Development of Novel Radiolabelling Method for Low Dose Drug Products for Investigation of in Vivo Performance in Gamma Scintigraphic Studies

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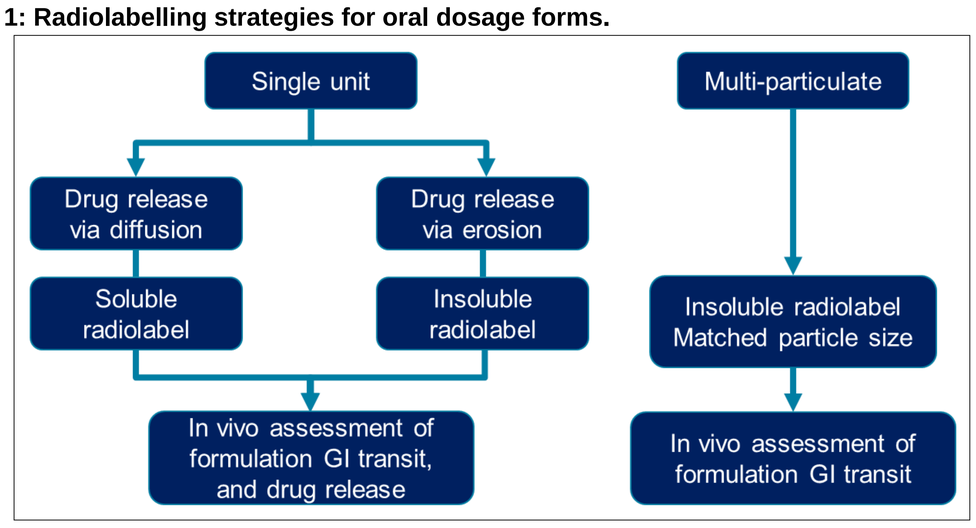
INTRODUCTION

Drug X is a 5HT4 receptor agonist in development for gastro oesophageal reflux disease in patients with persistent symptoms of regurgitation while on PPI therapy. To support this indication, a combined pharmacokinetic and scintigraphic imaging study is required to assess the *in-vivo* performance of a range of formulation platforms, including immediate release (IR) tablets, pulse release tablets, pulse release mini-tablets and a buccal film containing pulse release particulates.

In order to employ scintigraphic imaging, a gamma emitting isotope must be incorporated into the formulations. The conventional radiolabelling strategies implemented at Quotient are outlined in Figure 1. For this study an insoluble form of the radiolabel is required.

Figure 1: Radiolabelling strategies for oral dosage forms.



As drug X is a salt-form for a weakly basic compound with a very low therapeutic dose (0.5mg), it was possible that conventional radiolabelling using indium-111 (^{111}In) labelled cationic ion-exchange resin may result in API-resin interaction and hence may not be a suitable approach. Preliminary investigations confirmed significant drug-radiolabel interaction. With the minimum level of resin (5mg) in the tablet (total tablet weight 150mg) only 32.9% of Drug X was recovered. Therefore, it was concluded that the conventional radiolabelling approach was not suitable for this investigation. This poster describes the development of a novel radiolabelling strategy.

MATERIALS AND METHODS

Two approaches were investigated:

1. **Isolation of radiolabelled ion-exchange resin by coating:**
   - Ion-exchange resin was coated with a range of insoluble polymers (e.g. Eudragit S100) or paraffin wax.
   - Coated resin was mixed with Drug X solution in 0.1M hydrochloric acid (HCl) or pH 6.8 phosphate buffer for 30 minutes and the samples analysed to confirm any interaction with the API.
2. **Radiolabelled ethylcellulose microspheres :**
   - Microspheres were prepared using the oil in water (O/W) solvent evaporation technique.
   - The organic polymer solution was prepared by mixing ethylcellulose N10 with ^{111}In chloride solution. This was dried for 1 hour before dispersion in dichloromethane.
   - The O/W emulsion was prepared by emulsification of the organic polymer solution in the aqueous phase (0.5% HPMC solution) by stirring.
   - The microspheres were solidified by stirring the emulsions in additional water for 1 hour, and then collected under vacuum filtration and dried overnight.
   - Encapsulation efficiency and radioactive leaching were measured by suspending the radiolabelled microspheres in 0.1M HCl or pH 6.8 phosphate buffer for 6 hours.
   - Microsphere loaded Drug X tablets were manufactured to confirm any interaction with the API.
   - Optimisation of microsphere particle size was conducted by varying preparation conditions, with characterisation by light microscope and SEM.

RESULTS AND DISCUSSION

1. Isolation of radiolabelled ion-exchange resin by coating:

The results confirmed that API-resin interaction was reduced, particularly for polymeric solutions at a 5% concentration and for paraffin wax (Table 1). Nonetheless, the interaction between the two entities was not eliminated.

Table 1: Assay of Drug X solutions containing coated resin (n=1).

Sample	Drug X assay (%)	
	0.1M HCl	pH 6.8 buffer
Uncoated resin	1.8	28.4
Resin coated with 1% Eudragit S100	1.7	36.2
Resin coated with 5% Eudragit S100	27.3	59.8
Resin coated with paraffin wax	5.2	45.9

2. Radiolabelled ethylcellulose microspheres:

Encapsulation of ^{111}In chloride in ethylcellulose microspheres was successful. The majority of the radioactivity remained bound to the microspheres in 0.1M HCl (Figure 2) and incorporation of these microspheres into Drug X IR tablets did not result in an drug-microsphere interaction (Table 2).

Figure 2: Percent ^{111}In chloride bound to ethylcellulose microspheres after stirring for 6 hours in 0.1M HCl.

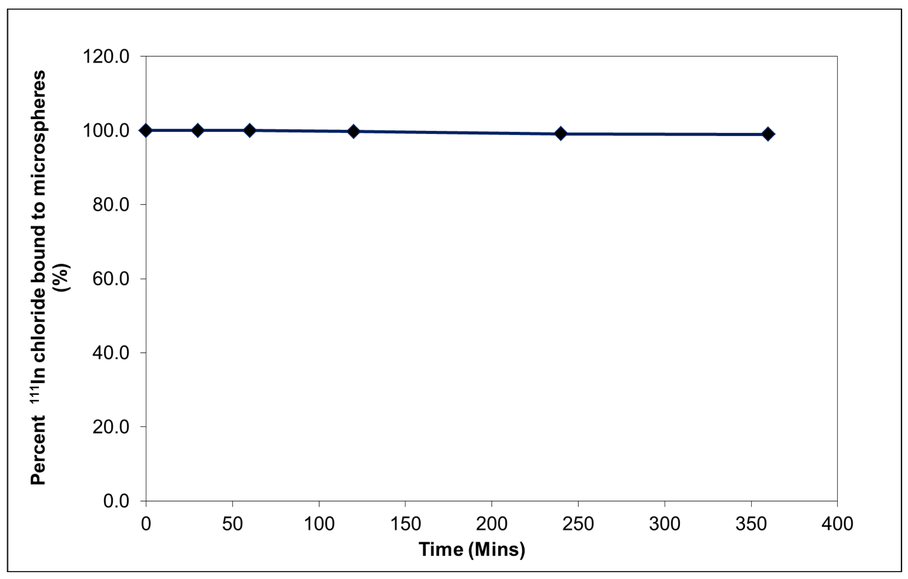
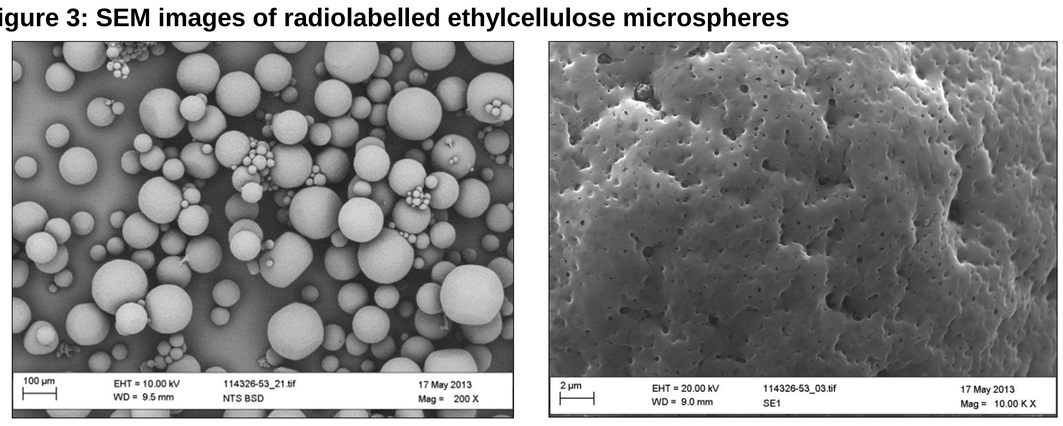


Table 2: Assay of Drug X tablets containing microspheres (n=10).

Sample	Drug X assay (%)
0.5mg Drug X tablet	95.7
0.5mg Drug X tablet + 20mg ethylcellulose microspheres	100.9
0.5mg Drug X tablet + 50mg ethylcellulose microspheres	101.0

The particle size of microspheres was approximately 180µm (Figure 3). By adjusting the mixing speed during the O/W emulsification process microspheres with different diameters were prepared for use in the different Drug X dosage forms.

Figure 3: SEM images of radiolabelled ethylcellulose microspheres



CONCLUSIONS

Conventional and novel approaches for radiolabelling low dose Drug X tablets have been investigated. The encapsulation of ^{111}In chloride in ethylcellulose microspheres allows incorporation of a radiolabel marker whilst minimising impact on key formulation performance characteristics. Larger microspheres can also be prepared and used as radiolabelled surrogates for scintigraphic studies involving microparticulate formulations.

FURTHER READING

[1] McDermott J, Scholes P, Connor A. Radiolabelling technologies for scintigraphic evaluation of oral pharmaceutical dosage Forms, AAPS poster 2008

[2] Lobo ED, Argentine MD, Sperry DC, Connor A, McDermott J, Stevens L, Almaya A. Optimization of LY545694 tosylate controlled release tablets through pharmacoscintigraphy. Pharm Res 2012; 29:2912-2925