Addressing Challenges in Pediatric Formulation Development to Improve Compliance and Therapeutic Outcomes

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INTRODUCTION

Dosage form design necessitates the formulator to consider the needs of the patient not only in terms of drug efficacy and safety but also to ensure convenience, palatability, compliance, and consequently therapeutic outcomes.

The use of orally disintegrating mini-tablets (ODMTs) is one approach that formulators should consider when designing novel, oral solid dosage forms for pediatric use, especially for very young children. It has been recently shown that children as young as six months can effectively swallow orally disintegrating mini-tablets (ODMTs)[1, 2].

In addition to enhanced swallowability, ODMTs also provide accurate and precise weight-based dosing, dose titration, fast-disintegration, and perhaps enhanced dissolution. They are designed to disintegrate on the tongue in approximately 10 seconds or less without the need for water; an important point when sources of fresh water are limited.

This approach gives formulators an opportunity to overcome some of the dosing challenges posed by alternate, inconvenient dosage forms such as syrups and reconstitutable suspensions.

GENERAL AIMS AND OBJECTIVES

ODMTs offer distinct advantages over traditional tablets; however they do require some specific considerations when formulated for pediatric populations. Chewable tablets are also more attractive than swallow tablets for children providing adequate palatability can be achieved.

Two specific examples of new formulations designed for pediatric patients are shown; the first example demonstrates Proof of Concept (POC) in orally disintegrating mini-tablet development. The second example demonstrates some considerations for “fine tuning” tablet formulations made from coated, taste-masked particles, and how taste panels can help optimize pediatric formulations.

ODMT POC Aims and Objectives

ODMTs are typically compressed to a tablet weight of approximately 10 to 12 mg using tablet tooling with a diameter of approximately 3 mm. To address the challenges of meeting content uniformity and other quality requirements in such small tablets, a study was conducted to demonstrate how orally disintegrating mini tablets could be formulated using an off-the-shelf co-processed drug delivery platform (Pharmaburst® 500 - SPI Pharma) specifically designed for use in directly compressible ODTs. Phenylephrine HCl and dextromethorphan HBr, two APIs used extensively in pediatrics, were utilized as model drugs in separate trials.

ODMT POC Materials and Methods

In both trials, the active was approximately 25% of the formulation composition, the co-processed system, Pharmaburst 500, comprised approximately 65%, and the balance of the formulation consisted of sweeteners, flavors, a flow aid (colloidal silicon dioxide), and a lubricant (sodium stearyl fumarate). The flavors and sweeteners were used to taste mask the actives. The two final formulations are given in Tables 1 and 2.

Table 1 – Phenylephrine HCl ODMT formulation

material	function	mg/tablet
phenylephrine HCL EP	API	2.50
Pharmaburst 500	ODT platform	6.63
Aerosil 200®	flow aid	0.20
Sucralose USP NF	sweetener	0.12
Strawberry flavor	flavor	0.30
Lubripharm® SSF	lubricant	0.25

Table 2 – Dextromethorphan HBr ODMT formulation

Material	Function	mg/tablet
dextromethorphan HBr EP	API	2.63
Pharmaburst 500	ODT platform	6.50
Aerosil 200	flow aid	0.20
Sucralose USP NF	sweetener	0.12
Strawberry flavor	flavor	0.30
Lubripharm SSF	lubricant	0.25

All ingredients were separately weighed and sifted prior to use. The API, colloidal silicon dioxide, and Pharmaburst 500 were added using an ordered process and blended for a total of 30 minutes. Sucralose, strawberry flavor and sodium stearyl fumarate were added and blended for another 15 minutes. Tablet compression was performed with 2.5 mm multi tip ‘D’ type punches on Rimek Mini press -II SF compression machine. Tablet weights (n =10) were measured on an analytical balance. Thickness and hardness measurements (n=6) were carried out using Dr. Schleuniger Pharmatron 8M hardness tester. The tensile strengths were calculated from the hardness results. Disintegration (n = 6) was performed using Pharma Test PTZ AUTO 2 EZ disintegration tester per USP 38. Tablet assay and content uniformity were determined. Friability was calculated based on 6.5 grams of tablets (650 tablets rotated at 25 RPM for 4 minutes) on a friability tester.

ODMT POC Results and Discussion

The test results are summarized in Table 3 and demonstrate acceptable physical and analytical characteristics.

Table 3 ODMT characteristics

Test Performed	Phenylephrine HCl	Dextromethorphan HBr
Mean Tablet Weight (mg ± 1 SD)	10.0 ± 0.09	10.1 ± 0.18
Assay (%)	103.3	99.0
Tablet Content Uniformity (AV)	5.2	7.1
Mean Disintegration Time (seconds)	2	2
Friability (%)	0.8	0.3
Tensile Strength (MPa)	1.21	1.48

Superior compression and flow characteristics are essential to ensure minimal tablet weight variation. The co-processed drug delivery platform, Pharmaburst 500, provided good flow (Carr’s Index of approximately 14) and compressibility[3] characteristics along with disintegration times well below the typical 30 second standard for ODTs.

Chewable Tablet POC Aims and Objectives

There are many considerations when developing a chewable tablet formulation. Palatability is particularly important in pediatric patients in order to ensure compliance and successful therapeutic outcomes. Many drugs are bitter in nature and some have been formulated with weak fruit acids such as citric acid to improve taste or sensory perception[4] or enhance drug dissolution by alteration of the local pH. The chemical nature of the formulation may have an adverse effect on the functionally of the system used to taste mask the API(s) and, consequently, on the palatability of the dosage form.

A screening study was conducted with the goal of developing an optimized chewable tablet formulation containing the actives guaifenesin (Gui) and dextromethorphan (Dex). A taste panel was used to determine which formulations were most palatable in terms of taste masking and sensory attributes.

Chewable Tablet POC Materials and Methods

Taste masked granules, containing a fixed dose combination (FDC) of Gui and Dex, coated with a reverse enteric polymer with solubility at pH ≤5, were formulated into six chewable tablet formulations. Formulations 1-5 contained weak fruit acids and citrus flavoring agents. Formulation 6 contained peppermint and menthol without an acid component. The FDC of 200mg Gui and 7.3mg Dex comprised 49% of each formulation. The trial formulations are shown in Table 4.

Table 4 – Tablet formulation details

Formulation	1	2	3	4	5	6
GUI/DEX Taste Masked beads (%w/w)	49	49	49	49	49	49
Microcrystalline Cellulose PH 102 (%w/w)	15	10	10	10	10	10
Copovidone (%w/w)	3.0	3.0	1.0	1.0	3.0	3.0
Silicon Dioxide (%w/w)	0.5	0.5	0.5	0.5	0.5	0.5
Crospovidone XL (%w/w)	5.0	2.5	2.5	2.5	2.5	2.5
Sucralose (%w/w)	1.0	1.5	1.5	1.5	1.5	1.5
Lubripharm SSF (%w/w)	2.5	2.5	2.5	2.5	2.5	2.5
Lemon and Lime flavor (%w/w)	2.0					
Orange Flavor (%w/w)		2.0	3.0	3.0	3.0	
Peppermint flavor (%w/w)						2.0
Citric Acid (%w/w)	1.0	1.0				
Tartaric Acid (%w/w)			1.0	1.0	2.0	
Menthol (%w/w)						1.0
Mannogem® EZ (%w/w)	QS to 100	QS to 100	QS to 100	QS to 100	QS to 100	QS to 100

The active multi-particulates and excipients were blended together for 15 minutes and the final blends were compressed on a Rimek Mini press-II SF tablet press to a final tablet weight of 1200 mg.

Chewable Tablet POC Results and Discussion

Each formulation was evaluated by a taste panel for palatability. Formulations 1-5 containing citrus flavors in combination with either citric or tartaric acid were judged by a taste panel to be bitter with an unacceptable taste. The taste panel also found that Formulation 6 containing peppermint and menthol without an acid component had acceptable taste without bitterness.

Tablets containing an acid (Formulations 1-5), when dissolved in 20ml of water, had a pH of approximately 4.3, while the tablets from Formulation 6 without an acidifying agent had a pH ≥8. It was believed that the solubility of the reverse enteric polymer coating at lower pH accounted for the bitterness encountered in Formulations 1-5 with acid components and not in Formulation 6 without these ingredients.

Following the taste panel assessment, an additional three trials were conducted to determine if the acidity was due primarily to the acid components or to the citrus flavors. The acid components were removed from the base formulation and tablets containing a citrus flavor were compressed without the acid component. The pHs were measured and determined to be approximately 7.8. From these results, it was concluded that the citrus flavors had no effect on pH, and the lower pH values seen previously were due to the acidic components. Based on these results, the formulators developed chewable tablets without acid components that had good palatability without bitterness.

These findings, although not unexpected, stress the need to use taste panel evaluations to uncover potential organoleptic issues and help guide formulation decisions.

OVERALL CONCLUSIONS

ODMTs are a novel dosage form that provide patient ease of dosing and effective dose titration. ODMTs can be administered to children as young as six month old and have distinct advantages over standard tablets and liquids. Their development, however, is not without challenges. The objectives of meeting tablet robustness and rapid disintegration requirements are essential. The use of co-processed excipient technology platforms can help facilitate product development and provide formulators with a possible approach to rapidly achieve these goals.

The chewable tablet work shows that formulators must carefully consider all formulation aspects that contribute to the final palatability of the dosage form. The use of taste panels in parallel to formulation development can be enlightening.

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