Poster Number 10T0130

RECONSTITUTED LIQUID FILLED HARD CAPSULES FOR PAEDIATRIC APPLICATIONS

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2016 AAPS ANNUAL MEETING AND EXPOSITION
NOVEMBER 13–17, 2016
COLORADO CONVENTION CENTER, DENVER
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PURPOSE

In a comprehensive review on oral paediatric dosage forms, Strickley *et al* (2008) categorised oral paediatric formulations in two broad categories: 1: the ready to use dosage forms such as a solution/suspension, a syrup, a chewable or fast dissolving tablets, oral strip; 2. Dosage forms that some manipulations may be required, for example, effervescent tablets, powders/granules or concentrated solutions that can be mixed with foods or drinks.

Generally the "Ready-to-use" dosage forms are convenient to administer and have a greater control of the uniformity of administered dose. However, dosage forms that require some manipulation can be easily adjusted for flexible doses of different body weights and ages. The reconstitution approach can be tailored to the child's favourite foods/drinks, thereby facilitating compliance. This approach is also useful when a larger dose is required where the "ready to use" dose can be too large to be administered.

Potentially, a re-constituted liquid filled hard capsule can combine some of the advantages of both the "Ready-to-use" and reconstituted dosages, i.e., when a larger dose is required then multiple capsules can be administered, therefore maintaining uniformity as well as flexibility of dosing, and providing an interesting solution to paediatric formulation development.

The purpose of this study is to investigate the reconstitution behaviour of hard capsules filled with a neutral tasting medium chain triglyceride in milk and several soft foods, thereby demonstrating feasibility of this approach.

METHOD

Plantcaps™ (pullulan), Vcaps+™ (HPMC) and Conisnap™ (gelatin) capsules were filled with Miglyol (unbanded).

The pullulan capsules were size one capsules filled with 523.6mg Miglyol, the HPMC capsules were size 2 with 277.3mg and Conisnap capsules were size 1 with 351.9mg fill weight. Different sizes of capsules were used because of their availability at the time of experimentation. As excess liquid/soft foods were used for the experiments, the difference in size would be unlikely to cause any differences in reconstitution behaviour.

Milk was first heated to 50°C. Then 10g of the warm milk was placed to 20ml glass vials and capsules placed within. To mimic the likely use conditions, the whole content was allowed to cool at the ambient conditions.

In a separate experiment, 10g of cold milk, custard or a children's fruit puree (prepacked) was placed in a 20ml glass vial and the filled capsules were submerged in the foods and left for approximately 40 minutes at room temperature. The dispersibility of the capsules were then assessed by gently mixing the contents and examining the presence of any capsule remnants.

RESULTS

Dispersibility in hot milk

The Conisnap™ (gelatin) capsules began to soften/disintegrate after 2min, however, the capsules shells were not fully disintegrated. Large remnant of capsule shells was clearly visible after 40min (seen through the bottom of the glass vial, Figure 1, left).

The Vcaps+™ (HPMC) capsules began to soften after 2min and the content started to leak out of the capsules after 4 minutes and the capsules appeared to be almost completely disintegrated after 10min. A final check after 40mins confirmed the capsule had fully disintegrated.

The Plantcaps™ (pullulan) capsules started to soften after 1 min. The capsules appeared to have disintegrated after 13min. At the end of the test (40min), minor fragments of the capsule shells could still be seen (about 2mm) which would have not presented any choking hazard (Figure 1, right).

Dispersibility at room temperature in milk, custards and fruit puree

Capsules were added to the different food mixes and observed after 40mins. The Plantcaps™ (pullulan) capsules were fully dispersed in all three foods (Figure 2). The Vcaps+™ (HPMC) capsules appeared to be partially dissolved in all 3 products, however on gentle stirring with a spatula, the capsule shells were fully dispersed in all 3 products. The Conisnap™ (gelatin) capsules were however not fully dispersed even after stirring with a spatula.

An oily layer was visible with capsules reconstituted with milk, however it was barely visible with the custard and not visible with the fruit puree perhaps due to the viscosity (consistency) of these products.

The reconstitution rates of these capsules are attributable to the nature of the capsule shell materials, pullulan being a non gelling polysaccharide and gelatin, a strong gelling polymer and HPMC somewhat in between, thereby exhibiting different hydration/disintegration characteristics.

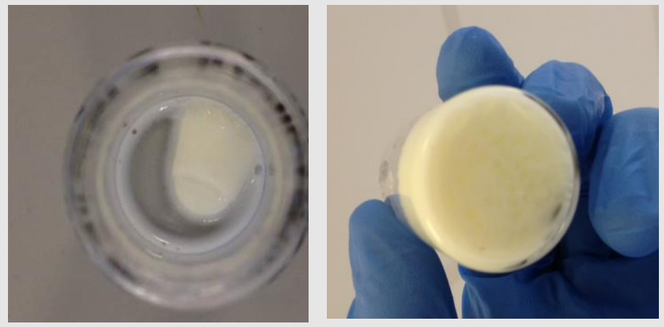

Figure 1: Capsules after 40minutes reconstitution in warm milk. Left, a gelatin capsule. Right, a pullulan capsule. A large remnant is visible with the gelatin capsule.

Figure 2: Reconstitution of Miglyol filled pullulan capsules in cold milk (left), custard (centre) and fruit puree (right).

REFERENCE

Strickley, R G, Iwata Q, Wu, S, Dahl, T C 2008 Paediatric drugs – a review of commercially available oral formulations. J Pharm Sci 97: 1731-1774

CONCLUSION

Liquid filled hard capsules, in particular those based on pullulan and HPMC can provide a viable solution to the challenges of paediatric formulations because of their ready dispersibility in liquid/soft foods. Multiple capsules can be used where a larger dose is needed, hence potentially meeting a wider range of dose/age requirements.