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ORIGINAL ARTICLE

Design, Development and Evaluation of Orally Disintegrating Mini-tablets (ODMTs) Containing Cefixime for Paediatric Use: A Novel Approach

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ABSTRACT

Objectives: The study aimed to combine instant-release and mini-tablet methodologies to develop novel orally disintegrating mini-tablets (ODMTs) for a frequently pescribed antibiotic, cefixime trihydrate (CT), in paediatric patients.

Materials and Methods: CT-loaded microcapsules were prepared using Eudragit® EPO and Hydroxy Propyl Methyl Cellulose E50 by spray drying technique. The optimized microcapsules were mixed with co-processed ready-to-use tableting excipients, Ludiflash and Pearlitol 200SD, in different proportions and then compressed into ODMTs and evaluated.

Results: The particle size of CT microcapsules was found to be between 111.8 and 225.87 µm, suitable for oral delivery. The entrapment efficiency was found to be between 94.8% and 95.45%. Pre-compression and post-compression parameters indicated suitability for formulation. *In vitro* evaluation of ODMTs showed immediate disintegration within 15 seconds in the oral cavity as soon as they came in contact with saliva. Upon swallowing these microcapsules, the microcapsules completely dissolve in the gastrointestinal tract, releasing 100% of the drug (CT) within 15 minutes. The release kinetics of ODMTs were found to follow Hixson-Crowell kinetics for Eudragit® EPO and Korsmeyer-Peppas kinetics for Hydroxy Propyl Methyl Cellulose E50 microcapsules. Scanning electron microscopy images demonstrated that the microcapsules were intact even after compression into ODMTs. Stability studies proved that the formulations were stable as per the International Council for Harmonisation guidelines.

Conclusion: A novel solid oral dosage form of CT ODMTs of 2 mm diameter was successfully developed using Eudragit® EPO and Hydroxy Propyl Methyl Cellulose E50 in combination with co-processed ready-to-use tableting excipients such as Ludiflash and Pearlitol 200SD.

Keywords: Cefixime, microcapsules, mini tablets, instant release, paediatrics

INTRODUCTION

Orally disintegrating mini-tablets (ODMTs) are innovative solid oral dosage systems that quickly disintegrate in the oral cavity when they come in contact with saliva, typically within 10 to 15 seconds, without the requirement of water. ODMTs are more appropriate for paediatrics as they are tiny, have an agreeable mouthfeel, and fast disintegration in the mouth.[1]

Powders, multiparticulates, and/or dispersible formulations were discussed to be suitable for 6 months to 2 years of age.[2] High temperature frequently causes stability problems for liquid preparations. High costs of transportation and storage are considered. Hence, fluids should be avoided whenever possible.[3] At the age of 6 months, the child can physiologically and structurally gulp multiparticulates in a soft diet and

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brews, depending on the dimensions, contour, and solidity of the particles.[4] Child-appropriateness of the doses is specified by stress-free administration, palatability, the option for weight-based medication, and the use of safe, entrenched, and established excipients.[5] Hence, expertise in flexible solid platforms is essential. Hence, the planning of mini-tablets is escalating in the paediatrics field as required by European regulatory necessities for paediatric use.[6]

The Food and Drug Administration of the USA permitted Cefixime trihydrate (CT) in April 1989. Similar to other cephalosporins, this antibiotic halts bacteria from proliferating by preventing the formation of cell walls. The walls are essential to protect bacteria from the environment and to retain the contents. It shows a 3-hour elimination half-life with twice daily intake or, in some cases, once daily intake. Relative trials show that the medical and microbiological effectiveness of CT is more effective compared to co-trimoxazole (trimethoprim + sulphamethoxazole) or amoxycillin/clavulanic acid, and also more effective than cefaclor and cefroxidine in cases of acute lower respiratory tract infections and acute tonsillitis or pharyngitis. CT is resistant to hydrolysis by variants of wide-spectrum β-lactamases, and its stability is superior to cephalexin, cephradine, and cefadroxil. It was hence planned to prepare CT ODMTs.[7]

In the present research, our formulated ODMTs have two portions, namely microcapsules and minitablets. The microcapsule portion contains a drug encapsulated within Eudragit® EPO (EPO) and Hydroxy Propyl Methyl Cellulose E50 (HPMC E50) polymer coatings, which exclusively disintegrate in gastric pH (<5) and are insoluble in the salivary pH of 7. Then minitablets are formulated by taking optimized microcapsules and mixing them with ready-to-use, co-processed tableting excipients, namely ludiflash and pearlitol, which are also super disintegrants that disintegrate in the oral cavity upon contact with saliva (pH about 7), typically within a few seconds. Therefore, this study aimed to investigate the suitability of ready-to-use tabletting excipients ludiflash and pearlitol, in formulating ODMTs, and also to examine the taste masking as well as controlled release ability of EPO and HPMC E50 polymers in formulating microcapsules based on the various parameters tested.

MATERIALS AND METHODS

Materials

The drug CT was obtained as a gift sample from Karnataka Antibiotics Pvt. Ltd. (Bangalore, Karnataka). The ready-to-use tablet excipients Ludiflash and Pearlitol 200SD were received as a gift sample from Evonik Industries (Mumbai, Maharashtra), the lubricants Sodium Stearyl Fumarate (SSF) and Magnesium Stearate were purchased from Loba Chemie Pvt. Ltd. (Mumbai, Maharashtra). Polymers EPO and HPMC E50 were purchased from Rolex Chemical Industries (Bangalore, Karnataka). Solvents dichloromethane (DCM) and ethanol were purchased from Welchem Chemicals (Bangalore, Karnataka), cherry flavour was purchased from Keva Flavours (Mumbai, Maharashtra), and tablet compression facilities were availed at Apotex Research Pvt. Ltd. (Bangalore, Karnataka).

Methods

Preformulation spectroscopic studies

Determination of absorption maxima (λ_{max}) and standard curve of CT in methanol, 0.1 N HCl, and phosphate buffer 6.8

A stock solution (1000 µg/mL) of CT was made separately in methanol, 0.1 N HCl, and phosphate buffer 6.8. The sample was suitably diluted to get a concentration of 10 µg/mL using respective solvents and analyzed in the range of 200 nm to 400 nm using a Shimadzu ultraviolet visible (UV) spectrophotometer UV-1800, and λ_{max} was determined against a reagent blank. The experimentation was done in triplicate, and a standard curve was generated and plotted for the Beer-Lambert range.

Drug-excipient compatibility studies

In the current work, the potassium bromide pellet technique was used to check the compatibility of excipients with drug CT by taking their Fourier transform infrared spectroscopy (FTIR) spectra using Shimadzu FTIR 84900.[8]

Preparation of taste-masked microcapsules of CT

A total of 10 microcapsule formulations were prepared by varying proportions of drug CT and polymer (EPO and HPMC E50) in 1:1 to 1:5 ratios, using the spray drying method as shown in Table 1. The weighed quantity (as shown in Table 1) of polymers EPO and HPMC E50 was dispersed in the required quantity of DCM and ethanol in a 1:1 ratio.[9] The mixture was stirred for 30 minutes to achieve complete dispersion of polymers. To this, weighed quantities of CT and magnesium stearate (used as a glidant) were added and stirred on a magnetic stirrer for another 30 minutes to ensure uniform dispersion of the drug. The investigational considerations of the spray drying procedure were: outlet temperature 400 °C, inlet temperature 500 °C, aspirator setting 40, feed pump rate 2.5 mL/min, and 0.5 mm spray nozzle.[10] The formulation of various CT microcapsules is shown in Table 1.

Evaluation and characterization of the prepared CT microcapsules

Physical appearance of CT microcapsules

Visual examinations of the prepared CT microcapsules were performed.

Theoretical yield of CT microcapsules

The theoretical yield was measured based on the quantity of solid added to formulate a solution.

Practical yield of CT microcapsules

Formulated CT microcapsules were recovered from the spray dryer and then weighed.

Table 1. Formulations chart of CT microcapsules

Formulation code	CT (gms)	EPO (gms)	HPMC E50 (gms)	Magnesium stearate (*w/w*%)	1:1 of DCM and ethanol
F1	5	5	-	1	q. s. to prepare a solution of 10%
F2	5	10	-	1	q. s. to prepare a solution of 10%
F3	5	15	-	1	q. s. to prepare a solution of 10%
F4	5	20	-	1	q. s. to prepare a solution of 10%
F5	5	25	-	1	q. s. to prepare a solution of 10%
F6	5	-	5	1	q. s. to prepare a solution of 10%
F7	5	-	10	1	q. s. to prepare a solution of 10%
F8	5	-	15	1	q. s. to prepare a solution of 10%
F9	5	-	20	1	q. s. to prepare a solution of 10%
F10	5	-	25	1	q. s. to prepare a solution of 10%

DCM: Dichloromethane, gms: Grams, HPMC: Hydroxypropyl methylcellulose, q. s.: Quantity sufficient

Percentage yield of CT microcapsules

The percentage yield was measured using the Equation 1:

$$\%\, yield = \frac{\text{practical mass (microcapsules)}}{\text{theoretical mass (drug + polymer)}} \times 100 \quad \text{(Equation 1)}$$

Encapsulation and entrapment efficiency of CT microcapsules

CT microcapsules were crushed in a glass mortar and pestle; the powder equivalent to 50 mg of CT was dissolved in 100 mL of methanol and sonicated for 5 minutes; filtered, and 1 mL of filtrate was pipetted out and diluted to 100 mL of methanol. One mL from this solution was pipetted out and made up to 10 mL using methanol. The drug content was determined using a Shimadzu spectrophotometer (UV-1800) against a reagent blank with a maximum absorbance at 290 nm.[11] The drug encapsulation effectiveness was calculated by the following equation:

$$\%\, encapsulation\, efficiency = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100 \quad \text{(Equation 2)}$$

Particle size examination of CT microcapsules

Particle size analysis of approximately 300 randomly selected CT microcapsules was conducted using optical microscopy.[12]

Surface morphology of CT microcapsules by scanning electron microscopy (SEM)

The CT microcapsules were prepared by mounting the sample on the sample-holder made with a solid Aluminium stage (Al slab) using carbon (C) adhesive tape. Then, samples are degassed for 72 hours in a desiccator. Then, 10 nm gold (Au) depositions for conductivity will be applied using Quorum Technology equipment. The samples are then loaded into the SEM machine (Ultra 55 FESEM from Carl Zeiss), and after achieving a high vacuum, SEM images of optimised microcapsule formulations were taken.[13]

In vitro dissolution of CT microcapsules

In vitro release of CT microcapsules was done using the United States Pharmacopoeia (USP) type II dissolution apparatus (paddle) (Electro lab TDT-08L). Using 900 mL of 0.1 N HCl as dissolution media, the apparatus was set at 50 rpm for 30 minutes and 37±0.5 °C temperature. At predetermined intervals (0, 5, 10, 15, 20, 25, 30 minutes), 5 mL of the samples were taken out and substituted with 5 mL of the fresh dissolution media. The samples withdrawn were suitably diluted, and the concentration of CT was measured using a UV spectrophotometer against a reagent blank.[14] The same procedure was performed by taking 900 mL of phosphate buffer, pH 6.8, as a dissolution medium.

Drug release kinetics of CT microcapsules

Based on the above evaluation parameters, selected CT microcapsule formulations were fitted to different kinetic models like zero-order, 1st order, Higuchi, Korsmeyer-Peppa's, and Hixson-Crowell cube root law using the software BCP soft to predict the drug release mechanism.[15]

Stability studies of CT microcapsules

Optimised CT microcapsule formulations were kept in an air-tight container and packed in aluminium foil, and sealed tightly. It was stored at temperatures and RH of 5 °C/ambient, 25°±2°C and 60±5% RH, 40°±2°C, and 75±5% RH, and evaluated at the time intervals of 30, 60, and 90 days as per ICH guidelines.[16]

Formulation of ODMTs

ODMTs of CT were prepared using a rotary tablet press in the direct compression process with multi-tip punches.[17] The optimised CT microcapsules were mixed with ready-to-use co-processed tableting excipients, ludiflash and pearlitol 200SD, in different proportions (1:1, 2:1 and 3:1) and blended with SSF in 3.5% *w/w* (as lubricant and anti-adherent) and cherry flavour. A compression force ranging from 8 kN to 10 kN was applied to compress biconvex mini tablets with a diameter of 2 mm and weighing approximately 12 mg each.[18] Various ODMTs formulations were shown in Table 2.

Evaluation of formulated ODMTs for pre-compression parameters[19]

Bulk density (D_b) of the ODMTs blend

It was calculated as the ratio of the entire mass of powder to its bulk volume. The evaluation was conducted by taking a known quantity of powder into a measuring cylinder, and its volume was noted. It was measured in gm/mL and was calculated by.

$$D_b = \frac{M}{V_b} \quad \text{(Equation 3)}$$

M = powder mass, V_b= powder bulk volume.

Tapped density (D_t) of the ODMTs blend.

It was calculated by the ratio of the entire mass of powder and its tapped volume. It was evaluated by tapping the powder to a constant volume and was measured in gm/mL, and was calculated by,

$$D_t = \frac{M}{V_t} \quad \text{(Equation 4)}$$

M = powder mass, V_t = powder tapped volume.

Angle of repose (θ) of ODMTs blend

It is a measure of the frictional forces within loose powder. The powder was directed to flow into a funnel fixed on a stand at a definite height. Then, θ was measured by taking the height of the pile of powder and its radius. It was measured in degrees and was calculated by,

$$\tan\theta = \frac{h}{r} \quad \text{(Equation 5)}$$

h = height, r = radius.

Carr's index (I) of ODMTs blend

It gives the ease of flow of the material, expressed as a percentage. It was calculated by,

$$I = \frac{D_t - D_b}{D_t} \times 100 \quad \text{(Equation 6)}$$

D_t= powder tapped density, D_b= powder bulk density.

Hausner's ratio of the ODMTs blend

It is an indirect measure of the ease of flow of powder and was measured by,

$$\text{Hausner's Ratio} = \frac{D_t}{D_b} \quad \text{(Equation 7)}$$

D_t= powder tapped density, D_b= powder bulk volume.

Evaluation of formulated ODMTs for post-compression parameters[20]

Physical appearance of ODMTs

Physical appearances of ODMTs were inspected visually.

Crushing strength of ODMTs

The ODMT's resistance to crushing was tested by the Dr. Schleuniger Pharmatron (USA) crushing tester and expressed in Kp or newtons.

Physical parameters of ODMTs

The diameter and thickness of the ODMTs were measured using a Vernier calliper, Digimatic caliper, Japan, and expressed in mm.

Friability test (F) of ODMTs

The *F* test was conducted to confirm the strength of the tablets to resist mechanical shocks, which may occur during preparation. The friability of the tablets in all the formulations

Table 2. Various ODMT formulations with ready-to-use co-processed tableting excipients ludiflash and pearlitol 200SD

Formulation code	Optimised EPO microcapsule powder (gms)	Optimised HPMC E50 microcapsule powder (gms)	Ludiflash (gms)	Pearlitol 200SD (gms)	SSF (*w/w*%)	Cherry flavour
FF1	10	-	9.3	-	3.5	q. s.
FF2	10	-	-	9.3	3.5	q. s.
FF3	10	-	4.5	-	3.5	q. s.
FF4	10	-	-	4.5	3.5	q. s.
FF5	10	-	2.9	-	3.5	q. s.
FF6	10	-	-	2.9	3.5	q. s.
FF7	-	10	9.3	-	3.5	q. s.
FF8	-	10	-	9.3	3.5	q. s.
FF9	-	10	4.5	-	3.5	q. s.
FF10	-	10	-	4.5	3.5	q. s.
FF11	-	10	2.9	-	3.5	q. s.
FF12	-	10	-	2.9	3.5	q. s.

EPO: Eudragit® EPO, gms: Grams, HPMC: Hydroxypropyl methylcellulose, ODMT: Orally disintegrating mini-tablet, q. s.: Quantity sufficient to 0.35 mL, SSF: Sodium stearyl fumarate

was determined using a friabilator (Electrolab, Mumbai, India). It was rotated for 100 revolutions, and the % friability was calculated by employing the equation:

$$F(\%) = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100 \quad \text{(Equation 8)}$$

The pharmacopoeial limit for F was not more than 1%.

Uniformity of the mass (weight variation) of ODMTs

For the test, 20 ODMTs were individually weighed, the average weight was calculated, and the % deviation was calculated using the equation,

$$\%\,deviation = \frac{|W_i - \bar{W}|}{\bar{W}} \times 100 \quad \text{(Equation 9)}$$

The pharmacopoeial limit was ±10%, and only if not more than two tablets fall outside the prescribed limits will the tablets pass the test.

Simulated wetting test (SWT) of ODMTs

SWT was the time taken for complete wetting of ODMTs using simulated salivary fluid to mimic the physiological environment of a wet tongue (*i.e.,* pH of saliva ranges from 6.2 to 7.6). It was carried out by placing a tablet on a piece of double-folded tissue paper in a Petri-plate containing 6 mL of simulated salivary fluid at pH 6.8 (phosphate buffer pH 6.8), and the time taken for the complete wetting of the upper plane of the tablet was noted. The SWT time of 10 randomly selected ODMTs in each batch was analysed.

In vitro dispersion test of ODMTs

In vitro dispersion time of ODMTs was analysed by keeping an ODMT in a beaker that contained 5 mL of distilled water, and the time necessary for complete dispersion was noted. The *in vitro* dispersion time of 10 randomly selected ODMTs in each batch was analysed.

Drug content of ODMTs

ODMTs were crushed and powder equivalent to 50 mg of CT was dissolved in 0.1 N methanol, filtered through Whatman filter paper (number 41), suitably diluted with 0.1 N methanol, and then the drug content was analysed by UV spectrophotometer against a blank.

In vitro disintegration test (DT) of ODMTs

The *in vitro* DT of ODMTs was analysed using a tablet disintegrator tester. Each of the six ODMTs was individually placed in a tube of the disintegrator, and then the discs were placed on them. The DT was carried out using distilled water as the medium with a temperature of 37±1 °C. The pharmacopoeial disintegration limit for tablets should not be more than 60 seconds.

In vitro dissolution studies of ODMTs

The test was performed by taking ODMTs equivalent to 50 mg of CT, which were first dispersed in phosphate buffer pH 6.8 to release the microcapsules. These microcapsules were then subjected to an *in vitro* dissolution test using a USP type II dissolution apparatus (paddle), utilizing 900 mL of 0.1 N HCl as the dissolution medium. The temperature of the water bath was maintained at 37.0±0.5 °C, and paddle rotation was set at 50 rpm. The sample (5 mL) was withdrawn at time intervals of 0, 5, 10, and 15 minutes and replaced with the same quantity of fresh dissolution media. The collected samples were suitably diluted with 0.1 N HCl and were analyzed using a UV spectrophotometer against a blank.

Drug release kinetics of ODMTs

In vitro drug release results of ODMTs were fitted to different kinetic models, namely zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell cube root law, using the software BCP Soft, to analyze the drug release pattern from ODMTs.

SEM of ODMTs

SEM studies were performed for selected final formulations of ODMTs, similar to SEM studies of microcapsule formulations as explained earlier.

Stability of ODMTs[21,22]

A stability study of ODMTs was carried out, similar to stability studies of microcapsules as explained earlier.

Statistical analysis

The data obtained for different formulations was analyzed by one way analysis of variance.

RESULTS

Preformulation spectroscopic studies

Determination of λ_{max} and standard calibration curve of CT

Absorption maxima of CT were found to be 290.0 nm in methanol, 285.0 nm in 0.1 N HCl, and 288.0 nm in phosphate buffer at pH 6.8. The linearity was established using the Beer-Lambert law in the concentration range of 2 to 16 µg/mL.

Drug-excipient compatibility studies

The FTIR spectral studies showed primary peaks at wavelengths of 3566, 3531 cm^{-1} (N-H stretching), 3295 cm^{-1} (symmetric and asymmetric N-H stretching), 2946 cm^{-1} (C-H stretching), 1772 cm^{-1} (C=O stretching), 1591 cm^{-1} (C=N stretching), 1063 cm^{-1} (C-O stretching), and 1025 cm^{-1} (N-O stretching). The principal peaks of the CT combinations with polymers (Eudragit EPO and HPMC E50) and excipients (Ludiflash and Pearlitol 200SD) showed no shift or loss of characteristic peaks, indicating no interaction between drug CT, polymers, and excipients, thereby proving the drug-excipient compatibility Figures 1-5.

Evaluation and characterization of the prepared CT microcapsules[22]

Physical appearance of CT microcapsules

The obtained EPO and HPMC E50 microcapsules were found to be free-flowing and white.

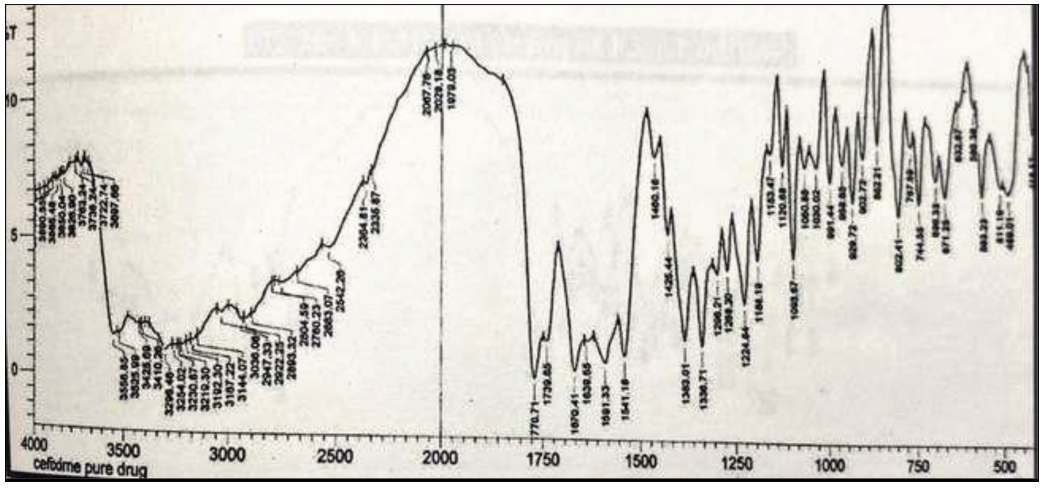

Figure 1. FTIR of the CT working reference standard

CT: Computed tomography, FTIR: Fourier transform infrared spectroscopy

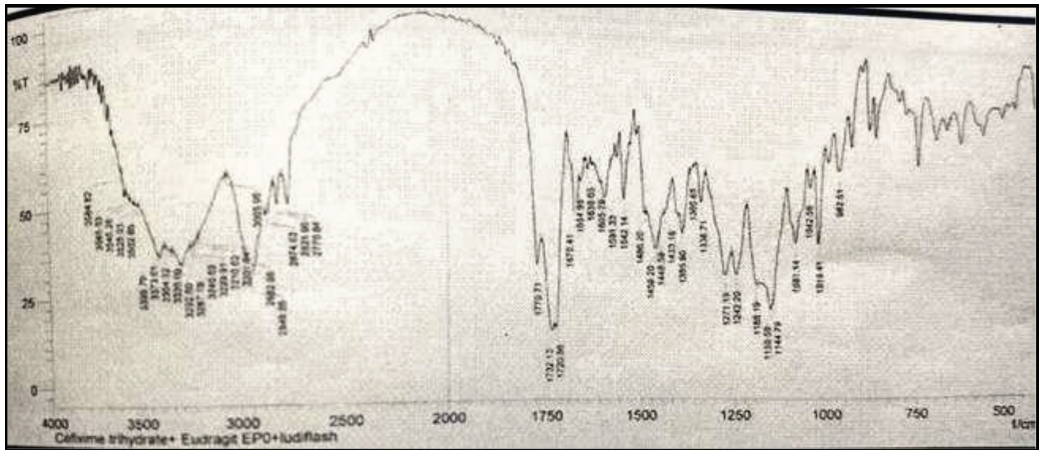

Figure 2. FTIR of FF5 ODMTs (CT + optimised EPO microcapsules + ludiflash)

CT: Computed tomography, EPO: Eudragit® EPO, FTIR: Fourier transform infrared spectroscopy, ODMTs: Orally disintegrating mini-tablets

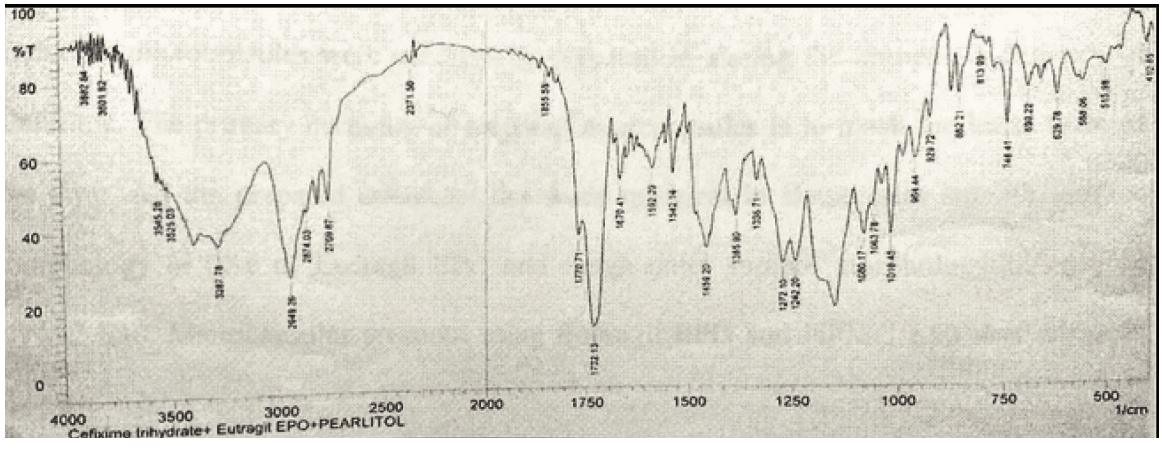

Figure 3. FTIR of FF6 ODMTs (CT + optimised EPO microcapsules + pearlitol)

CT: Computed tomography, EPO: Eudragit® EPO, FTIR: Fourier transform infrared spectroscopy, ODMTs: Orally disintegrating mini-tablets

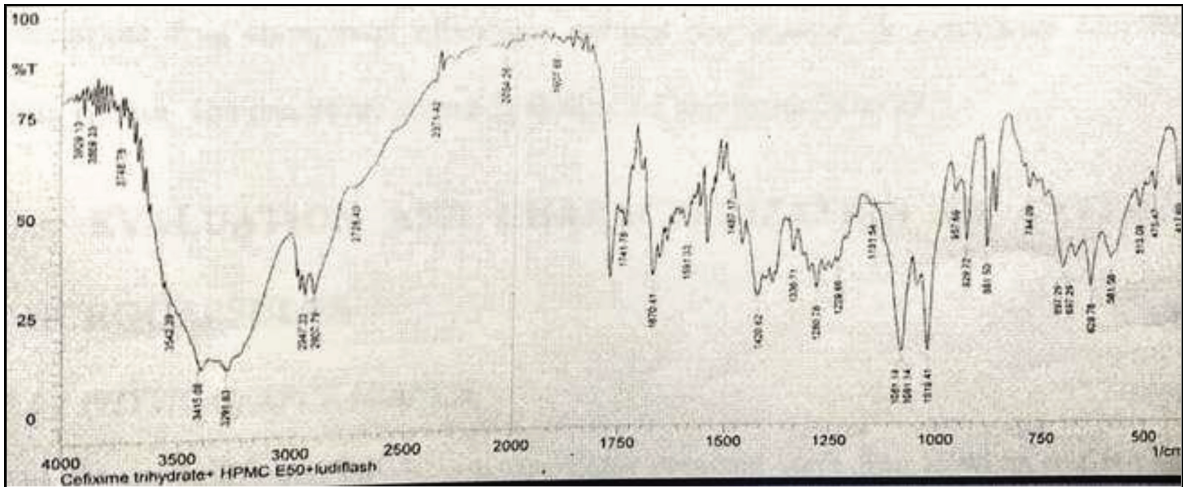

Figure 4. FTIR of FF11 ODMTs (CT + optimised hydroxypropyl methylcellulose E50 microcapsules + ludiflash)
CT: Computed tomography, EPO: Eudragit® EPO, FTIR: Fourier transform infrared spectroscopy, ODMTs: Orally disintegrating mini-tablets

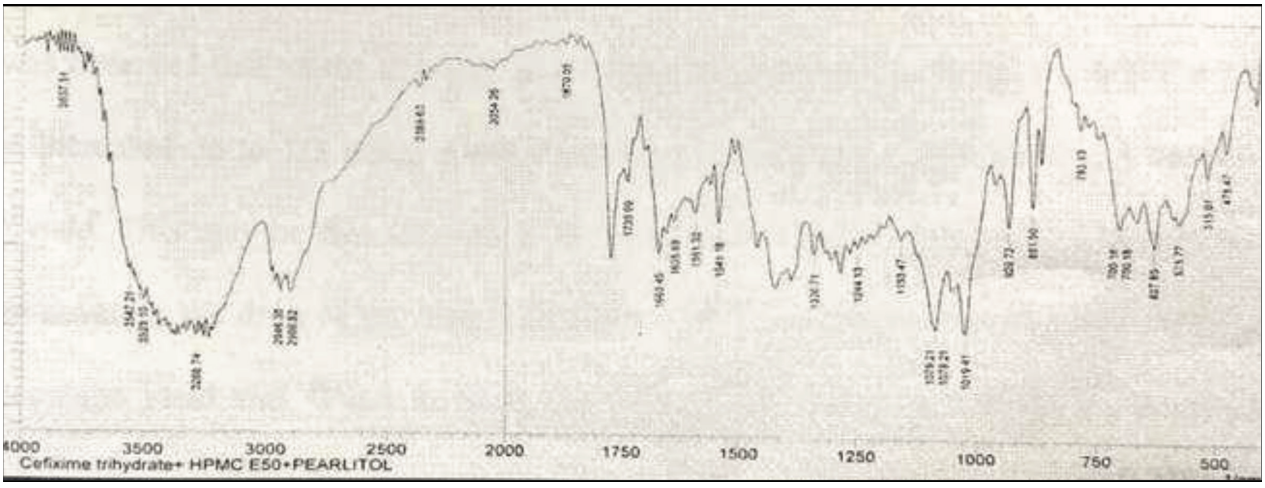

Figure 5. FTIR of FF12 ODMTs (CT + optimised hydroxypropyl methylcellulose E50 microcapsules + pearlitol)
CT: Computed tomography, EPO: Eudragit® EPO, FTIR: Fourier transform infrared spectroscopy, ODMTs: Orally disintegrating mini-tablets

Theoretical yield, practical yield, percentage yield, and encapsulation efficiency of CT microcapsules

The practical yield was compared with that of the theoretical yield, and the percentage yield was found to be in the range of 83.5% to 92.5%. It was observed that as the polymer ratio in the CT Eudragit EPO and HPMC E50 microcapsule formulation increased, the % yield, drug content, and entrapment efficiency also increased up to a 1:3 ratio of drug and polymer. A further increase in polymer concentration has decreased the yield. Thus, the optimized Eudragit EPO and HPMC E50 microcapsule formulation was found to be F3 and F8, respectively. These results were shown in Table 3.

SEM of CT microcapsules

The results of SEM of the optimised batch of CT Eudragit EPO and HPMC E50 microcapsules showed that they were spherical, having a smooth outer plane and particle size 125.45± 6.15 µm in case of CT Eudragit EPO microcapsules (F3) and rough outer surface and particle size 200.20±8.94 µm in case of CT HPMC microcapsules (F8) Figures 6, 7.

In vitro dissolution of CT microcapsules

The *in vitro* dissolution of CT Eudragit EPO and HPMC E50 microcapsules revealed that there was no drug release at phosphate buffer pH 6.8 (salivary pH) and 100% cumulative drug release (CDR) at a pH of 1 in 0.1 N HCl (gastric pH) within 15 minutes for optimised formulations F3 and F8. It was proven that microcapsules remained intact in the oral cavity and dissolved only in the stomach, releasing the complete drug within 15 minutes, as shown in Table 4.

Drug release kinetics of CT microcapsules

The linearity regression coefficient (R^2) values of the Hixson-Crowell cube root equation for CT-loaded Eudragit EPO microcapsules were found to be 0.9992, and the plot revealed linearity. The R^2 values of the Korsmeyer-Peppas model equation for CT-loaded HPMC E50 microcapsules were found to be 0.9997, and the plot revealed linearity. From these models, it was evident that at the initial stages, it might follow Hixson-Crowell release and Korsmeyer-Peppas pattern due to the small size of the microcapsules, which maintained

Table 3. Various evaluation parameters of CT microcapsules

Formulation	Physical appearance	Average particle size (µm) (Mean ± SD)	Yield %	Drug content (mg)	Drug entrapment Efficiency %
F1	Free-flowing and white	111.80±4.67	89.00	38.5	77.19
F2	Free-flowing and white	117.97±18.23	86.33	42.10	84.20
F3	Free-flowing and white	125.45±6.15	92.50	47.36	94.8
F4	Free-flowing and white	131.30±13.08	88.00	45.61	91.22
F5	Free-flowing and white	145.60±16.15	83.66	43.83	87.66
F6	Free-flowing and white	120.90±15.58	90.00	39.64	79.29
F7	Free-flowing and white	167.62±9.21	87.00	43.85	87.71
F8	Free-flowing and white	200.20±8.94	90.45	47.71	95.45
F9	Free-flowing and white	216.45±23.20	83.50	42.45	84.91
F10	Free-flowing and white	225.87±26.15	82.00	40.35	80.70

CT: Computed tomography, Mean: Average of 3 trials, mg: Milligrams, SD: Standard deviation, µm: Micrometre

Table 4. % CDR of EPO and hydroxypropyl methylcellulose E50 CT microcapsules in 0.1 N HCl

	% CDR (Mean ± SD)						
Time (min)	0	5	10	15	20	25	30
F1	0	46.52±1.24	76.85±2.15	100.0±0.03	-	-	-
F2	0	44.62±2.67	79.16±1.82	100.0±0.11	-	-	-
F3	0	46.41±1.44	76.27±1.28	100.0±0.14	-	-	-
F4	0	23.42±2.66	52.96±1.85	85.33±2.74	99.21±1.69	-	-
F5	0	14.45±1.21	42.41±2.18	66.30±2.95	84.50±3.46	100.0±0.05	-
F6	0	42.91±1.32	72.33±1.55	100.0±0.40	-	-	-
F7	0	40.86±2.59	70.63±1.06	100.0±0.93	-	-	-
F8	0	38.96±1.84	74.17±1.58	100.0±0.51	-	-	-
F9	0	22.65±2.32	51.88±1.47	79.36±2.88	100.0±0.11	-	-
F10	0	16.29±0.96	38.77±2.77	57.62±2.62	79.82±2.65	98.87±2.21	-

% CDR: Percentage cumulative drug release, EPO: Eudragit® EPO, Mean: Average of 3 trials, min: Minutes, SD: Standard deviation,

integrity, shape, and diameter during the dissolution Figure 8 (A), (B).

Stability studies of CT microcapsules

The optimised CT Eudragit EPO and HPMC E50 microcapsules were subjected to stability studies as per ICH guidelines, and analysed for their physical form, drug content, encapsulation efficiency, and percent CDR. There was no change in the parameters tested, proving their stability.

Evaluation of formulated ODMTs

Evaluation of pre-compression parameters ODMT blend

All the ODMTs formulation blends were free-flowing due to the presence of co-processed ready-to-use tableting excipients, Ludiflash and Pearlitol SD. There was no significant difference between bulk density and tapped density, suggesting that microcapsules had a uniform particle size and similar shapes. Carr's index of less than 20 indicated good compressibility. Hausner's ratio was found to be around 1.18 (<1.25 is good), demonstrating excellent flow property and appropriateness for compression. Table 5 shows the micromeritic properties of the ODMT blend regarding bulk density, tapped density, angle of repose, Carr's Index, and Hausner's ratio.

Evaluation of post-compression parameters of ODMTs

Physical appearance of ODMTs

Upon visual inspection, the formulated ODMTs were found to be tiny, white, biconvex-shaped mini tablets with a smooth texture.

Crushing strength of ODMTs

ODMTs with ludiflash showed crushing strength >4.1 N, and those with pearlitol showed >4.4 N, indicating good strength for handling.

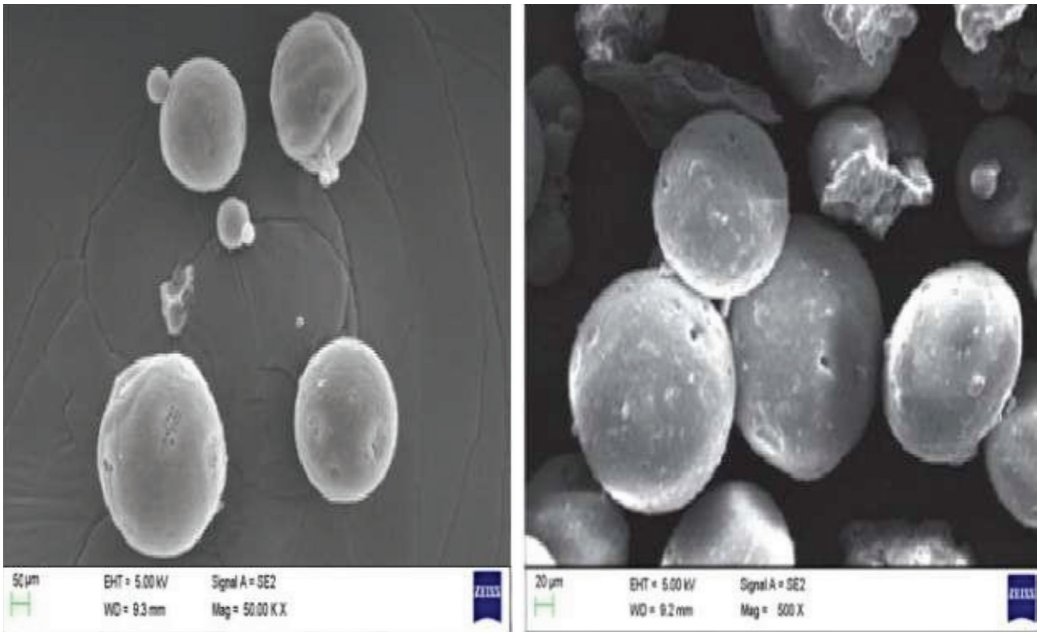

Figure 6. SEM images of optimised CT EPO microcapsules (F3)
CT: Computed tomography, EPO: Eudragit® EPO, SEM: Scanning electron microscopy

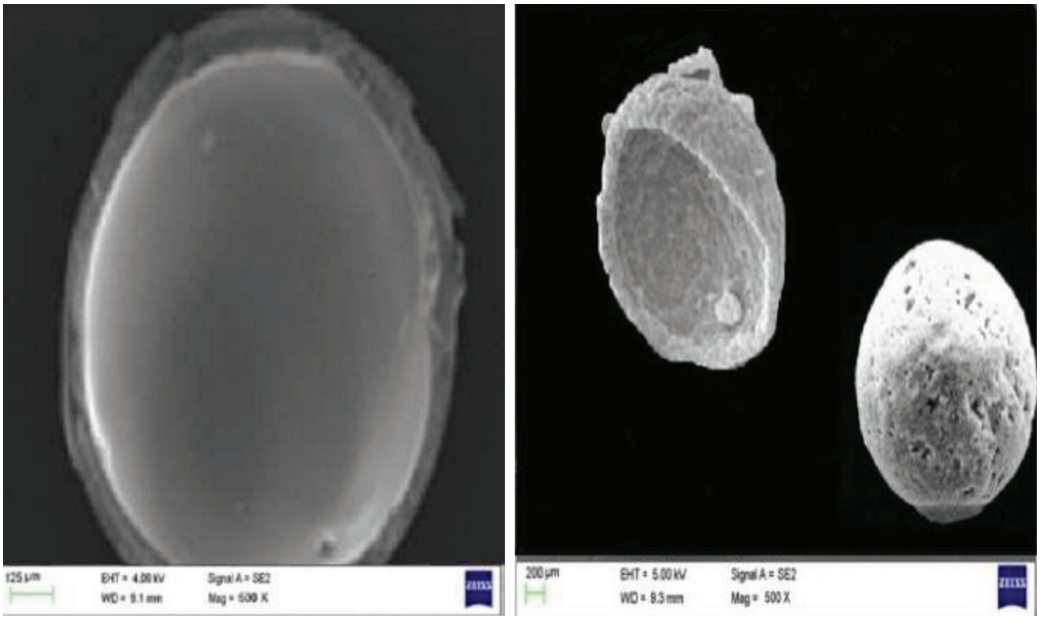

Figure 7. SEM images of optimised CT hydroxypropyl methylcellulose E50 microcapsules (F8)
CT: Computed tomography, SEM: Scanning electron microscopy

F of ODMTs

All the formulated ODMTs showed low friability of <1%, indicating good mechanical strength during handling, packing, and transportation.

Uniformity of mass (weight variation) of ODMTs

Each ODMT was found to weigh around 12 mg±0.44, thereby passing the uniformity of weight variation test.

SWT time of ODMTs

The SWT time of all the ODMTs was found to be less than 10 seconds in phosphate buffer pH 6.8 (simulated salivary fluid), indicating immediate disintegration in the mouth. This achieves the requirement of fast oral disintegration due to the ready-to-use tabletting excipients Ludiflash and Pearlitol 200SD, which disintegrated at pH 6.8.

In vitro dispersion of ODMTs

The *in vitro* dispersion time of all the ODMTs was less than <20 seconds, indicating fast disintegration. This rapid disintegration is attributed to the presence of ready-to-use tabletting excipients Ludiflash and Pearlitol 200SD, which act as super disintegrants.

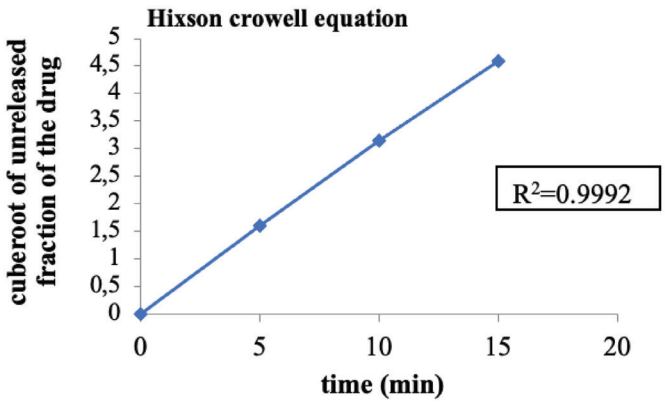

Figure 8 (A). Model fitting curve for optimised CT EPO microcapsules formulation (F3) in 0.1 N HCl

CT: Computed tomography, EPO: Eudragit® EPO, R^2: Regression coefficient

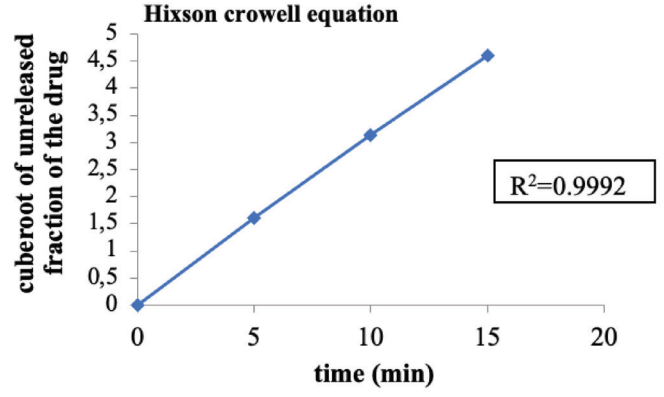

Figure 8 (B). Model fitting curves for optimised CT hydroxypropyl methylcellulose E50 microcapsules formulation (F8) in 0.1 N HCl

CT: Computed tomography, R^2: Regression coefficient

Drug content of ODMTs

The drug content in ODMTs was found to be 1.5 mg/tablet with to drug-to-polymer ratio of 1:1, 2 mg/tablet with to drug-to-polymer ratio of 2:1, and 3 mg/tablet with to drug-to-polymer ratio of 3:1. Thus, the optimised formulation would be FF5 and FF11 with 3 mg drug/tablet. Uniformity of drug content was demonstrated with optimised formulations.

In vitro disintegration test of ODMTs

In vitro disintegration of all the ODMTs was found to be <20 seconds, indicating an immediate disintegration due to the presence of super disintegrants, namely Ludiflash and Pearlitol 200SD.

In vitro dissolution studies of ODMTs

In vitro dissolution studies of optimized ODMTs exhibited an immediate release mechanism (disintegrated <10 secs), characterized by a burst effect in phosphate buffer pH 6.8 (pH of salivary fluid), releasing only drug-entrapped microcapsules, with no drug released in the oral cavity. These microcapsules released the complete drug in a gastric pH of 0.1 N HCl (pH of stomach) within 15 minutes. Thereby concluding that ludiflash and pearlitol dissolve completely in the oral cavity, giving a sweet, smooth, and pleasant mouth feel, which are more acceptable for paediatric patients. It is hence proved that these co-processed ready-to-use tabletting excipients, ludiflash and pearlitol 200SD, were suitable for ODMT formulations aimed at paediatric use. The results were depicted in Table 6A-D.

Drug release kinetics from ODMTs

The R^2 values of the Hixson-Crowell cube root equation for Eudragit EPO ODMTs and those of the Korsmeyer-Peppas equation for HPMC E50 ODMTs were similar to those of their respective microcapsules.

Table 5. Pre-compression parameters of ODMTs blend

Formulation code	Bulk density (g/mL) (Mean ± SD)	Tapped density (g/mL) (Mean ± SD)	Carr's Index (%) (Mean ± SD)	Hausner's ratio (Mean ± SD)	Angle of repose (Mean ± SD)
FF1	0.45±0.018	0.52±0.020	13.46±2.48	1.15±0.036	34.070±0.815
FF2	0.48±0.025	0.55±0.021	12.06±2.23	1.14±0.056	34.430±0.960
FF3	0.49±0.032	0.58±0.063	15.51±1.325	1.18±0.046	33.410±1.600
FF4	0.50±0.028	0.59±0.055	15.25±2.012	1.18±0.061	33.240±1.266
FF5	0.48±0.015	0.55±0.021	12.72±0.837	1.14±0.011	28.080±0.869
FF6	0.51±0.013	0.57±0.024	10.52±0.937	1.11±0.021	26.390±0.415
FF7	0.50±0.018	0.58±0.016	13.79±0.885	1.16±0.036	29.150±0.360
FF8	0.52±0.019	0.59±0.048	11.86±0.822	1.13±0.045	27.250±0.944
FF9	0.49±0.021	0.59±0.087	16.94±2.237	1.20±0.047	31.150±1.392
FF10	0.52±0.026	0.61±0.044	21.15±3.937	1.17±0.051	30.470±1.216
FF11	0.51±0.018	0.60±0.057	15.00±4.012	1.17±0.059	31.150±0.944
FF12	0.50±0.018	0.58±0.064	13.79±4.034	1.16±0.062	33.650±0.562

SD: Standard deviation, Mean: Average of 3 trials, ODMTs: Orally disintegrating mini-tablets

Table 6A. Physical characteristics of our ODMTs

Parameters	Found
Description	White coloured biconvex mini tablets with a smooth texture
Weight of 20 mini tablets	240.00±0.2 mg
Average mass (n=20)	12.00±0.01 mg
Uniformity of the mass (n=20)	12.00±0.01 mg
Diameter (n=20)	2.0±0.00 mm

ODMTs: Orally disintegrating mini-tablets, n: Number of samples tested

Table 6B. Compression force, crushing strength, wetting time and friability of ODMTs

Formulation code	Compression force (kN)	Crushing strength (N) (Mean ± SD)	Wetting time (sec) (Mean ± SD)	Friability (*w/w* %)
FF1	8	4.2±0.8	6±0.4	0.05
FF2	10	4.4±1.7	7±1.7	0.06
FF3	8	4.1±0.9	6±0.6	0.04
FF4	10	4.8±1.2	7±1.4	0.07
FF5	8	4.4±0.6	7±0.5	0.05
FF6	10	4.3±1.6	8±1.2	0.04
FF7	8	4.5±0.8	8±0.3	0.05
FF8	10	4.4±1.4	8±1.4	0.05
FF9	8	4.6±0.9	9±0.5	0.07
FF10	10	4.7±1.8	10±1.4	0.05
FF11	8	4.8±0.8	9±0.7	0.06
FF12	10	4.5±1.5	10±1.9	0.06

kN: KiloNewton, Mean: Average of 3 trials, N: Newton, ODMTs: Orally disintegrating mini-tablets, SD: Standard deviation, Sec: Second

Table 6C. Thickness, uniformity of mass, *in vitro* dispersion time, drug content, *in vitro* disintegration of ODMTs

Formulation code	Thickness (mm) (Mean ± SD) (n=10)	Uniformity of mass (mg) (Mean ± SD) (n=10)	*In vitro* dispersion time (sec) (Mean ± SD) (n=10)	Drug content (mg per tablet) (Mean ± SD) (n=3)	*In vitro* disintegration time (sec) (Mean ± SD) (n=10)
FF1	3.34±0.2	12.1±0.41	13 ±0.7	1.51±0.05	17±0.2
FF2	3.32±0.1	12.1±0.39	16±1.4	1.49±0.04	19±1.6
FF3	3.33±0.1	12.0±0.44	14±0.8	2.0±0.01	18±0.7
FF4	3.31±0.1	12.0±0.40	17±1.9	2.02±0.00	20±1.3
FF5	3.32±0.2	12.0±0.28	14±0.6	3.03±0.04	19±0.4
FF6	3.32±0.2	12.0±0.26	18±1.3	3.01±0.04	21±1.5
FF7	3.34±0.1	12.0±0.29	15±0.4	1.50±0.04	19±0.2
FF8	3.34±0.1	12.0±0.28	18±1.5	1.50±0.05	20±1.3
FF9	3.33±0.2	12.1±0.33	20±0.9	2.0±0.00	20±0.7
FF10	3.34±0.1	11.9±0.32	21±1.2	2.01±0.02	21±1.8
FF11	3.34±0.1	12.1±0.39	19±0.8	3.02±0.05	19±0.9
FF12	3.31±0.2	12.0±0.28	20±1.7	3.01±0.05	20±1.9

Mean: Average of 3 trials, mg: Milligram, mm: Millimetre, n: Number of samples, ODMTs: Orally disintegrating mini-tablets, SD: Standard deviation, Sec: Seconds

Table 6D. *In vitro* dissolution studies of ODMTs in 0.1 N HCl

ODMTs formulations	% CDR in time (minutes) ± SD			
	0	5	10	15
FF1	0	42.21±2.47	70.96±1.28	100.00±0.39
FF2	0	44.97±1.83	71.15±2.98	100.00±0.67
FF3	0	43.76±2.84	69.55±1.21	100.00±0.27
FF4	0	42.34±1.38	68.89±1.53	100.00±0.48
FF5	0	40.57±2.69	67.32±2.54	98.12±1.48
FF6	0	39.94±2.24	66.94±3.76	97.83±2.91
FF7	0	32.76±3.57	65.86±2.64	100.00±0.71
FF8	0	31.96±2.87	64.72±2.74	100.00±0.64
FF9	0	31.12±1.19	65.97±1.56	100.00±0.13
FF10	0	30.65±1.97	64.31±1.64	100.00±0.89
FF11	0	32.11±2.46	64.97±3.39	98.61±1.24
FF12	0	31.85±3.79	63.64±2.81	98.43±0.54

% CDR: Percentage cumulative drug release, SD: Standard deviation, ODMTs: Orally disintegrating mini-tablets

SEM images of ODMTs

Based on the above evaluation parameters, selected ODMTs FF5, FF6, FF11, and FF12 were subjected to SEM studies. Upon visualisation, microcapsules were found to be intact in the ODMTs even after compression. Thus, it is demonstrated that the polymers Eudragit EPO and HPMC E50 can endure the compression pressure owing to their elastic nature. Other excipients also contributed to protecting the microcapsules from being cracked or chipped Figure 9 (A), (B).

Stability studies of ODMTs

The stability studies of ODMTs showed no modification in the appearance, drug content, and *in vitro* dissolution (% CDR). This demonstrates that they were stable when exposed to different atmospheric conditions as per International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use guidelines.

DISCUSSION

CT is a broad-spectrum third-generation cephalosporin used to treat a wide range of infections caused by gram-positive and gram-negative organisms. The recommended dose of CT in adults is 400 mg daily, especially in cases of UTI, LRTI, and URTI. The recommended child dose is 8 mg/kg/day. This may be administered as a single daily dose or may be given in 2 divided doses as 4 mg/kg every 12 hours. For infants and toddlers, the recommended dose is 1.5-3 mg/kg given orally twice a day. Presently in the market, only suspensions of CT are available for paediatric use, in strengths of 100 mg/5 mL or 200 mg/5 mL.[23] Thus, administration of these suspensions for infants and toddlers based on their body weight is difficult, leading to inaccurate dosing and posing stability problems.

Hence, there is a need for flexible, dose-adjustable, safe, and stable solid oral dosage forms that could replace the existing liquid dosage forms. There comes the need for ODMTs. These ODMTs combine the concept of a mini tablet and fast-dissolving approaches to formulate a novel child-appropriate dosage form. ODMTs are less than 3 mm in diameter, tiny, very easy to administer, and disintegrate in the mouth as soon as they come in contact with saliva, without the need for water. As they disintegrate in the mouth, they should give a pleasant mouthfeel, which necessitates taste masking of the drug.[24]

Taste masking technology should be compatible with ODMT formulation. This means that the coating should not be broken during compression or dissolved during granulation. Thus, taste masking of bitter-tasting drugs is crucial to the success of ODMT formulation. In an ideal ODMT, the drug property should not affect the tablet property. Based on previous research works and literature survey, the microencapsulation technique was selected for drug taste masking. Microencapsulation is a widely used technique in the pharmaceutical industry to mask the bitter taste of drugs as well as to achieve better bioavailability. During microencapsulation, a thin coating is applied onto small particles of solids, droplets of liquid, or dispersions. In our study, the spray drying technique was employed as a microencapsulation, wherein the bitter drugs are first encapsulated to give free-flowing microcapsules, which are then blended with co-processed ready-to-use tableting excipients and then compressed into minitablets.[25-28]

In our present research, commercially available polymers, namely HPMC E50 and Eudragit EPO, were selected for the microencapsulation technique to mask the bitter taste of the drug. The selected polymers were tasteless and insoluble in the salivary pH and dissolved only at an acidic pH of <5. As a result, the drug was not released in the oral cavity, whereas it was released only after reaching the stomach. Thus, these polymers were employed in our research to control the release of the drug in the stomach and to prevent its release

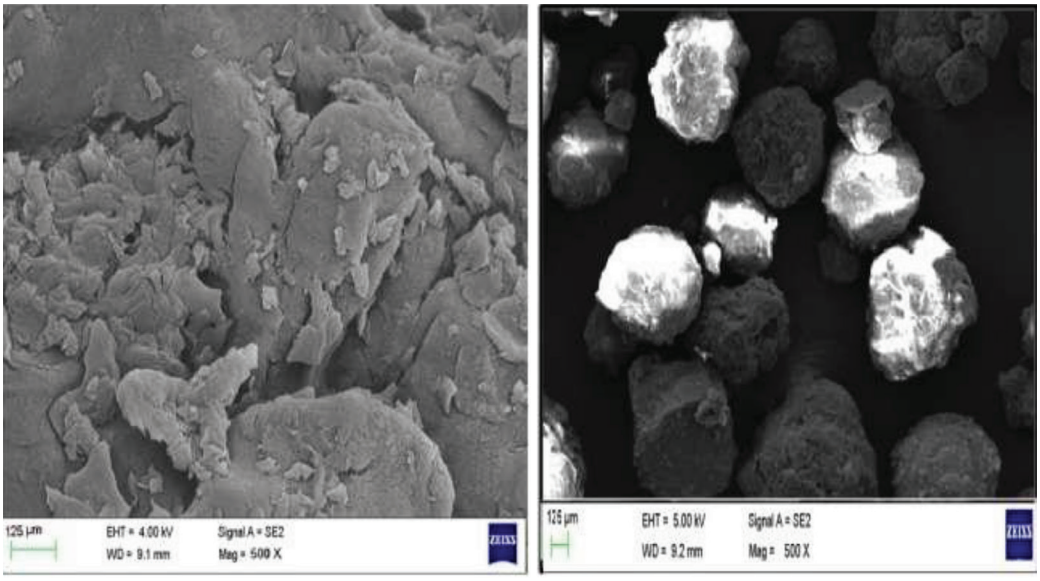

Figure 9 (A). SEM images of ODMTs FF5 and FF6
ODMTs: Orally disintegrating mini-tablets, SEM: Scanning electron microscopy

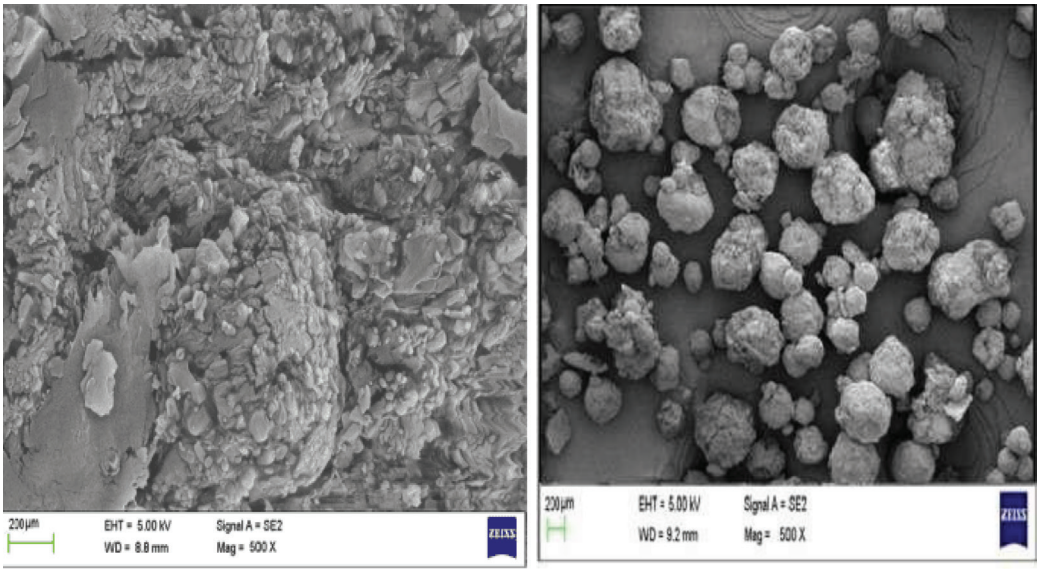

Figure 9 (B). SEM images of ODMTs FF11 and FF12
ODMTs: Orally disintegrating mini-tablets, SEM: Scanning electron microscopy

in the oral cavity.[29,30] After the formulation and optimization of microcapsules, the optimized batch was blended with ready-to-use tableting excipients, namely ludiflash and pearlitol.

Ludiflash is a commercially available, ready-to-use tablet excipient mainly composed of the following:

90% D-Mannitol – Fast-dissolving filler with a mildly sweet taste.

5% Kollidon® CL - SF (Cross povidone) – Superior tablet disintegrant and offers a smooth and creamy mouth feel.

5% Kollidon® SR 30 D (polyvinyl acetate) – Hydrophobic binder for enhanced disintegration.[31]

Pearlitol is also a commercially available, ready-to-use tablet excipient mainly composed of 100% D-mannitol. Both ludiflash and pearlitol have uniform particle size distribution, high bulk density, and provide good flowability. Our research proved that they produce excellent content uniformly, even at high tableting speeds. All the above polymers have been proven safe by European regulatory requirements on products for paediatric use, and hence they are employed in our current research.[32]

Further, our research demonstrated the instant disintegration of ODMTs in the oral cavity due to the presence of ready-to-use co-processed tableting excipients, namely, ludiflash and pearlitol, which resulted in the release of microcapsules rather

than the drug. After swallowing these microcapsules, and only after reaching the gastric region, they release the complete drug within 15 minutes (due to the presence of HPMC E50 and Eudragit EPO), thus achieving taste masking.

Typically, our study demonstrated that, in the first step, disintegration of ODMTs in the oral cavity takes place within a few seconds, releasing taste-masked microcapsules, followed by their swallowing. In the second step, these microcapsules, after reaching the gastric environment, released the complete drug within 15 minutes for drug action. The formulation successfully achieved taste masking (of the bitter drug CT) and also developed novel ODMTs for ease of administration and fast disintegration in the oral cavity for pediatric use.

Present research work revealed that the EPO microcapsules (F3) and HPMC E50 microcapsules (F8) had a drug CT to polymer concentration ratio of 1:3 and were found to be optimized formulations, showing 94.8% and 95.45% drug entrapment efficiency and particle size of 125.45±6.15 µm, and 200.20±8.94 µm, respectively. *In vitro* dissolution of optimized CT EPO microcapsules and CT HPMC E50 microcapsules (F3, F8) exhibited release only at pH in 0.1 N HCl, and followed the Hixson-Crowell cube root equation and the Korsmeyer-Peppas model equation for drug release kinetics. Stability studies proved that the optimized CT EPO and HPMC E50 microcapsules were stable under various atmospheric conditions. Further, ODMTs of CT FF5, FF6, FF11, and FF12 were found to be optimized formulations, containing 3 mg/tablet. Co-processed excipients Ludiflash and Pearlitol 200SD proved to be excellent ready-to-use tableting excipients and acted as super disintegrants. Thus, our ODMTs exhibited fast disintegration (SWT<10 seconds) only at pH 6.8 (phosphate buffer mimicking salivary fluid). The *in vitro* dissolution of ODMTs exhibited release only at phosphate buffer pH 6.8, and followed the Hixson-Crowell cube root equation and the Korsmeyer-Peppas model equation for drug release kinetics. Finally, stability studies of optimized ODMTs proved that the formulations were stable under different atmospheric conditions, as checked per ICH guidelines.

With this technology, a novel solid oral dosage form was developed, satisfying all existing demands for a child-appropriate dosage form: ease of weight-based dose administration without breaking or modifying the tablet, thereby providing flexible dose adaptation. This replaces the less stable liquid oral dosage forms for paediatric groups.

For further research, the suitability of other essential paediatric drugs, as well as potent drugs, should be evaluated.

CONCLUSION

Thus, our ODMTs proved to be an ideal paediatric dosage form with the use of minimal excipients. We were able to formulate a taste-masked, fast-disintegrating, easy-to-swallow, and stable formulation with flexible dose increments. This facilitates the development of a novel oral solid dosage with regard to industrial applicability, with ease of production and bulk scale-up, low transport and storage costs.

Ethics

Ethics Committee Approval: Not required.

Informed Consent: Not required.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: V.S., V.G.J., Concept: V.S., V.G.J., Design: V.S., S.B.C., Data Collection or Processing: V.G.J., S.B.C., Analysis or Interpretation: V.S., V.G.J., S.B.C., Literature Search: V.S., S.B.C., Writing: V.S., S.B.C.

Conflict of Interest: The authors declare no conflicts of interest.

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