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An Investigation into the Feasibility of a Novel Genericised Paediatric Dispersible Platform

Introduction

Health agencies such as the European Medicines Agency (EMA) require age-appropriate formulations to be developed for paediatric patients. [1] Dispersible tablets are commonly used paediatric dosage forms due to their high level of patient compliance, stability, and ease of manufacturing. Genericising a placebo dispersible tablet platform which enables drug substance to be added to form an appropriate dosage form would reduce complexities associated with formulation development and therefore reduce timelines enabling accelerated patient access. This project was designed to develop a genericised placebo platform and assess the feasibility of using a lipid carrier. Six lipids were assessed as vehicles for API addition. These lipids had varying hydrophilic-lipophilic balance (HLB) values. Those with a higher HLB value should disintegrate quicker. [2]

Materials and Methods

Tablet Manufacture

The materials were blended and compressed into 10 mm round tablets with an appropriate design feature to enable API addition post-compression.

Stage 1

Tablets underwent disintegration testing (DT) and fineness of dispersion testing to ensure they passed British Pharmacopeia (BP) requirements.

Stage 2

The lipids were melted and 20 µL was added to each tablet. Lipids were allowed to re-solidify and return to room temperature. DT and fineness of dispersion testing were performed, and physical appearance noted. The criteria to pass stage 2 were:

- 1. The lipid must solidify and not penetrate the tablet core.
- 2. The lipid tablet must disintegrate with an average disintegration time of less than 10 minutes.
- 3. The lipid tablet must pass fineness of dispersion testing.

Stage 3

The lipids that passed stage 2 were then melted and they were combined with API at a suitable concentration to achieve 5 mg / 20 µL of lipid. Two repeats of 6 tablets were tested with the mean and maximum disintegration times assessed in statistical analysis. A one-way analysis of variance (ANOVA) approach with the factor lipid was used to test overall difference between lipids.

	Appearance	DT Result (Pass < 10 minutes)	Average DT Time	Fineness of Dispersion Result
Lipid A	Off-White Solid	Pass	07:07	Pass
Lipid B	Pale Yellow Solid	Pass	09:32	Pass
Lipid C	Off-White Solid	Fail	N/A	N/A
Lipid D	Pale Yellow Solid	Pass	03:31	Pass
Lipid E	Off-White Solid	Pass	03:31	Pass
Lipid F	Penetrated Tablet Core	Fail	N/A	N/A

Table 1 – Stage 2 testing results

Results

Stage 1

The placebo cores disintegrated within 16 seconds (Fig. 1) and passed fineness of dispersion testing.

Stage 2

Lipids C and F were not progressed, due to the DT time exceeding the 10-minute limit (Table 1). Lipids A, B, D, and E passed the 3 criteria.

Stage 3

The data appears to show increased variability with an increase in DT time (Fig. 2) and hence was log transformed prior to analysis to stabilize the variance. The one-way ANOVA table revealed the lipid group means were statistically significantly different from each other (0.0423) (Table 2). The pairwise comparisons suggest that lipids B and E are significantly lower than lipid A, with a fold change of 0.49 and 0.31 respectively from A. The pairwise comparisons suggest that is some evidence of a statistical difference between lipid E and lipid D, with a fold change of 0.50 (Table 3). Hence, lipids B and E show the most promise in terms of low disintegration time.

Conclusions

Lipids B, D and E have HLB values of >14 and are to be progressed for onward experimentation. Lipids A, C and F are not recommended for use in this platform due to their long disintegration time.

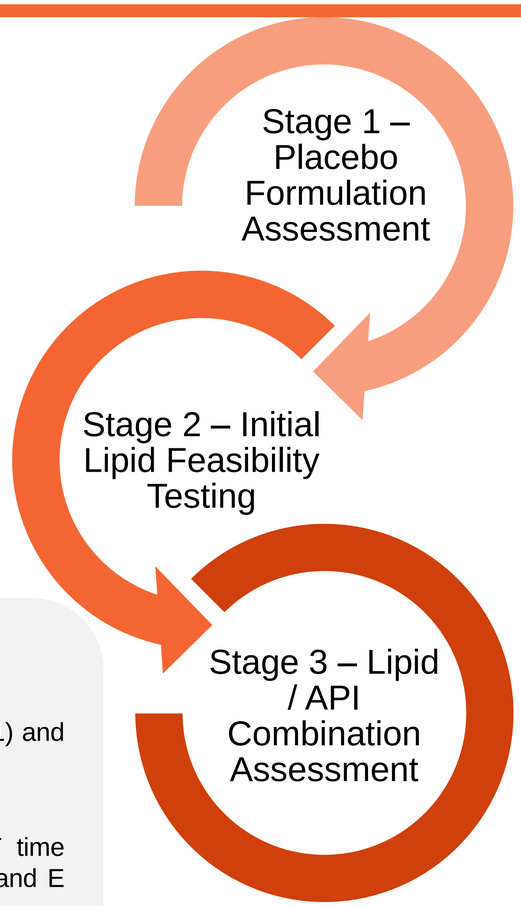

Figure 1 – DT of tablet cores

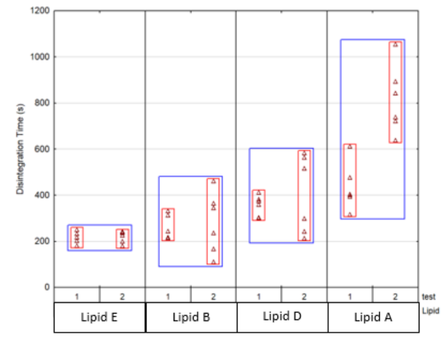

Figure 2 – Variability Plot showing Individual DT Results in Stage 3

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Lipid	3	0.273078	0.091026	7.30	0.0423
Error	4	0.049867	0.012467		
Corrected Total	7	0.322946			

Table 2 – One-Way ANOVA Table

Group1	Group2	Pr >|t|	Fold Change	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Lipid E	Lipid D	0.0554	0.50245	0.24609	1.02587
Lipid E	Lipid A	0.0101	0.30672	0.15022	0.62625
Lipid B	Lipid A	0.0490	0.48740	0.23872	0.99516

Table 3 - Pairwise Comparisons between lipid disintegration time, presented (due to the log transformation of the data) as fold changes of the form Group 1 / Group 2, with 95% confidence intervals around the fold changes.

1. EMA, 2013. Guideline on pharmaceutical development of medicines for paediatric use. 805880 Rev. 2
2. Pouton. C. W. and Porter, C. H. 2008 Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. Adv Drug Deliv Rev, 60(6), 625-637.