to SIF, which could be explained by formation of low swellable pectinic acid in SGF. Drug release in SIF

was lowest from formulation containing pectin and tablets containing HPMC K100 and K4M had the higher drug release at SIF(p-value<0.01) which could be due to more erosion and the less swelling of polymers compared to pectin. Balance between swelling and erosion of these tablets caused a more rapid release of theophylline from their structure. Fig. 4 demonstrates this feature and it can be seen that after 180 min tablets were lower in the dimension scale than the shorter periods (30 and 60 min) which obviously could be due to predominance of erosion mechanism in the matrix tablet. Tablets containing HPMC K4M had the higher drug release rate compared to HPMC K100 (p-value<0.01), due to its lower viscosity and higher erosion rate.

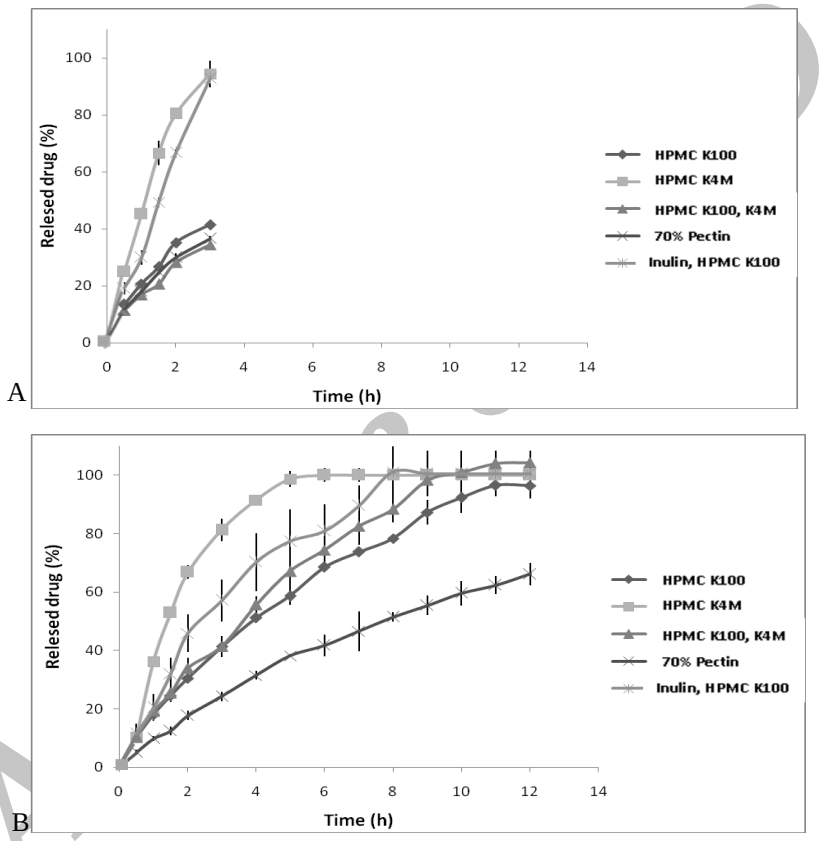

Fig. 3: Dissolution profiles of different matrix tablets in: A) SGF, B) SIF.

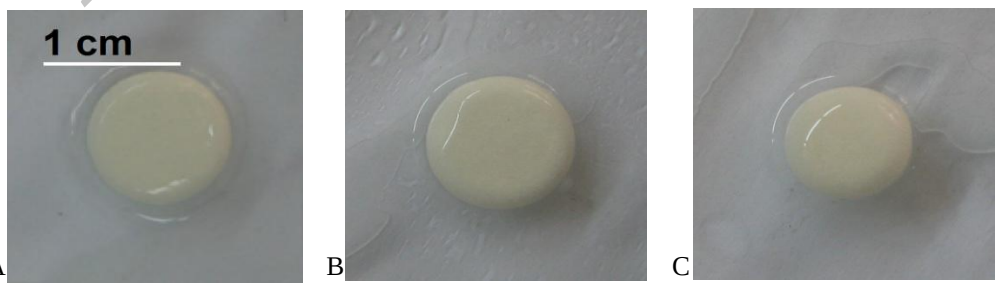

Fig. 4: Photographs of a tablet made of HPMC 100K:HPMC 4000 (1:1) during dissolution in simulated gastric fluid (SGF) after; A)30 min, B) 60min, and C) 180min.

Also, among the formulations, tablets with HPMC K4M released drug at the highest rate in SGF and SIF. Unlike pectin tablets, drug release rate from HPMC tablets in SIF and SGF was similar and independent of pH, because their swelling rate was the same in both media. Despite the similar erosion of tablets containing HPMC K100-K4M and K100-inulin, drug release was higher from the last formulation which could be due to the presence of inulin in HPMC K100 and increase in hydrophilicity of matrix tablet.

In overall, among the formulations tablets containing pectin and HPMC K100 had high swelling, low erosion and slow drug release and these characteristics candidate them as extended release system for theophylline tablets.

Conclusion

Substituting the common hydrophilic polymers by polysaccharides in the structure of matrix tablets could be more likely regarding safety and cheapness of polysaccharides. The results of this study showed that pectin has potential for controlling the release of theophylline even more than HPMC K100. While inulin had the weaker swelling characteristics and it could be a candidate for substituting agent of HPMC K4M in combination with HPMC K100.

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