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Note

Drug release properties of pectinate microspheres prepared by emulsification method

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Abstract

This study explored the potential of pectin for use in making microspheres for sustained-release of drugs. The pectin microspheres were prepared by external gelation using an emulsification technique with calcium chloride as the crosslinking agent. The influences of drug core (sulphanilamide, sulphaguanidine and sulphathiazole) and dissolution media (distilled water, USP HCl and phosphate buffers) on the drug release properties of the pectinate microspheres were examined. The morphology and drug content of the microspheres, and the solubility and solution pH of the drugs were also determined. Pectinate microspheres were successfully prepared by the emulsification technique. The rate of drug released from microspheres was highest in USP HCl buffer, followed by USP phosphate buffer and distilled water. Interestingly, the lowest percentage of drug released was produced by microspheres which were smallest in size and therefore largest in specific surface area, and consisting of sulphanilamide, the most water soluble drug. Further investigation showed that the microspheres consisted of both bound and unbound drugs. The percentage of drug released was predominantly determined by the relative contents of bound and unbound drugs embedded in the pectinate matrix.

Keywords: Core; Media; Microspheres; Pectin; Release properties

1. Introduction

Pectin is a heterogeneous polysaccharide found in the cell wall of plants. The principal constituent of pectin is D-galacturonic acid, which is joined to one another in chains by means of α-(1→4) glycosidic linkages. Crosslinking of pectin with divalent cations, such as Ca^{2+}, leads to sol–gel transformation. This study employed pectin as a matrix polymer crosslinked with calcium chloride to produce microspheres. The influences of drug core and dissolution media on the drug release properties of the pectinate microspheres were examined.

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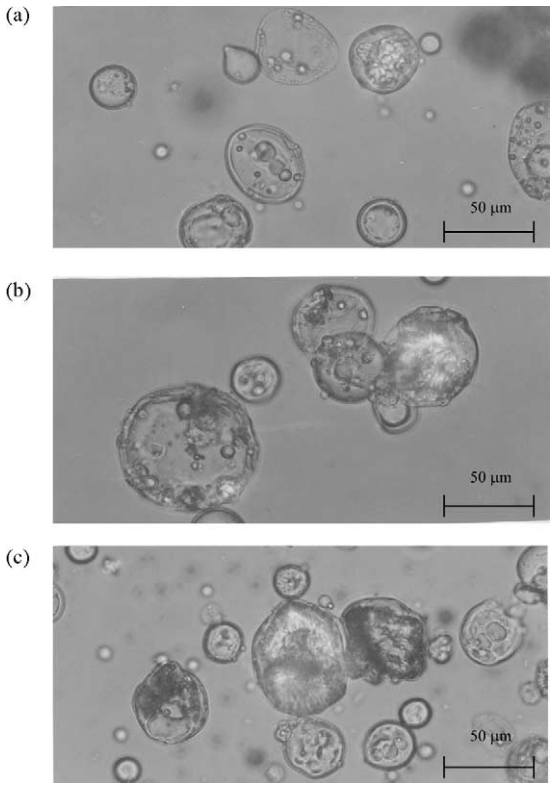

Fig. 1. Photographs of microspheres containing (a) sulphanilamide, (b) sulphaguanidine and (c) sulphathiazole.

2. Materials and methods

The pectinate microspheres were prepared by external gelation using a modified emulsification technique of that employed in our laboratory (Wan et al., 1993, 1994; Chan et al., 1997). Fifty gram of solution containing 3% w/w of pectin (LM208, Degussa Texturant, France) and 1% w/w of drug were dispersed in 75 g of isooctane (Merck, Germany) containing 1.7 g of Span 85 (Sigma, USA) at 1000 rpm for 10 min. At the tenth minute, 5 g of solution containing 0.9 g of Tween 85 (Merck, Germany) were added and stirring continued at 1000 rpm for 5 min. Subsequently, 20 g of 30% w/w of calcium chloride solution (Merck, Germany) were added and stirred for 10 min. Microspheres were collected by in-vacuo filtration, washed with 120 ml of distilled water and dried in the oven at 45 °C until constant weight. Three model drugs were selected: sulphanilamide, sulphaguanidine and sulphathiazole (BP grade, passed through 75 μm aperture sieve before use).

The size and size distribution of the microspheres were determined from a total of 200 projected images of microspheres using a light microscope (BH2, Olympus, Japan) which was connected to a monitor (PVM-145E, Sony, Japan) via a video camera (CCD-IRRS, Sony, Japan). The specific surface area of a microsphere was calculated as the ratio of surface area to volume of a sphere. In the determination of drug content, a known amount of microspheres was ultrasonicated in USP HCl buffer (pH 1.2) for three consecutive periods of 20 min and left to stand for 1 day at 29 ± 1 °C. An aliquot sample was removed for assay spectrophotometrically (UV 1201, Shimadzu, Japan) at the appropriate wavelength. The drug content was expressed as the percentage of drug encapsulated in a unit weight of microspheres. The drug release properties of the microspheres in three different dissolution media: distilled water (pH 5.5), USP HCl buffer (pH 1.2) and USP phosphate buffer (pH 7.4) were studied. Microspheres were placed in the dissolution media (sink condition) which were agitated at 69 cycles/

Table 1
Solution pH of sulphanilamide, sulphaguanidine and sulphathiazole and their solubilities in different dissolution media

Drug	pH of 1.96×10^5 M drug solution	Solubility (g/100 ml)		
		USP HCl buffer	Distilled water	USP phosphate buffer
Sulphanilamide	6.5 ± 0.1	2.296 ± 0.192	0.840 ± 0.039	0.826 ± 0.087
Sulphaguanidine	5.2 ± 0	1.976 ± 0.048	0.102 ± 0.008	0.109 ± 0.013
Sulphathiazole	3.9 ± 0.1	0.812 ± 0.121	0.051 ± 0.006	0.083 ± 0.002

Table 2
Physical properties and drug release profiles of microspheres containing sulphanilamide, sulphaguanidine and sulphathiazole

Drug	Drug content (%)	Mean diameter (μm)	Specific surface area (mm^{-1})	Percentage drug released in different dissolution media (%)											
				USP HCl buffer				Distilled water				USP phosphate buffer			
				P_{30}	P_{90}	P_{150}	P_{1350}	P_{30}	P_{90}	P_{150}	P_{1350}	P_{30}	P_{90}	P_{150}	P_{1350}
Sulphanilamide	7.38 ± 0.98	32.25 ± 5.74	186.08	2.24 ± 0.02	3.87 ± 1.51	5.64 ± 1.33	7.11 ± 0.70	1.48 ± 0.12	2.15 ± 0.27	2.37 ± 0.16	2.14 ± 0.49	1.08 ± 0.05	2.72 ± 0.14	4.20 ± 0.06	5.87 ± 0.26
Sulphaguanidine	18.64 ± 0.42	37.54 ± 7.40	159.83	70.22 ± 5.30	78.30 ± 1.83	80.94 ± 1.54	83.60 ± 3.58	29.20 ± 0.25	50.89 ± 0.39	61.89 ± 1.05	70.17 ± 1.16	31.16 ± 2.99	62.55 ± 2.98	72.59 ± 1.71	75.05 ± 1.15
Sulphathiazole	19.74 ± 0.68	43.35 ± 9.36	138.41	65.87 ± 6.23	85.85 ± 0.63	86.31 ± 0.19	85.96 ± 0.26	10.27 ± 0.67	27.29 ± 1.96	41.10 ± 2.73	80.37 ± 6.84	34.79 ± 7.90	69.17 ± 0.73	77.16 ± 0.30	80.42 ± 2.14

Table 3
Drug content of microspheres after 1350 min in dissolution media

Drug	Drug content of microspheres (%)		
	USP HCl buffer	Distilled water	USP phosphate buffer
Sulphanilamide	6.89	7.23	6.98
Sulphaguanidine	3.62	6.40	5.41
Sulphathiazole	3.34	4.61	4.59

min (MT20S, Lauda, Germany) at 37 ± 1 °C. Samples were withdrawn at various time intervals, diluted and assayed spectrophotometrically. The percentage of drug released at 30 min (P_{30}), 90 min (P_{90}), 150 min (P_{150}) and 1350 min (P_{1350}) were calculated with respect to the drug content of the microspheres. Determination of drug content and drug release of each batch of microspheres was carried out in triplicates and the results averaged. The pH of the aqueous drug solution and the solubility of the drug in different dissolution media were also determined at 29 ± 1 °C. Each determination was carried out in duplicates and the results averaged.

3. Results

Calcium pectinate microspheres were successfully prepared by the emulsification technique. The microspheres produced were generally discrete and spherical (Fig. 1). Drugs of lower water solubility were found to produce larger microspheres with a higher drug content (Tables 1 and 2). All the batches of microspheres showed the most rapid release of drug in USP HCl buffer, followed by USP phosphate buffer and distilled water (Table 2). The higher rates of drug release in USP HCl and phosphate buffers were partially attributed to the conversion of calcium pectinate to pectin due to ion exchange and sequestration of calcium in buffers (Østberg et al., 1994). The higher solubility of the drug in these buffers also contributed to the more rapid release of the drug from the microspheres (Tables 1 and 2).

Interestingly, the lowest percentage of drug release was produced by the microspheres with the lowest mean size and corresponding largest specific surface area, consisting of the most water soluble drug, sulphanilamide. The percentage of sulphanilamide released from the microspheres was extremely low after 1350 min in distilled water and buffers (Table 2). The opposite was observed for microspheres containing sulphaguanidine and sulphathiazole. The amount of drug released after 1350 min ranged from 2.14 to 85.96%, indicating that the drugs interacted to different extents with the pectinate matrix. Sulphanilamide, sulphaguanidine and sulphathiazole have basic amino groups for interaction with the carboxyl group of pectin. The formed microspheres consisted of both bound and unbound drug molecules. The unbound drug molecules were more readily released into the dissolution media than the bound fraction.

4. Discussion

Sulphanilamide has a relatively high water solubility (0.840 ± 0.039 g/100 ml). During the process of microencapsulation, a significant fraction of the drug was lost to the aqueous phase. Consequently, the resultant microspheres had a low drug content. The consistently low rate and extent of drug released in all the dissolution media studied indicated that a large fraction of the encapsulated drug was strongly bound to pectin. On the other hand, sulphaguanidine and sulphathiazole have markedly lower water solubilities, 0.102 ± 0.008 and 0.051 ± 0.006 g/100 ml, respectively. Consequently, the microspheres produced contained markedly higher drug contents. These microspheres probably had a lower fraction of

bound drug as the percentage of drug released was higher than that of sulphanilamide.

The amount of drug remaining in the microspheres after 1350 min in all the three dissolution media was highest for sulphanilamide, followed by sulphaguanidine and sulphathiazole (Table 3). Based on the chemical structure and higher basicity of sulphanilamide (Table 1), it is probably more positively charged than the other two drugs in the three dissolution media. Hence, the extent of interaction of sulphanilamide with the negatively charged pectin was expected to be greater.

In USP phosphate buffer, the percentages of drug released from the microspheres containing sulphaguanidine at 90 and 150 min were lower than the corresponding values of microspheres containing sulphathiazole. The opposite was observed for dissolution study in distilled water. Under the conditions of pH 5.5 and 7.4, the pectin (pK_a of –COOH = 3.5) was completely deprotonated and gave rise to negatively charged carboxylate groups. Unlike the other two drugs, sulphathiazole had a significantly higher water solubility at pH 7.4 than at pH 5.5 (Table 1, Student's t-test, $P < 0.05$), indicating that sulphathiazole was charged at pH 7.4. Based on its chemical structure, it was likely to be negatively charged. Repulsion between pectin and sulphathiazole of similar charge could reduce the drug–pectin interaction and thus enhance the release of sulphathiazole from the microspheres.

5. Conclusion

In conclusion, the dissolution medium affected drug release of pectinate microspheres by modifying drug solubility and integrity of the pectinate matrix. The rate of drug release generally decreased in the following order: USP HCl buffer > USP phosphate buffer > distilled water. The drug core also influenced drug release through interaction with the pectin polymer.

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