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Sigmoidal release of indomethacin from pectin matrix tablets: Effect of in situ crosslinking by calcium cations

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Abstract

Sigmoidal release pattern is therapeutically beneficial for timed release and colonic drug delivery, and is always observed in coated systems. In this study, sigmoidal release from pectin matrix tablets with indomethacin as a model drug was investigated. The underlying mechanisms are calcium cation-induced in situ crosslinking that retard the initial drug release to a limited percentage. Power law equation *n* values were estimated for sigmoidal release profiles. Results indicated that calcium chloride incorporated in pectin matrix functioned as retarding mechanisms on drug release. Larger amount of calcium chloride led to slower drug release and matrix erosion. Even at extremely high levels, retarding on drug release and matrix erosion rate was obvious, which highlighted the effect of calcium-induced in situ crosslinking as calcium chloride was a freely water-soluble salt. The sigmoidal release profiles were characterized by power law equation with high correlation coefficients of about 0.99 or over. Power law *n* values increased up to as high as 1.20 when calcium chloride content kept increasing. Erosion correlated well with release in almost all pectin matrix tablets indicating erosion-controlled mechanisms. It is concluded that large amount of calcium induces in situ crosslinking of pectin matrix and leads to sigmoidal release of indomethacin, and power law *n* values, sometimes larger than 1.0, are suitable to be used to describe sigmoidal release profiles.

Keywords: Pectin; Calcium chloride; Indomethacin; Matrix tablets; In situ crosslinking; Power law

1. Introduction

Sigmoidal or bimodal release profile is characterized by slower release at initial stage followed by increased release at later stage (Narisawa et al., 1994). This kind of release profile may be therapeutically beneficial for timed release or site-specific delivery of drugs (Maggi and Conte, 1997). For diseases influenced by circadian rhythms such as ischemic heart disease, asthma and arthritis, incremental release rate may be helpful to prevent exacerbation of nocturnal or early morning symptoms (Lemmer, 1991). Colonic delivery of drugs through sigmoidal release mechanisms is aimed to treat local diseases of the colon or to maintain sustained blood drug levels (Macleod et al., 1999).

Sigmoidal release is usually observed in press-coated or film-coated systems with tablets or pellets as substrate. This kind of release pattern needs triggering mechanisms such as degradation of the polysaccharide coating by colonic microbial degradation (Krishnaiah et al., 2002a; Macleod et al., 1999) or organic acid-induced enhancement of drug release (Narisawa et al., 1994). For reasons of simple manufacturing process, polysaccharide-based matrix tablets have also been studied for sigmoidal release with microbial triggering mechanisms (Krishnaiah et al., 2002b; Tugcu-Demiroz et al., 2004). One of the drawbacks of these systems is the relatively larger initial release rate compared with that of the coated systems. The crucial point in developing matrix tablets with sigmoidal release characteristics should be tight controlling on initial release rate. However, release rate at the initial stage of a common matrix system with a residing diffusion/erosion mechanisms is typically fast. It seems that alternative retarding mechanisms other than diffusion/erosion is desired to further reduce initial drug release.

Pectin, a naturally occurring polysaccharide of high hydrophilicity, has been used for drug delivery systems, especially

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colon-specific ones (Ashford et al., 1993; Munjeri et al., 1997; Vandamme et al., 2002). To warrant tight controlling on drug delivery, calcium pectinate which is more water-resistant has been developed for colonic drug delivery purposes (Adkin et al., 1997; Rubinstein et al., 1993; Rubinstein and Radai, 1995). Calcium binding to pectin reduces solubility and induces crosslinking of carbohydrate chains, typical of changes in chain conformation and in the manner of chains packing (Morris et al., 1982; Powell et al., 1982). The calcium-induced associations of pectin chains are stable at low solution pH and able to resist extensive hydration in the gastrointestinal tract. Effect of incorporating calcium ions in drug delivery systems has also been studied by several authors. For pectin gel, the gel strength increases with calcium ion added to a critical concentration (Ashford et al., 1994). Calcium acetate in various amounts has been incorporate in pectin matrix tablets as in situ crosslinking agent to sustain in vitro drug release (Sungthongjeen et al., 2004). However, only relatively small amount of calcium was reported to have such effect. The in situ crosslinking pectin matrix system is advantageous over calcium pectinate-based ones in that the degree of gelation is adjustable simply by change the amount of calcium salt initially added. Moreover, incorporation of calcium salts into pectin matrices should enhance its susceptibility to enzymes at proximal colon, because many pectinases were supposed to be stimulated by or have an absolute requirement for calcium ions for their activity (Miller and MacMilan, 1970).

In this study, large amount of calcium chloride was incorporated into pectin matrix tablets to induce in situ crosslinking of pectin molecules. Effect of variables such as incorporating calcium chloride into pectin matrix, pectin/calcium ratio and drug/matrix material ratio on release characteristics were studied. Release kinetics was characterized by the power law equation. Indomethacin, a non-steroid anti-inflammatory drug frequently studied by other authors (Rubinstein et al., 1993) for colon-specific delivery was incorporated as a model drug.

2. Materials and methods

2.1. Materials

Micronized indomethacin (<5 μm in diameter) was purchased from Fengyan Pharmceuticals (Anhui province, China). Pectin HM (high methoxylated) 70 and PVP K30 were kindly gifted from International Specialty Products (Hong Kong). Calcium chloride ($CaCl_2$) and Sodium chloride (NaCl) were of analytical purity and purchased from Shanghai Chemical Regent Corp. (Shanghai, China). Sodium dodecyl sulfate (SDS) was purchased from Farco Chemical Supplies (Hong Kong). All other chemicals were of analytical grade.

2.2. Preparation of in situ crosslinking pectin matrix tablets

Matrix tablets containing 10 mg of indomethacin, pectin and calcium chloride in varying ratios were prepared by wet granulation/compression method using 10% (w/v) PVP ethanol solution as binder. In detail, all ingredients including pectin and calcium chloride were sieved through 80-mesh sieve and indomethacin was sieved through 200-mesh sieve before being mixed homogeneously in a Turbula T2 F shaker-mixer (Glen Mills Inc., USA). The mixed powder was transferred to a mortar, and 10% PVP K30 ethanol solution was added and the mixture was milled continuously to make paste. The wet mass was forced through a 20-mesh sieve and dried at 50 °C for 3 h. Magnesium stearate in 1% was added and mixed thoroughly with the granules. The lubricated granules were compressed into flat 8 mm tablets using a ZDY-8 model single punch compressor (Yuandong Pharmaceutical Machinery Co., Shanghai, China). Similarly, matrix tablets containing only pectin, pectin and sodium chloride instead of calcium chloride were prepared. The tablet formulations were given in Table 1. All the tablet batches were monitored for weight, crushing strength, friability and drug content uniformity. To avoid effect of variation in tablet hardness on release characteristics, crushing strength (shown in Table 1) was con-

Table 1
The composition, properties and power law correlation details of pectin matrix tablets

Formulation no.	Ingredients (mg)				Weight (mg)	Crushing strength (kg)	Friability (%)	Power law correlation			
	Indomethacin	Pectin	$CaCl_2$	NaCl				Correlation time span (h)	K	n	r
For evaluation of the effect of $CaCl_2$											
(1) Pectin/$CaCl_2$	10	75	75	0	158.7	6.0	0.05	0.5–8	0.075	1.20	0.989
(2) Pectin/NaCl	10	75	0	75	162.4	6.2	0.08	0.5–5	0.139	1.20	0.971
(3) Pectin	10	75	0	0	86.3	7.0	0.10	0.5–5	0.237	0.89	0.986
For evaluation of effect of pectin/$CaCl_2$ ratio											
(4) 75/15	10	75	15	0	102.5	6.1	0.09	0.5–5	0.220	0.93	0.980
(5) 75/25	10	75	25	0	109.8	7.3	0.08	0.5–6	0.193	0.90	0.980
(6) 75/50	10	75	50	0	137.4	6.4	0.04	0.5–7	0.129	1.03	0.990
(1) 75/75	10	75	75	0	158.7	6.0	0.05	0.5–8	0.075	1.20	0.989
(7) 75/100	10	75	100	0	188.6	6.8	0.04	0.5–8	0.077	1.18	0.990
For evaluation of effect of drug/(pectin + $CaCl_2$) ratio											
(8) 10/100	10	50	50	0	114.1	6.3	0.07	0.5–6	0.142	1.04	0.966
(1) 10/150	10	75	75	0	158.7	6.0	0.05	0.5–8	0.075	1.20	0.989
(9) 10/200	10	100	100	0	212.3	7.5	0.08	0.5–7	0.072	1.21	0.991