

In vivo evaluation of pH-sensitive polymeric microparticles for site specific drug delivery to the small intestine and colon

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ABSTRACT SUMMARY

A novel emulsification/solvent evaporation process was developed to formulate prednisolone-loaded Eudragit L and S microparticles as drug delivery vehicles to target different regions of the gastrointestinal tract. Microparticles were characterised in vitro and in vivo. This is the first report of drug absorption from orally administered Eudragit L and S microparticles.

INTRODUCTION

Delayed release oral dosage forms are designed to target either the small intestine (for gastric irritant or labile molecules) or the colon (for the treatment of localised disorders or delivery of peptides and proteins). The most commonly used method for targeting these regions is to exploit the increasing luminal pH from stomach to colon by applying a pH-sensitive film coating to a core dosage form. The film coating polymer is expected to ionise and dissolve above a threshold pH specific to either the duodenum (pH 5-6) or colonic region (pH 7-7.5).

Unfortunately, as the application of pH-sensitive coatings generally renders the dosage form non-disintegrating in the stomach, gastric emptying becomes delayed and variable from both tablets (Khosla et al., 1989) and pellets (Clarke et al., 1993), making the onset of drug action highly unpredictable. Furthermore, pharmacoscintigraphic studies have shown a lag time of 1-1.5 hours post gastric emptying before enteric coated dosage forms disintegrate (Ebel et al., 1993; Wilding et al., 1993), which further impacts onset of action and drug bioavailability. Due to the limited fluid content in the colonic region, pH-sensitive coating dissolution may be further retarded, and tablets intended to deliver drug to the colonic region have been observed, on occasion, to be voided intact.

The aim of this research was to formulate pH-sensitive microparticles for small intestinal or colonic delivery, which may suspend in the stomach contents therefore emptying rapidly and reproducibly. The large surface area of the pH-

sensitive microparticles should facilitate rapid drug release above the threshold pH of the pH-sensitive polymer. The in vivo performance of the pH-sensitive microparticles was tested in fed rat, given the similarities between rat and man gastrointestinal (GI) transit times and pH.

EXPERIMENTAL METHODS

A novel but simple emulsification/solvent evaporation method was developed to produce Eudragit L (soluble pH>6) and S (soluble pH>7) prednisolone-loaded microparticles (5:1 polymer:drug), for small intestinal and colonic drug delivery, respectively. Drug encapsulation efficiency was calculated. Microparticles were characterised by SEM, particle size analysis (Malvern Mastersizer), and X-ray diffraction (XRD). In-vitro dissolution experiments were carried out using USP II dissolution apparatus using a pH-change method, simulating gastric to small intestinal and colonic conditions. Eudragit L and S microparticles and micronized prednisolone (control, crystalline drug substance, 5µm particle size) suspensions were administered to rats by oral gavage (2ml, 200mg/kg prednisolone). Plasma samples were collected by tail vein sampling at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hours post dose, and the plasma was assayed for prednisolone content by HPLC-MS/MS.

RESULTS AND DISCUSSION

Prednisolone encapsulation efficiency was ~90% for both polymers. SEM showed microparticles to exhibit excellent morphology, being spherical, non-aggregated and non-porous (Fig. 1).

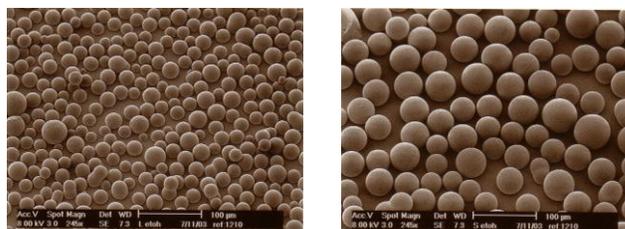


Figure 1: SEM image of Eudragit L100 (left) and S100 (right) microspheres (bar is 100 µm)

Median microparticle size was $<50\mu\text{m}$, with a narrow size distribution, for both polymers. XRD revealed that encapsulated drug was in the amorphous form. In vitro, Eudragit L and S formulations displayed pH-responsive release, leaking a negligible amount of drug after 2 hour incubation in acid, and releasing all the drug rapidly (within 5 minutes) at small intestinal and colonic pH, respectively.

The in vivo absorption profiles for the two test formulations and the control and summary of pharmacokinetic data are shown in Figures 2 and Table 1 below.

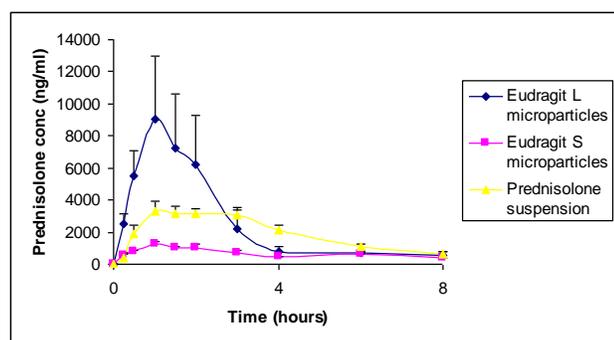


Figure 2: Mean (\pm SEM) plasma concentration-time profiles for the three test formulations

Formulation	AUC (ng.h/mL)	C_{max} (ng/mL)	T_{max} (min)
Susp.	15372 (\pm 2377)	4152 (\pm 829)	102 (\pm 45)
Eud L	20435 (\pm 18377)	8704 (\pm 8765)	48 (\pm 15)
Eud S	5414 (\pm 1570)	1376 (\pm 444)	72 (\pm 24)

Figure 3: Summary of pharmacokinetic parameters for the three test formulations

Prednisolone absorption from Eudragit L microparticles was more rapid than from the control suspension (Table 1). Relative bioavailability was also increased by one third compared to prednisolone suspension. This is likely to be due to the rapid increase in pH from stomach to duodenum (from 4.5 to 6.9) in the fed rat (Ward and Coates, 1987), which led to the rapid dissolution of the Eudragit L matrix (threshold pH = 6) and rapid release of entrapped prednisolone in a pre-solubilised (amorphous) form. Prednisolone was therefore available for rapid absorption from the proximal small intestine, which is the optimal site for the absorption of most drugs.

In contrast, prednisolone absorption from Eudragit S microparticles was more sustained. The lower

absorption is due in part to the GI physiology of the rat, where pH above 7 (threshold pH for Eudragit S) only occurs in the ileal region, where fluid volume is also limited. The luminal contents of the rat ileal region represent a far from ideal environment for dissolution of Eudragit S microparticles, and this results in a relative reduced bioavailability compared to the control suspension whose dissolution was aided by the small particle size and which occurred along the whole length of the GI tract. Furthermore, absorption of prednisolone in the ileal region is less than half as efficient as from the duodenum due to the presence of intestinal P-glycoprotein in this region (Nakayama et al., (1999). Prednisolone may not have been the ideal model drug to test absorption in the lower ileum. It is interesting to note, however, that although the level of prednisolone absorption was low for the Eudragit S microparticles, C_{max} occurred more rapidly than from the control suspension. This is probably due to release of amorphous prednisolone located near to the surface of the microparticle in the upper small intestine, where absorption of prednisolone is favoured.

CONCLUSION

A novel yet simple method was developed for the production of Eudragit L and S microparticles, for small intestinal and colonic delivery. The microparticles are of a size that may facilitate rapid gastric emptying and less variable GI transit than conventional delayed release dosage forms. In vivo experiments in rats suggest that Eudragit L microparticles released a model drug, prednisolone, rapidly in the proximal small intestine, hastening the onset of drug action and improving bioavailability. Enhancement of bioavailability is one of the major challenges faced in the field of biopharmaceutics, given the ever increasing number of poorly soluble, and often basic, compounds currently in development. Prednisolone absorption from Eudragit S microparticles was lower than anticipated considering the similarity of human and rat GI pH, but a result of low fluid volume in the rat GI tract which hinders dissolution and the diminished absorption in the lower small intestine. The rat pharmacokinetic data provides the proof of concept data required for forthcoming studies in man.

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