DEVELOPMENT OF A SIMPLE PATIENT CENTRIC SOLID DOSE CONCEPT AS ALTERNATIVE TO LIQUID MEDICINES

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INTRODUCTION

Oral liquids and suspensions have several disadvantages relating to stability, accuracy of dosing and patient convenience[1&2]. Recently[3] there has been reported deaths from kidney injury in Indonesia of up to 100 children due to consumption of unregistered syrups that has led to the Indonesian authorities banning all syrups pending an investigation. The root cause of the problem was thought to be incorporation of liquids such as ethylene glycol and diethylene glycol in the formulations. In this regard, the FDA has issued a guidance for mandatory testing of ethylene glycol and diethylene glycol and uphold the threshold of NMT 0.1% by applicable USP-NF monograph for each high risk drug components identified in the Guideline[4]. These sad events have placed into context the stark reality of the requirement to look for safer and more convenient alternatives to liquid based medicines.

AIMS and OBJECTIVES

UltraBurst (UB) is a co-processed platform consisting of well established excipients routinely used in paediatric formulations. Its utility as an alternative to syrups and suspensions was investigated for a range of API's formulated as tablets that could subsequently be dropped into various liquids; water, apple juice, mango juice, yoghurt and syrup (added to a 5ml spoon), giving a convenient and palatable alternative to liquid medicines. The compatibility in these vehicles was not studied as the intended use is for the patient or carer to administer the medicine 1-2 minutes after addition of the tablet to the liquid in question. The performance of the UB platform was also compared to other marketed ODT platforms. API's considered included low dose, e.g. loperamide HCl (2mg), taste masked Diphenhydramine (1.25mg), as well as higher dose API's such as taste masked paracetamol (doses of at least 60mg). Several tablet weights were investigated; mini tablets (10-20mg), small (50mg) and standard sized tablets (400mg). Acceptable USP dissolution of the tested API's has been well established in UB orodispersible tablets.

MATERIALS and METHODS

Flash ODT (FODT) formulations were formulated as placebos and with 3 different model API's; Loperamide HCl (LOP), Diphenhydramine (DPH) and Paracetamol (APAP). The performance of the UB platform was also compared to other ODT platforms, indicated as platforms P1-P4. All formulations were manufactured via a direct compression process requiring simple sieving of components, followed by blending and lubrication step, then compression on a Pacific Rotary Tablet Press. Prior to compression, blend flow attributes were assessed by Flowdex (USP method) or visually. The formulations were compressed using the requisite tooling at the appropriate compression force and the resultant tablets were then assessed for their physical properties. Table 2 illustrates physical parameters for 50mg tablet weights. Friability and DT were measured according to USP methods. Tablet hardness was measured using a hardness tester, thickness measured using a calibrated micrometer, and weight on a calibrated analytical balance. Resultant tablets were then added to a range of different palatable liquids on a 5ml spoon and the dispersion event videoed and the time and extent of spread versus times were noted. Viscosities were not measured by Brookfield but visibly, as it was clear that water and apple juice were lower viscosity than the mango juice and syrup.

RESULTS AND DISCUSSION

Table 1 shows a typical concept formulation of UB tablets, 50mg in weight containing 20mg of APAP (as taste masked Actimask®).

Table 2 shows the physical properties of the tablets. The tooling used was 6.2mm round FFBE. Flowdex values varied from free flowing (5 and 6) for the placebo and DPH formulations to 12 for LOP.

Table 1

material	mg/tab
Actimask APAP	22.0
Ultraburst	25.9
Raspeberry Flavour	0.65
sucralose	0.65
magnesium stearate	0.75
total	50.0

Table 2

Weight (mg)	50.1
Thickness (mm)	1.45
Hardness (N)	16
Friability (%)	0.22
DT (sec)	4
Comp Force (kN)	3.4 to 3.8

As shown in Figure 1, UB based placebo tablets show significantly faster and more complete dispersion versus the other systems studied and so is the most viable base for this approach. Dispersion of UB based placebo tablets is faster in the lower viscosity apple juice and dispersion in mango juice gives an acceptable result.

COMPARISON OF ODI PLATFORMS

Figure 1 – shows the dispersion of the different ODT base 100mg placebo tablets (7mm diameter) in apple juice after 25 secs

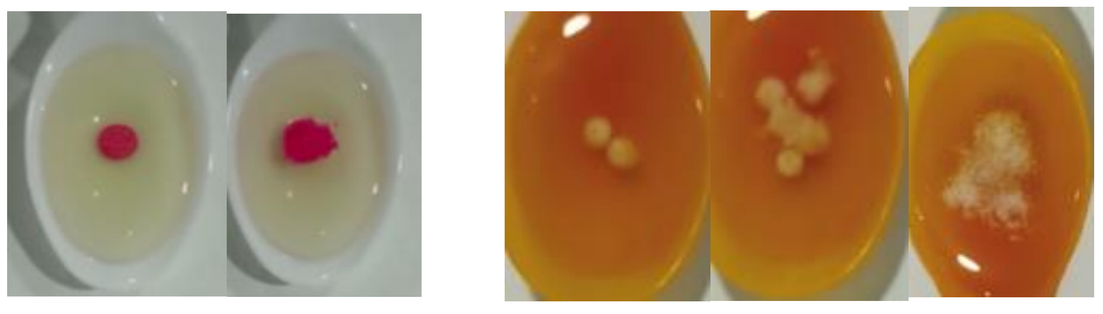
UB (pink left) vs P1 | UB vs P2 | UB vs P3 | UB vs P4

UB tablets were fully dispersed after 25 secs regardless of formulation tablet size or media used. The other platforms studied were much slower to disperse and in some cases, did not disperse well at all.

PERFORMANCE OF UB

Figure 2 – shows the effect of the viscosity of the liquid media on the dispersion. Images are of 100mg UB placebo tablets dispersed in mango juice and apple juice after 32 and 27 secs respectively (LHS). Images on RHS show the effect on tablet size (weight) on dispersion and are of UB placebo tablets (400mg/11.11mm diameter and 100mg/7mm) dispersed in water after the indicated dispersion time. Complete dispersion was seen at the higher 400mg tablet weight after only 25s.

Figure 3 LHS – shows the UB based 50mg tablet (6.2mm diameter) containing 20mg APAP detailed in Tables 1 and 2 at initial time point and after 20 secs when dispersed in apple juice. RHS shows dispersion images of a UB based taste masked DPH mini tablets weighing 10mg (4.0mm diameter) containing 1.25mg of taste masked DPH per tablet added to apple juice at 4, 10 and 18 secs respectively. Inclusion of the active has not significantly slowed the dispersion.



For safety/ethical reasons, the palatability of the API containing formulations was not assessed, however the APAP and DPH formulations were both formulated with taste masked API's and the placebo tablets were assessed by a taste panel and found to be extremely pleasant. It is reasonable to conclude that the concepts shown would have at least the same palatability as the liquid versions.

CONCLUSION

We have demonstrated a novel and simple means of converting current liquid medicines into FODTs that when added to palatable liquids in a 5ml spoon, such as apple juice, mango juice, syrup or even water, will quickly and completely disperse within less than 30 seconds to give a slurry of dispersed API that could easily be given to a child. The concept is feasible across a wide range of tablet sizes (10 – 400mg weights / 4.0-11.11mm diameter investigated), thus enabling both low and high dose API's to be dosed via a number of tablets added at each required dosing time. The viscosity of the liquid will slow the time for full dispersion, however, even in the higher viscosity mango juice studied, complete dispersion in around 30 seconds was possible. The dispersion propensity is significantly slower and incomplete with the other systems studied. This concept could considerably improve paediatric treatment by eliminating the need for liquid medicines and the disadvantages associated with the liquids. Choice of juice needs to be considered by consulting a healthcare professional, as some juices (e.g., grapefruit juice) are known to interfere with the metabolism of certain drugs.[5]

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