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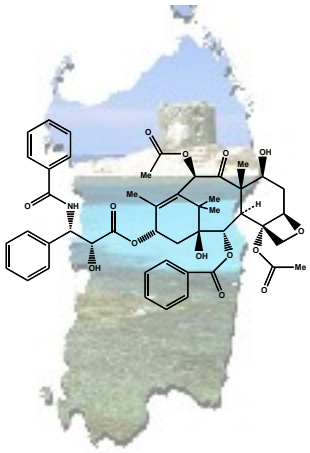
GIORNATA DI STUDIO DEDICATA ALLA CHIMICA ORGANICA DELLE MOLECOLE BIOLOGICAMENTE ATTIVE

30 Maggio 2008, Aula Magna della Facoltà di Scienze – Sassari



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STUDY OF DISSOLUTION RATE ENHANCEMENT OF POORLY WATER SOLUBLE DRUG

Giovanna Rassu, Elisabetta Gavini, Gianpiera Spada, Paolo Giunchedi

Dipartimento Scienze del Farmaco, Università degli Studi di Sassari, via Muroni 23/a, 07100 Sassari,

Chitosan (C), a linear polysaccharide produced by a process of deacetylation from chitin, is one of the most used polymer in pharmaceutical products. In recent years, chitosan salts and derivatives have been studied to improve polymer solubility at different pH [1]. Chitosan is able to enhance the dissolution rate of low water soluble drugs and thus can be exploited for bioavailability enhancement of such drugs [2-4]. Recently, Gavini *et al.* found that the loading of carbamazepine into the chitosan microspheres always led to an increase in the dissolution rate compared to the raw material and the microparticulate system based on chitosan glutamate was able to promote rapid drug absorption through the nasal mucosa and to remarkably improve the bioavailability of the drug [5]. Rokitamycin (RK) is a macrolide antibacterial which recently has shown antiamoebic effects *in vitro* [6]; it is a weak base only slightly soluble in water and its solubility in water depends on pH [7]. Thus, aim of this work is the preparation of spray-dried microspheres as drug delivery systems for RK, using chitosan (C) and its salt, chitosan glutamate (CG) to improve the dissolution rate of the drug. The work further aimed to investigate the effect of the type of chitosan and feed solution concentration on the microsphere properties. Four microparticulate formulations (Table 1) containing C or CG loaded with RK were prepared using a spray-drying technique. Drug to polymer ratio 1:5 and feed solution concentrations (SC) of 0.25% and 1.0% (w/v) were employed. The microspheres were characterised with respect to properties such as drug content, particle size and particle size distribution, morphology and *in vitro* release of RK.

Table 1. Preparation and characterization of microspheres

Formulations	Polymer	SC (% w/v)	RDC (%) ± SD	EE (%) ± SD	d_{vs} (μm)	SPAN
C A	C	1	14.1 ± 0.2	84.5 ± 1.1	2.57 ± 0.12	3.65
C B	C	0.25	12.5 ± 1.0	72.5 ± 5,5	2.04 ± 0.17	4.64
CG A	CG	1	12.6 ± 0.4	75.4 ± 2.5	2.19 ± 0.08	2.32
CG B	CG	0.25	10.4 ± 0.2	62.3 ± 1.0	1.71 ± 0.13	1.17

Results show that spray-drying appears a suitable method for the preparation of RK-loaded microspheres containing C and CG, with good yields of production ranging from 53% to 60%.

The real drug contents values found (RDC), expressed as percentage, are lower than theoretical one (16.7%) and thus, the encapsulation efficiencies (EE) are ranging from 62% to 84% (Table 1). All microspheres prepared are characterised by small size: the volume-surface diameter values, d_{vs} (μm), range from 1.7 μm to 2.6 μm. Drug-loaded microspheres prepared from the most concentrated feed solution (1%) have a larger particle size than corresponding microspheres prepared from a less concentrated solution (0.25%). CG microspheres show the narrowest particle size distribution. All microspheres produced show spherical shape and smooth surface. No free drug crystals are found outside the microspheres confirming good encapsulation efficiencies. The *in vitro* release of RK from the different formulations prepared was evaluated and compared with the dissolution profile of pure drug (Figure 1). The crude RK is characterised by poor water solubility and its dissolution rate is very slow (about 15% dissolved within 3 h). The encapsulation of RK into chitosan microspheres gives an increase in the drug dissolution rate regardless polymer used, except for C B microspheres whose release profile is almost superimposed to the pure drug profile within 90 min; then the polymer, slightly improve dissolution rate of RK. The enhancement effect depends on the concentration of feed solution: high concentration corresponds to a more rapid dissolution rate.

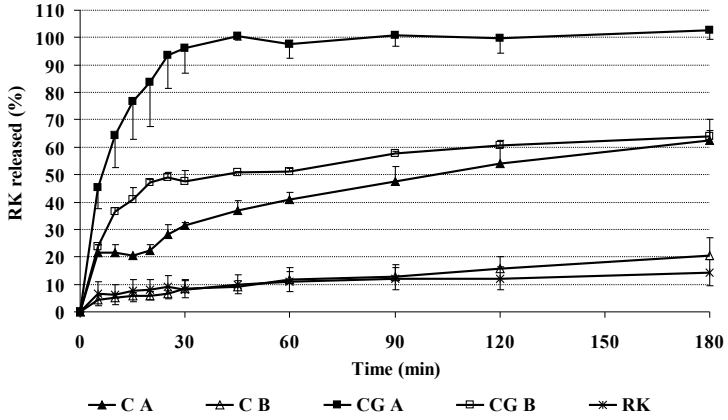

Figure 1. The *in vitro* RK release from formulations

References

[1] Gavini *et al*., Eur. J. Pharm. Biopharm. 68 (2008) 245-252. [2] Giunchedi *et al*., Eur. J. Pharm. Biopharm. 53 (2002) 233-239. [3] Maestrelli *et al*., Int. J. Pharm. 271 (2004) 257-267. [4] Sinha *et al*., Int. J. Pharm. 274 (2004) 1-33. [5] Gavini *et al*., Int. J. Pharm 307 (2006) 9-15. [6] Mattana *et al*., Antimicrob. Agents Chemoth. 48 (2004) 4520-4527. [7] Petitjean *et al*., J. Pharm. Biomed. Anal. 13 (1995) 817-822.