Poster no
T2107

Can radiolabelled placebo pellets be used as GI transit markers for drug-loaded pellets?

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ABSTRACT

Purpose
To validate the use of radiolabelled placebo pellets as GI transit markers for drug-loaded pellets in scintigraphic studies.
Methods
Placebo and drug loaded pellets were prepared by extrusion spheronisation and coated with 10 % (w/w) Surelease® using a Caleva Mini Coater/Drier 2. Placebo pellets were composed of 95 % (w/w) MCC and 5 % (w/w) ion exchange resin and soaked in 99mTc-pertechnetate prior to film coating. Drug loaded pellets were composed of 10 % (w/w) paracetamol, 45 % (w/w) MCC and 45 % (w/w) lactose. Pellets were subjected to USP I dissolution (900 mL water, 37 ºC, 100 rpm) for 18 hours with additional scintigraphic monitoring of placebo radioactive pellets.
Size and density of placebo and drug-loaded pellets were measured before and after dissolution. Additional measurements were taken at 2, 4 and 12 h for drug-loaded pellets. Pellet size was measured using a Malvern Mastersizer 2000 and density was calculated from the volume and weight of approximately 200 pellets. The radioactive counts associated with placebo pellets at 0 and 18 h were determined by drawing regions of interest around the pellets and background and decay-correcting the counts obtained.
Results
Placebo pellets had minimal size and density changes after dissolution. Mean size and density pre-dissolution were 1.30±0.01mm and 0.84±0.02 g/cm^3 respectively. Post-dissolution, the corresponding values were 1.29±0.03 mm and 0.85±0.02 g/cm^3.
The size of drug-loaded pellets varied minimally but their density decreased over time (Table 1), due to drug loss as a consequence of dissolution.
The change in radioactive counts within the radioactive placebo pellets after 18 h dissolution was minimal, with a mean of 99.0% of the radiation retained within the pellets.
Conclusion
Clarke *et al.* (1995) indicated that GI transit behaviour of pellets with a size range of 1.2-1.4 mm and densities below 2.4 g/cm^3 are independent of size and density. This method of using radiolabelled placebo pellets is potentially suitable for scintigraphic monitoring of GI transit.

Table 1. Drug loaded pellets' size and densities (±SD) during dissolution.

Time post-dissolution start (h)	Size (mm)	Density (g/cm^3)
0	1.25±0.01	1.04±0.02
2	1.26±0.01	0.81±0.02
4	1.21±0.04	0.71±0.01
12	1.26±0.04	0.52±0.01
18	1.23±0.03	0.56±0.01

PURPOSE

Two different pellet formulations may transit the gastrointestinal (GI) tract at different rates due to differences in size and/or density. However, Clarke *et al.* (1995) found that there is no difference in GI transit for pellets of size 1.2-1.4 mm and density below 2.4 g/cm^3. When using placebo pellets as markers for GI transit of an investigated pellet formulation, it is important that the placebo pellets mimic the size and density of the investigated pellet formulation or that both pellets are of size 1.2-1.4 mm and density below 2.4 g/cm^3. This study validates the use of radiolabelled placebo pellets as GI transit markers for drug-loaded pellets in gamma scintigraphic studies.

EXPERIMENTAL METHODS

PELLETISATION: Placebo and drug-loaded pellets were prepared by extrusion spheronisation. Placebo pellet cores were composed of 99 %(w/w) microcrystalline cellulose and 1 %(w/w) anion exchange resin. Drug-loaded pellet cores were composed of 10 %(w/w) paracetamol, 45 %(w/w) MCC and 45 %(w/w) lactose. Pellet cores of size range 1.00-1.18 mm were sieve collected and coated with Surelease® to achieve a weight gain of 9 %(w/w) using a Caleva Mini Coater/Drier 2. The addition of a film coat to the pellet cores increased the size of the final pellet formulation. Placebo pellet cores were soaked in a ^{99m}Tc-pertechnetate solution prior to film coating.

***IN VITRO* SCINTIGRAPHIC STUDY:** Radioactive placebo pellets of 2 MBq (200 mg) (n=3) were subjected to USP I dissolution (900 mL water, 37 ºC, 100 rpm) for 18 hours. The radioactive counts associated with the pellets during dissolution were determined by drawing regions of interest (ROI) around the pellets and background and decay-correcting the counts obtained.

PELLET SIZE AND DENSITY: Size and density of placebo and drug-loaded pellets were measured before and after the *in vitro* dissolution. Additional dissolution experiments were carried out for the measurement of size and density at 2, 4 and 12 h for drug-loaded pellets. Pellet size was measured using a Malvern Mastersizer 2000 and density was calculated from the total volume and weight of all pellets from each dissolution experiment (n=3).

***IN VITRO* DRUG RELEASE STUDY:** Drug-loaded pellets (200 mg) (n=3) were subjected to USP I dissolution (900 mL water, 37 ºC, 100 rpm) for 18 hours. Paracetamol release was monitored by UV spectrophotometry at 257 nm.

RESULTS AND DISCUSSION

PELLETISATION: Film coated extruded and spheronised pellets were successfully produced. The pellet cores had smooth surface areas which aided the coating process.

***IN VITRO* SCINTIGRAPHIC STUDY:** Gamma scintigraphic imaging confirmed that the radiolabel was retained within the radioactive placebo pellets. A gamma scintigraphic image during dissolution of radiolabelled placebo pellets at t=2 h is shown in Figure 1.

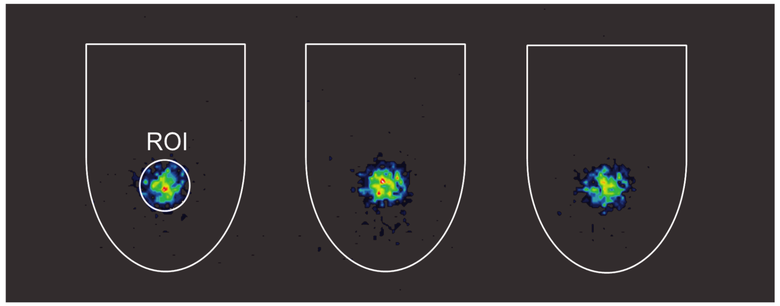

Fig. 1. Gamma scintigraphic image during dissolution of radioactive placebo pellets at t=2 h. An ROI and the dissolution vessels are drawn on the image.

The change in radioactive counts within the radioactive placebo pellets during the 18 h dissolution was negligible. A graph of change in radioactive counts is shown in Fig. 2. This confirms that during any *in vivo* scintigraphic study any image captured will accurately reflect the GI position of the radiolabelled placebo pellets.

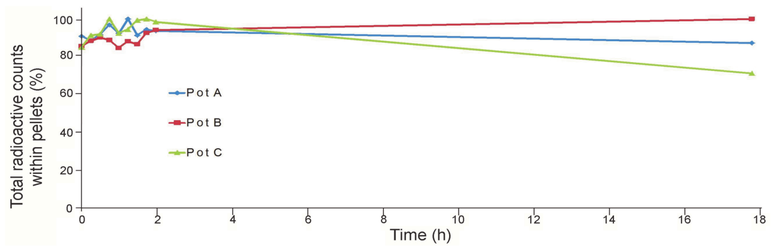

Fig. 2. Graph of change in radioactive counts in the ROI of the three batches.

PELLET SIZE AND DENSITY: Prior to dissolution the size of the drug-loaded pellets and the placebo pellets was almost similar and within the range of 1.2-1.4 mm. The density of the placebo pellets was lower than the drug-loaded pellets but both formulation had densities below 2.4 g/cm^3 (Table 1).

Table 1. Size and density of drug-loaded pellets and placebo pellets at various dissolution times (mean±SD, n=3).

Time post-dissolution start (h)	Pellet size (mm)		Pellet density (g/cm^3)	
	Drug-loaded pellets	Placebo pellets	Drug-loaded pellets	Placebo pellets
0	1.25±0.01	1.30±0.01	1.04±0.02	0.84±0.02
2	1.26±0.01		0.81±0.02	
4	1.21±0.04		0.71±0.01	
12	1.26±0.04		0.52±0.01	
18	1.23±0.03	1.29±0.03	0.56±0.01	0.85±0.02

The placebo pellets had minimal size and density changes after 18 hours of dissolution. The drug-loaded pellets also had minimal size changes but their density decreased over time. The size was within 1.2-1.4 mm and the density below 2.4 g/cm^3 during the entire 18 h dissolution studies of both pellet formulations. These are the size and density limitations suggested by Clarke *et al.* (1995) where no difference in GI transit is observed.

***IN VITRO* DRUG RELEASE STUDY:** The large decrease in density of the drug-loaded pellets is due to drug and excipient loss as a consequence of dissolution. This is illustrated in Fig. 3 where it can be observed that the density change plateaus as the pellets approach 100 % drug release.

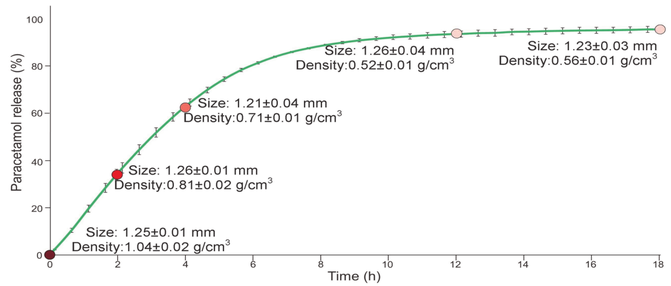

Fig. 3. Size and density during dissolution of drug-loaded pellets at dissolution points represented by dots (mean±SD, n=3).

CONCLUSION

During the 18 h of dissolution, the size and density of the drug-loaded and the placebo pellets were within the suggested limits of which no difference in GI transit is observed. The radiolabel of placebo pellets was retained within the pellets. This method of using radiolabelled placebo pellets is therefore potentially suitable for scintigraphic monitoring of GI transit.

REFERENCE

Clarke, G. M., Newton, J. M., Short, M. B. (1995) Comparative gastrointestinal transit of pellet systems of varying density. International Journal of Pharmaceutics. 114, 1-11.

ACKNOWLEDGEMENT

T. Jónsson is a Knowledge Transfer Partnership Associate funded by the Technology Strategy Board and Bio-Images Research Ltd.