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COMMUNICATION

Studies on Pectins as Potential Hydrogel Matrices for Controlled-Release Drug Delivery

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ABSTRACT

Polymeric hydrogels are widely used as controlled-release matrix tablets. In the present study, we investigated high-methoxy pectins for their potential value in controlled-release matrix formulations. The effects of compression force, ratio of drug to pectin, and type of pectin on drug release from matrix tablets were also investigated. The results of the in vitro release studies show that the drug release from compressed matrix tablets prepared from pectin can be modified by changing the amount and the type of pectin in the matrix tablets. However, compression force did not significantly affect the drug release. The mechanisms controlling release rate were discussed with respect to drug diffusion through the polymer matrices, but may be more complex.

Key Words: *Controlled release; Hydrogel matrices; Indomethacin; Matrix tablets; Pectin; Sustained release.*

INTRODUCTION

The development of oral controlled-release dosage forms has attracted much attention in recent years. Polymeric hydrogels are being increasingly investigated for controlled-release applications because of their good compatibility (1). In addition, the ability of hydrogels to release an entrapped drug in aqueous medium and to regulate the release of such drug by control of swelling and by cross-linking makes them particularly suitable for

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controlled-release applications (2,3). Hydrogels can be applied for the release of both hydrophilic and hydrophobic drugs and charged solutes.

Recently, many controlled-release formulations based on hydrogel matrices have been developed. Pectins have been the successful choice for this purpose (4–9). The nontoxicity and the low production costs of the pectins make them of great interest for the formulation of controlled-release dosage forms. Pectins are hydrophilic polysaccharides derived from plant cell walls. They contain linear chains of (1 → 4)-linked α-D-galacturonic acid residues. These uronic acids have carboxyl groups, some of which are naturally presented as methyl esters. The degree of esterification (DE), which is expressed as a percentage of the esterified carboxyl groups, is important way to classify pectins. High-methoxy pectins (with DE above 50%) require a relatively high concentration of soluble solids and a low pH for gel formation (10,11).

In the present investigation, pectin hydrogel matrices were used as carriers for the controlled release of indomethacin, a drug that is poorly water soluble. The aim of this study was to evaluate pectins as potential matrices for controlled-release dosage forms. The effects of compression force, ratio of drug to pectin, and type of pectin on drug release from matrix tablets were also investigated.

MATERIALS

The pectins were obtained from two sources. The pectin from citrus fruit was purchase from Sigma Chemical (St. Louis, MO) and is referred to as PS. GENU pectin type B was the generous gift of Copenhagen Pectin A/S (Lille Skensved, Denmark) and is referred to as PG. According to the manufacturer's specifications, PS is 70% esterified, while PG is 72% esterified and contains about 60–65% solid sucrose. Indomethacin (Sigma Chemical) was chosen as a model drug. All other materials were used as supplied without further purification.

METHODS

Preparation of Pectin Matrix Tablets

The matrix tablets were formulated such that each tablet contained 75 mg of indomethacin. The formulation composition of pectin matrix tablets is listed in Table 1. All ingredients were passed through a 60-mesh sieve and thoroughly mixed in a blender for 15 min. The blend was compressed into tablets on an automatic hydraulic press (model 2I-15710, Perkin Elmer) with 13-mm diameter flat-faced tooling. Tablets were compressed at varying compression forces, ranging from 2000 to 8000 kg.

Table 1

Composition and Code of Pectin Matrix Tablet

Formulation Code	Indomethacin (mg)	PS (mg)	PG (mg)	Compression Force (kg)
PSA 1:4	75	300	—	2000
PSB 1:4	75	300	—	4000
PSC 1:4	75	300	—	8000
PSA 1:6	75	450	—	2000
PSB 1:6	75	450	—	4000
PSC 1:6	75	450	—	8000
PSA 1:8	75	600	—	2000
PSB 1:8	75	600	—	4000
PSC 1:8	75	600	—	8000
PGA 1:4	75	—	300	2000
PGB 1:4	75	—	300	4000
PGC 1:4	75	—	300	8000
PGA 1:6	75	—	450	2000
PGB 1:6	75	—	450	4000
PGC 1:6	75	—	450	8000
PGA 1:8	75	—	600	2000
PGB 1:8	75	—	600	4000
PGC 1:8	75	—	600	8000

Matrix Tablet Evaluations

Tablet Thickness Testing

The thickness of the matrix tablets was determined using a Mitutoyo caliper, and the results are expressed as mean values of 10 determinations.

Tablet Weight Variation Testing

To determine batch-to-batch variations, 20 matrix tablets were selected and accurately weighed using a Mettler analytical balance (Greifensee, Switzerland). The results are expressed as mean values of 20 determinations.

Hardness Determination

For hardness determination, 10 matrix tablets were sampled and individually subjected to the test for hardness using a Stoke-Monsanto hardness tester (St. Louis, MO). The tablet hardness is expressed in kilograms (kg). The mean and standard deviation of the tablet hardness were calculated.

Friability Studies

The tablet friability test was performed on 20 tablets at 25 rpm for 4 min using an Erweka Abrasion Tester (Heusenstamm, Germany). The percentage of friability was calculated based on the weight lost after the test.

In Vitro Release Studies

To examine the effects of type of pectin, compression force, and ratio of drug to pectin on drug release, dissolution studies were carried out using USP dissolution apparatus I equipped with baskets; the apparatus was operated at 75 rpm. Phosphate buffer (pH 6.2, 750 ml), as the dissolution medium, was placed in the glass vessel; the apparatus was assembled and equilibrated with the dissolution medium to 37°C. The amount of drug released was measured at the suitable time interval and was then determined spectrophotometrically (model DU 605i, Beckman Instrument, Fullerton, CA) in a 1-cm cell at 318 nm. Each in vitro release study was performed in triplicate.

RESULTS AND DISCUSSION

The comparison of the hardness, thickness, weight variation, and friability of pectin matrix tablets prepared from PG and PS at varying ratios of drug to pectin and compression force is shown in Table 2. The friability values decreased as the tablet hardness increased for the different matrix formulations. Further, the friability values obtained for formulations containing either PS or PG decreased as the fraction of pectin in the formulation increased (Table 2).

The effect of compression force on tablet hardness for the matrix formulations is shown in Fig. 1. As expected, the tablet hardness increased as the compression force increased at all ratios of drug to polymer and for both types of pectin. It was suggested that the apparent density and the porosity of a tablet are related to the applied pressure. The apparent density increased, while the porosity decreased with an increase in compression pressure, and the tablet hardness is proportionally related to the applied pressure. Moreover, tablet hardness is considerably less in formulations containing PG. Since PG contains about 60–65% soluble solid sucrose, which binds to a moderate hardness depending on the amount used, the relative lack of hardness is surprising. This suggests that there is little influence of sucrose in PG on tablet hardness.

Figure 2 shows the release of indomethacin from matrix tablets prepared from either PG or PS at three different compression forces: 2000, 4000, and 8000 kg. Although the hardness of matrix tablets compressed with

Table 2

Comparison of the Physical Properties of the Matrix Tablets Containing Pectin

Formulation	Hardness (kg) (n = 10)	Thickness (mm) (n = 10)	Weight (mg) (n = 20)	Friability (%)
PSA 1:4	1.96 (0.10)	2.44 (0.02)	373.1 (2.10)	12.22
PSB 1:4	3.55 (0.28)	2.39 (0.04)	377.0 (1.63)	4.97
PSC 1:4	3.65 (0.24)	2.52 (0.30)	379.4 (6.51)	1.35
PSA 1:6	3.60 (0.21)	3.42 (0.04)	522.2 (7.93)	10.52
PSB 1:6	4.75 (0.26)	3.30 (0.02)	519.7 (2.89)	2.93
PSC 1:6	5.40 (0.21)	3.35 (0.02)	526.6 (1.62)	1.36
PSA 1:8	4.30 (0.75)	4.50 (0.02)	680.0 (2.44)	7.41
PSB 1:8	7.35 (0.24)	4.35 (0.05)	689.5 (2.35)	2.29
PSC 1:8	7.65 (0.47)	4.30 (0.03)	674.1 (2.11)	1.44
PGA 1:4	1.40 (0.39)	2.17 (0.02)	365.6 (1.06)	5.48
PGB 1:4	3.55 (0.60)	2.13 (0.02)	371.8 (0.68)	2.13
PGC 1:4	3.65 (0.24)	2.15 (0.03)	366.0 (3.14)	1.73
PGA 1:6	2.65 (0.47)	3.00 (0.03)	514.7 (2.22)	1.18
PGB 1:6	3.15 (0.34)	2.98 (0.03)	514.7 (1.16)	0.99
PGC 1:6	3.75 (0.54)	2.95 (0.02)	510.5 (1.75)	0.54
PGA 1:8	3.30 (0.26)	3.87 (0.02)	646.8 (4.54)	2.34
PGB 1:8	4.40 (0.74)	3.78 (0.03)	656.0 (1.03)	1.25
PGC 1:8	4.90 (0.57)	3.76 (0.03)	643.3 (4.55)	0.66

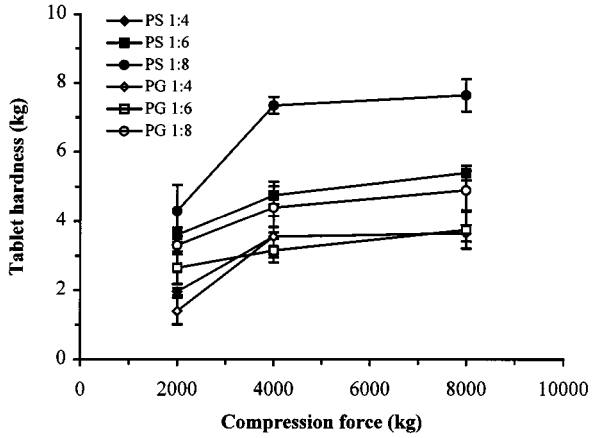

Figure 1. Tablet hardness as a function of compression force for matrix formulations containing indomethacin and PS or PG as polymeric excipients at a varying ratio of drug to pectin (error bars indicate the standard deviation; $n = 3$).

different compression forces is varied, the release from those matrix tablets prepared with both types of pectin indicated no significant different. In this case, it can be said that the influence of compression force on release behaviors is not important, which was also demonstrated by Bamba et al. (12).

Figures 3 and 4 show the effect of the ratio of drug to pectin on indomethacin release from matrix tablets at compression forces of 2000 and 4000 kg, respectively. The release profiles of matrix tablets compressed at 8000 kg are not shown, but they displayed similar characteristics as those seen in Figs. 3 and 4. Considering the results obtained, it was found that the proportion of pectin modified the release rate of indomethacin. Increasing the amount of pectin in the tablet resulted in increased retardation of drug release in dissolution medium. The higher concentration of pectin, especially in PS, will form a more resistant gelatinous layer to water penetration, drug diffusion, and hence release (5).

The effect of types of pectin on indomethacin release from pectin matrix tablets can be seen in Figs. 2–4. The release of indomethacin from matrix tablets prepared from PG is faster, and the duration of release is shorter when compared with release from tablets prepared from PS in all formulations. Both pectins are high-methoxy

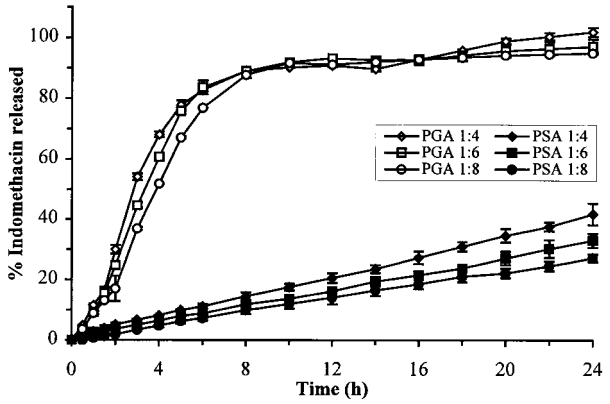

Figure 3. The effect of drug-to-pectin ratio on indomethacin release from pectin matrix tablets at a compression force of 2000 kg (error bars indicate the standard deviation; $n = 3$).

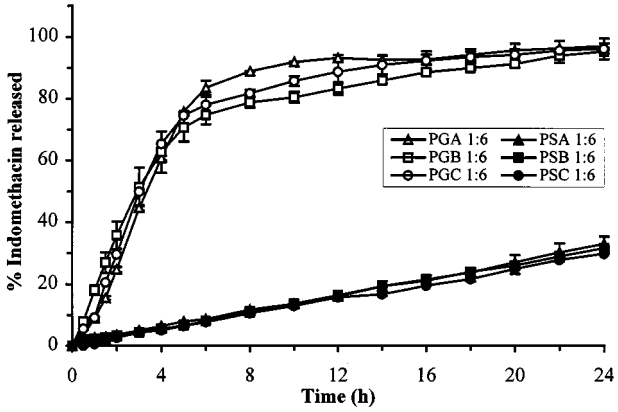

Figure 2. The effect of compression force on indomethacin release from pectin matrix tablets at a 1:6 ratio of drug to pectin (error bars indicate the standard deviation; $n = 3$).

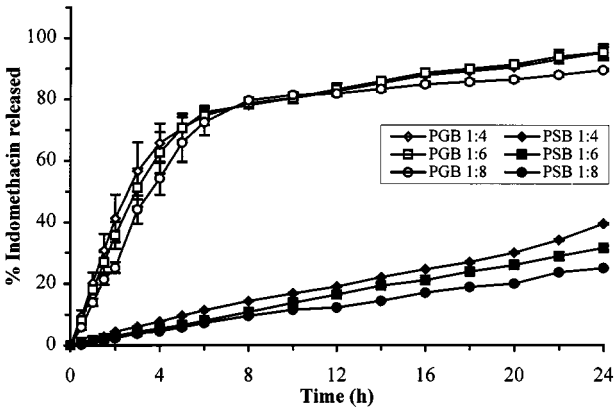

Figure 4. The effect of drug-to-pectin ratio on indomethacin release from pectin matrix tablets at a compression force of 4000 kg (error bars indicate the standard deviation; $n = 3$).

pectins with DEs of 72% and 70%, respectively, so the degree of esterification of pectin would not affect to the release rate of drug. Drug release from PS matrix tablets is controlled by the formation of a gel layer around the tablet on contact with aqueous media. The formation of the gel is dependent on tablet hydration, which relies on a host of factors that influence the surface gel: viscous, swelling, porous, and homogeneous properties. The drug release from PS matrices follows zero-order kinetics in all cases. A linear regression analysis of release data was performed. The correlation coefficient r^2 for indomethacin release was greater than 0.99 in each case, which confirms the linearity of the release data.

Regarding the zero-order release obtained, such release rate may attributed to the fact that the path length for drug diffusion remains fairly constant with time. Indeed, pectin swelling, which is appreciable in water, diminishes the rate of solvent penetration inside the polymer matrix, and hence a decrease in the rate of gel formation results with time (13). Moreover, the decreased rate of polymer dissolution resulting from the decreased rate of solvent penetration is accompanied by a decrease in drug diffusion due to ionic interactions, which would be at maximum at a certain drug to polymer ratio; thus, a constant drug release rate is maintained (5).

On the other hand, the higher drug release rate of PG matrix tablets, as compared to drug release from PS matrix tablets, may be attributed to dissolution of sucrose molecules, which are the component of PG, creating pores and thus facilitating the solvent front penetration. A high sucrose concentration creates increased porosity on dissolution, resulting in an increase in release rate. Indeed, high sucrose concentrations lead to an initially faster linear drug release up to 70% released drug. However, at this level, the tablet is completely wetted (14), and the swelling of polymer occurs. This indicates that release is controlled by diffusion of the drug through the swollen polymer and consequently by erosion of the swollen polymer, as visually inspected during dissolution testing. Hence, diffusion in the matrix appears to be an important factor in controlling the drug release rate of PG matrix tablets.

Drug release mechanisms from swellable and erodible hydrophilic matrices have been described by several authors (15–17). As a matrix contacts the dissolution medium, the polymer undergoes a relaxation process, and two fronts are established around the matrix: the penetration front and the dissolution front. The *penetration front* is defined as the interface between the nonrelaxed polymer and the gel; the *dissolution front* is defined as the interface between the gel and the dissolution medium. At the penetration front, the hydration, swelling, and coalescence of polymer particles occur, whereas at the dissolution front, polymer chain disentanglement and dissolution of the hydrated matrix occur. The gel layer thickness, which determines the diffusional path length of the drug, corresponds to the distance between the penetration and dissolution fronts (15–17). According to the physical picture described above, drug release from hydrophilic matrices can be attributed to polymer dissolution (matrix erosion mechanism), drug diffusion through the gel layer (diffusion mechanism), or a combination of both.

In general, the drug release rates decreased with decreased matrix dissolution rates. This indicates that the swelling kinetics of the matrices, which control the matrix dissolution, were an important determinant of drug release. However, changes in the swelling kinetics of the matrices can lead to the changes in drug release through two distinct mechanisms. If the drug does not completely dissolve in the hydrated matrix, faster matrix dissolution would result in increased drug release through what is often called matrix erosion. Alternately, swelling kinetics changes can lead to changes in the diffusion path length and/or diffusional resistance of the gel layer. Specifically, for a drug that completely dissolves at the medium penetration front and is released by a diffusional mechanism, a thickness and/or more tortuous gel layer should result in slower drug release (15).

The results of this investigation enable us to state that the hydrophilic matrices are an interesting way of formulating oral controlled-release matrix tablets using a fabrication process that is easy and inexpensive and does not require special production equipment. Therefore, it is possible to achieve a firmer basis for their use. It is also demonstrated, in the present study, that the release of indomethacin from directly compressed matrix tablets prepared from pectin can be modified by changing the type of pectin and the amount of pectin in the matrix tablets. However, compression force did not significantly affect the release rate. More information on the influence of different variables on release needs to be studied further. In addition, it is essential to consider the mechanisms implied in the release and the physicochemical properties of the active principles and polymers.

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