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Original Article

Development and Evaluation of Fast Dissolving Oral Films of Mefenamic Acid for the Management of Fever

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ABSTRACT

The marketed formulations of Mefenamic Acid (MA) used for the treatment of fever in the paediatric population are reported to have several drawbacks. This study aimed to develop and evaluate the mefenamic acid–loaded oral dispersible films which may be a better alternative than the existing formulations. The solubility of mefenamic acid was enhanced by forming inclusion complexes with β cyclodextrin. The best ratio for the mefenamic acid-β cyclodextrin inclusion complex, 1:0.5 was selected based on the drug content and *in vitro* drug release. Fourier transform Infrared spectroscopy and scanning electron microscopy analysis was performed on the complex. The oral dispersible films were developed by solvent casting method and evaluated for parameters such as average weight, thickness, pH, folding endurance, percentage moisture uptake and loss, drug content, *in vitro* disintegration time and drug release. The statistical analysis of the data suggested that oral dispersible films with 4% w/v of crospovidone (coded P3) as the best. Drug content (95.46±0.93%), disintegration time (28.6±2.0 s), cumulative percentage drug release (97.41±0.68% in 180 s), and all other investigated parameters of P3 were well within the acceptable limit. The *in vitro* dissolution profile of P3 showed no significant difference from the marketed mefenamic acid suspension and has a good stability profile at in-house testing conditions. The data obtained from this investigation revealed that mefenamic acid oral dispersible films could act as an excellent alternative to existing marketed paediatric formulations.

Keywords: Oral dispersible films, Mefenamic acid, β Cyclodextrin, Paediatric, Kneading method, Solvent casting.

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INTRODUCTION

Mefenamic Acid (MA) is a Non-Steroidal Anti-Inflammatory Drug (NSAID), that belongs to the Biopharmaceutical Classification System II (BCS II).[1] It is a registered NSAID used in the paediatric population from 6 months of age for the management of fever and may be an effective alternative to ibuprofen. The MA is recommended to administer not more than three times a day, in a dose of 6.5 mg/kg of body weight.[2] The suspensions, syrups, capsules and tablets are the most commonly available dosage forms of MA for paediatrics. But the solid oral dosage form of MA has less acceptance in the paediatric population due to fear of choking and the bitter taste of the drug. Moreover, the MA tablet needs splitting to get an accurate dose, which may lead to the loss of the drug. Nowadays, oral liquid dosage forms like syrups and suspensions of MA are commonly prescribed to the paediatric population. The taste–related concerns and viscous consistency may also lead to poor acceptance of paediatric MA liquid dosage forms. The associated problems of liquid dosage forms such as the possibility for inaccurate dosing, microbial contamination, stability issues and accidental breakage of containers reduce the popularity of MA liquid dosage forms.[3]

To overcome the drawbacks associated with existing MA oral dosage forms, alternative delivery approaches such as Oral Disintegrating Tablets (ODT) and Oral Dispersible Film (ODF) may be considered. ODT had superiority over the existing oral solid dosage forms, such as no swallowing difficulty, consumption without water, reduction in drug loss, and rapid onset of action.[4] But the fear of choking may keep some sections of the patient population away from using the ODT.[5] The ODT were fragile and friable, which required special packaging for safe storage and transportation. The higher cost of the formulation and specialised packaging made the ODT more expensive in

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comparison with standard oral tablets.[6] The oral dispersible film (ODF) may be considered as an alternative for the conventional solid and liquid dosage forms as well as ODT. The ODF is a thin film placed in the oral cavity, hydrated with saliva, rapidly dissolved and release medicament/s for quick absorption. The ODF gained popularity with its impressive ability to deliver active pharmaceutical ingredients.[7] The ODF had advantages over other oral solid formulations, which included no difficulty in swallowing, disintegrating instantaneously, avoiding a situation of splitting large tablets and water not required for consumption.[3,8] When compared with popular oral liquid dosage forms, the advantages of ODF included, accuracy in dose, minimal contact with mouth while administration, convenience in storage as well as transportation, no additional measuring cups or devices required and improved stability and taste.[9,10] The large surface area for quick disintegration, increased flexibility, resistance to mechanical stress and improved patient compliance may provide superiority for the ODF over ODT.[8,9] The possibilities of ODF were exclusively explored in the paediatric and geriatric populations to administer drugs effortlessly. This study aimed to develop and evaluate the MA–loaded ODF which may be a better alternative than the existing paediatric formulations of MA. The objectives of the study included solubility enhancement of MA by forming inclusion complexes with β Cyclodextrin (βCD) and comparing the *in vitro* release profile with the marketed product of MA.

MATERIALS AND METHODS

Materials

MA, β Cyclodextrin (βCD) and Orange flavour were procured from Yarrow chemicals (Mumbai, India), Hydroxypropyl Methylcellulose E5 (HPMC E5) was collected from Balaji chemicals (Gujarat, India), Polyvinyl Alcohol (PVA), Polyethylene Glycol–400 (PEG–400), Crospovidone (CP), Citric Acid (CA) and Saccharin sodium were purchased from Nice Chemicals (Kochi, India).

Drug–excipient compatibility studies

The chemical interactions between the pure MA, as well as the physical mixture of MA and βCD and MA with selected excipients, were analysed by Fourier Transform Infrared (FT–IR) spectroscopy. Dried pellets were formed by mixing the samples with a sufficient quantity of potassium bromide, and were then scanned from 4000 cm^{-1} to 400 cm^{-1} using a Bruker alpha II FT–IR spectrophotometer.[11]

Preparation of MA-βCD inclusion complexes

The solubility of MA was enhanced by forming inclusion complexes with βCD using the kneading method. The MA-βCD inclusion complexes were developed at different molar ratios such as 1:0.5, 1:1, and 1:2. The weighed quantity of βCD was taken in a glass mortar and added a sufficient volume of distilled water to obtain a homogenous paste. The paste was dried at 40°±2°C for 6hr. The dried complex was kept in a desiccator and used for further investigation.[12]

Evaluation of MA-βCD inclusion complexes

Drug content estimation

MA-βCD inclusion complexes equivalent to 10 mg of MA were weighed and dispersed in 100 mL of Phosphate Buffered Saline (PBS) of pH 6.8. The solution was shaken well and allowed to settle. 1mL of the supernatant solution was pipetted out from this stock solution and made up to 10mL by using PBS of pH 6.8. Drug content was measured using a UV–visible spectrophotometer at 285 nm using PBS of pH 6.8 as a blank.[13]

In vitro drug release study

The *in vitro* dissolution study was performed in USP type–II apparatus. MA-βCD inclusion complexes equivalent to 65 mg of MA were dispersed in 900 mL PBS of pH 6.8 taken in a vessel. The temperature was maintained at 37°±0.5°C. The dissolution was performed at 100 rpm and 10 mL of sample was withdrawn at 0, 30, 60, 90, 120, 150, 180, 210, and 240th ses and replaced with an equal volume of fresh medium. The absorbance of the resulting solutions was measured using a UV–visible spectrophotometer at 285 nm.[12]

Selection and analysis of the best ratio of MA-βCD inclusion complex

The best ratio for the MA-βCD inclusion complex was selected after the evaluation of complexes. The selected ratio was analysed using Scanning Electron Microscopy (SEM) and FT–IR to confirm the formation of the inclusion complex.[12]

Preparation of MA oral dispersible films

The solvent casting method with necessary modifications was used for the development of ODF based on the composition given in Table 1. The weighed quantity of HPMC E5 was dissolved in a one-by-the–fourth volume of distilled water taken in a beaker. The solution was continuously stirred using a magnetic stirrer at 600 rpm. MA-βCD inclusion complexes equivalent to 65 mg of MA were dissolved in a sufficient volume of distilled water and vortexed. The drug solution was added drop by drop to the polymer solution, which was kept under continuous stirring. In a separate beaker, weighed quantity of CP, CA, PEG–400, and saccharin sodium was dissolved in the remaining volume of distilled water, which was stirred for 30 m using a magnetic stirrer at 600 rpm. The resultant solution was added to the drug–polymer blend, followed by the addition of orange flavour, and continued stirring for the next 1 hr. The solution was kept aside and allowed for the removal of any entrapped air bubbles. The solution was poured into a previously designed glass mould of

Table 1: Composition of developed oral dispersible films.

Ingredients	Formulation Code							
	H1	H2	H3	H4	P1	P2	P3	P4
MA-βCD complex equivalent to (mg)	65	65	65	65	65	65	65	65
HPMC E5 (mg)	390	390	390	390	-	-	-	-
PVA (mg)	-	-	-	-	260	260	260	260
PEG–400 (mL)	0.39	0.39	0.39	0.39	0.39	0.39	0.39	0.39
Crospovidone (%w/v)	-	2	4	6	-	2	4	6
Citric acid (mg)	103	103	103	103	103	103	103	103
Saccharin sodium (mg)	103	103	103	103	103	103	103	103
Orange flavour (mL)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Distilled water (mL)	13	13	13	13	13	13	13	13

7.5cmx5.5cm (W x L) dimension and allowed for drying at room temperature (30°±2°C) for the next 24–48 hr. The dried film was cut into strips of 2cmx2cm size, wrapped in aluminium foil, and stored in a desiccator until used for further studies. A similar procedure was followed for ODF based on PVA and ODF without CP.

Evaluation of MA oral dispersible film strips

To determine the average weight, three ODF strips (2cm x 2cm) were randomly selected from each developed batch of formulations. The individual weight of each strip was measured in a previously calibrated digital weighing balance and the average weight was calculated (n=3).[14] The thickness of the strip (2cmx2cm) at three different spots was measured using a previously calibrated screw gauge and the mean average thickness was calculated (n=3).[15] The folding endurance for the MA oral dispersible film strips was measured by folding the film strip repeatedly at the same point, till it was broken.[14] To determine the pH of the oral dispersible film, the strips were allowed to dissolve in a petri dish containing 2 mL of distilled water and the pH of the resulting solution was measured at room temperature (30°C±2°C) using a digital pH metre.[16] The percentage moisture loss from ODF strips (2cmx2cm) was analysed by measuring the initial weight of each selected strip using a digital weighing balance followed by storage in a desiccator containing calcium carbonate for three days and reweighed. The percentage moisture loss for the developed ODF strip was calculated using equation 1. To identify the percentage moisture uptake the initial weight of each selected strip was weighed using a digital weighing balance followed by exposure to a relative humidity of 75%±5% at room temperature (30°±2°C) for 7 days and reweighed. The percentage moisture uptake of the ODF strips was calculated using equation 2.[15]

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \ldots\ldots (1)$$

$$\text{Percentage moisture uptake} = \frac{\text{Final weight-Initial weight}}{\text{Initial weight}} \times 100 \quad (2)$$

Drug content estimation for MA oral dispersible film strips

The drug content estimation was performed over three randomly selected ODF strips from each batch. The strips were dissolved in 100 mL PBS of pH 6.8. The solution was filtered, and 1 mL was diluted to 10 mL by using PBS pH 6.8. The drug content was measured using a UV–visible spectrophotometer at 285 nm with PBS pH 6.8 as a blank. The average drug content was calculated for each of the developed batches of ODF strips and reported.[14]

In vitro disintegration time of oral dispersible film strips

The disintegration study was carried out by randomly selecting, three ODF strips (2cmx2cm) from each batch and were placed in a beaker containing 10 mL PBS of pH 6.8. The time taken to disintegrate into tiny particles was measured. The average time in seconds was analysed in triplicate.[17]

In vitro drug release study of oral dispersible film strips

The *in vitro* dissolution of MA from ODF strips was performed in a 50 mL beaker containing 30 mL of PBS of pH 6.8 maintained at 37°C±0.5°C. Three ODF strips (2cmx2cm) were randomly selected from each batch of the developed formulations and placed into three different beakers containing PBS solution. 5 mL of sample solution was withdrawn at 0, 30, 60, 90, 120, 150, 180, 210, 240, and 300th sec and replaced with an equal volume

of fresh medium. The beaker was intermittently shaken using the mechanical beaker shaker. The absorbance for the withdrawn samples was measured using a UV–visible spectrophotometer at 285 nm.[18]

Statistical optimization of developed MA oral dispersible film strips

The data from *in vitro* disintegration and *in vitro* release studies were statistically analysed using GraphPad software, Prism version 9.0 to select the best MA ODF developed during the investigation.[19]

Drug release kinetics

The drug release kinetics of MA ODF was studied by fitting the release of the optimised batch to various kinetic models such as zero–order, first–order, Higuchi, Korsmeyer–Peppas and Hixson–Crowell models. Criteria for selecting an appropriate model were based on the best goodness of fit.[20,21]

Comparison of *in vitro* drug release profile against a marketed suspension

The *in vitro* drug release profile of the best formulation was compared with the available marketed product of MA i.e., Suspension (MS). The study was conducted using USP type–II dissolution apparatus. The selected MA ODF and suspension equivalent to 65 mg of MA were placed in dissolution vessels containing 900 mL of PBS pH 6.8 maintained at 37°C±0.5°C and 50 rpm. 5mL of sample solution was withdrawn at 0, 1, 3, 5, 10, 20, and 45 m and replaced with an equal volume of fresh medium. The absorbance for the withdrawn samples was measured using a UV–visible spectrophotometer at 285 nm.[20,22]

Stability studies

The stability study of the optimised batch was performed under in-house testing conditions. The samples were stored at different conditions 4°C±2°C–8°C±2°C (Refrigerated temperature), 30°C±2°C/70%RH±5%RH (Room temperature), 40°C±2°C (Elevated temperature) for 30 days in two primary packaging materials i.e., aluminium foil and transparent polyethene ziplock. The samples were evaluated for folding endurance, percentage moisture loss, percentage moisture uptake, *in vitro* disintegration time, drug content and cumulative percentage drug release.[23]

Statistical analysis

The measurements were taken in triplicates and the corresponding results were reported as averages with standard deviations. All the data were statistically analysed by one-way ANOVA followed by Tukey's *post hoc* analysis using GraphPad Prism software 9.0.

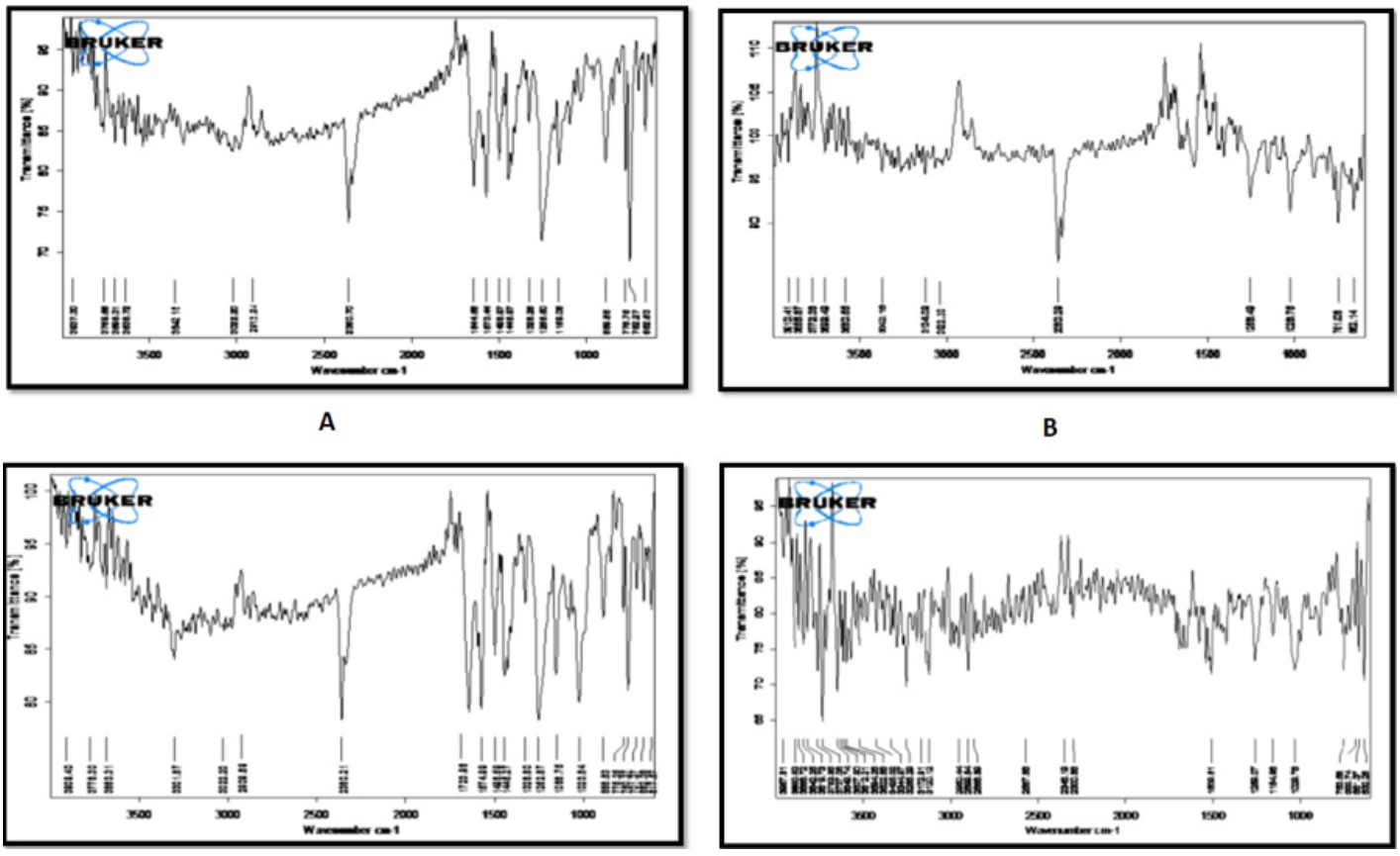

Figure 1: FT–IR spectrum 1A MA, 1B MA & βCD, 1C final physical mixture and 1D MA-βCD inclusion complexes at 1:0.5 ratio.

Table 2: *In vitro* dissolution study of selected ratios of MA-βCD inclusion complexes.

Time (s)	*Cumulative % drug release		
	1:0.5	1:1	1:2
0	2.39±1.12	2.23±0.08	3.14±0.61
30	7.88±1.69	7.96±0.54	7.99±0.35
60	25.15±1.17	26.10±0.46	27.11±0.67
90	28.13±2.07	28.28±2.86	29.30±1.18
120	55.98±0.04	56.12±1.27	57.01±1.24
150	79.09±0.21	80.26±1.57	82.19±1.96
180	88.22±1.18	89.15±0.94	90.52±1.30
210	90.21±0.43	90.66±1.18	91.88±2.10
240	92.25±0.38	92.99±1.16	93.01±1.28

*Values SD. Samples taken in triplicates (n=3), p>0.05.

RESULTS AND DISCUSSION

Drug–excipient compatibility studies

The MA showed characteristic peaks at 2500–3400 cm^{-1} for O–H stretching of COOH, C–H stretching of aromatic C–H bond at 3022 cm^{-1} and 2900–3000 cm^{-1} for C–H stretching of aliphatic C–H bond, N–H stretching of secondary amine showed at 3310–3350 cm^{-1} and 1644 cm^{-1} for C=0 stretching of carboxylic acid as well as C–N stretching showed at 1255 cm^{-1} (Figure 1A). The FT–IR spectrum of the MA and βCD blend (Figure 1B) and the final physical mixture (Figure 1C) suggested that all the characteristic peaks reported in MA were present in the MA and βCD blend and the final physical mixture. There were no new or missing significant peaks in the final physical mixture indicating that MA and selected excipients are compatible with each other in the final formulation.

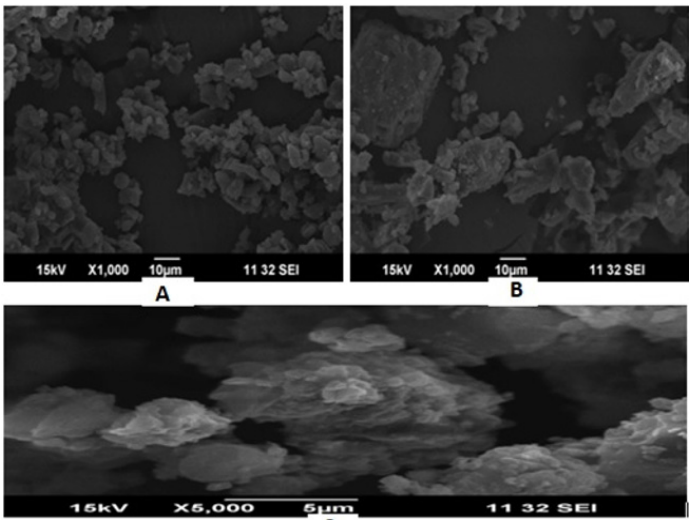

Figure 2: SEM photomicrograph 2A MA, 2B βCD, 2C MA-βCD inclusion complexes (1:0.5).

Evaluation of MA-βCD inclusion complexes

Drug content estimation

More than 90% MA was available in the developed inclusion complexes of MA-βCD. The highest percentage of drug content was observed in the 1:0.5 MA-βCD inclusion complex i.e., 97.00±1.55 and 93.13±1.12 for 1:1 as well as 93.07±1.23 for the 1:2 complex. A statistically significant difference was observed in the percentage drug content for the complex at the molar ratio of 1:0.5 and the other two complexes whereas, no significant difference was reported between the 1:1 and 1:2 molar ratio by one-way ANOVA followed by Tukey's *post hoc* test.

In vitro drug release study

All three complexes showed more than 90% of drug release within 240 sec (Table 2). When compared to the drug release from MA-βCD inclusion complexes, less than 30% release was reported for the pure MA suggesting the significant improvement in drug release from the MA-βCD inclusion complexes. Statistical assessment by One–way ANOVA indicated that no statistically significant difference was observed between the three (1:0.5, 1:1, and 1:2) molar ratios of MA-βCD in terms of the cumulative percentage drug release. Based on the literature, no further improvement in drug release may be possible from drug-βCD complexes, beyond a certain level of molar ratio.[12] Hence, beyond the 1:0.5 molar ratio, a significant improvement in drug release may not be achieved. The MA-βCD inclusion complex at 1:0.5 was selected as the best molar ratio for the development of an ODF which had the highest drug content of 97.00±1.55% and greater than 90% drug release, and later it was subjected to SEM analysis and FT–IR spectroscopy.

SEM and FT–IR analysis of MA-βCD inclusion complexes

The photomicrograph of pure MA and βCD were loose aggregates of heterogeneously distributed particles with irregular shapes and rough surfaces which also suggested a crystalline nature for both (Figure 2A and 2B). But the photomicrograph of MA-βCD at 1:0.5 suggested compact solids with smooth surfaces as well

Table 3: Average weight, thickness, folding endurance, pH, percentage moisture loss and percentage moisture uptake of ODF strips containing MA.

Formulation Code	*#Average weight (mg)	*#Thickness (mm)	*#Folding endurance	*pH	*Percentage moisture loss	*Percentage moisture uptake	*Percentage Drug content	*#Disintegration time (s)
H1	0.094±0.004	0.062±0.0005	121±1	6.56±0.11	1.28±0.20	1.51±0.30	88.85±1.11	120±2.64
H2	0.120±0.010	0.092±0.001	84.3±1.52	6.56±0.15	1.21±0.11	1.62±0.13	89.67±1.54	80.33±0.57
H3	0.148±0.008	0.113±0.006	66.6±1.52	6.56±0.18	1.15±0.75	1.85±0.17	93.35±1.25	45.33±0.57
H4	0.174±0.001	0.140±0.003	54.6±0.57	6.55±0.20	1.06±0.21	1.99±0.15	90.70±0.97	48.0±1
P1	0.087±0.007	0.048±0.0005	299±1	6.65±0.01	1.90±0.18	1.21±0.11	94.05±1.64	45.0±1
P2	0.113±0.016	0.068±0.0005	293.6±0.33	6.71±0.03	1.85±0.39	1.25±0.11	92.44±2.15	37.0±1
P3	0.139±0.009	0.092±0.001	253.3±0.33	6.67±0.01	1.39±0.27	1.36±0.09	95.46±0.93	28.6±2.0
P4	0.165±0.006	0.103±0.005	150.6±0.33	6.63±0.04	1.35±0.15	1.38±0.14	94.45±0.76	28.0±1.52

*Values SD. Samples taken in triplicates (n=3), # p<0.05.

as a possible change of crystalline structure to amorphous, which may be the reason behind the enhanced solubility and dissolution profile for the inclusion complexes (Figure 2C). The FT–IR spectrum of MA-βCD inclusion complexes at 1:0.5 molar ratio (Figure 1D) showed all the peaks present in the individual spectrum of MA and βCD inclusion complexes. However, the peak at 1644 cm^{-1} corresponding to C=0 stretching of carboxylic acid disappeared in the FT–IR spectrum of MA-βCD inclusion complexes. It indicates that the chemical interaction may have occurred between the MA and a polar cavity of βCD. Similar results were reported in the literature on drug-βCD complexes prepared by the kneading method.[12] The SEM analysis and FT–IR spectroscopy of the MA-βCD inclusion complex at a 1:0.5 molar ratio suggested a modification in physicochemical parameters, which was supporting the reason laid down for the improvement of solubility and successful formation of the complexes.

Evaluation of MA oral dispersible films strips

Based upon the proposed composition, eight formulations were developed i.e., four each for HPMC E5 and PVA. The formulations with HPMC E5 were coded between H1–H4 and PVA were P1–P4. The average weight of the developed ODF strips ranged from 0.087±0.007 mg to 0.174±0.001 mg. The ODF strips with HPMC E5 i.e., H1–H4 had a slightly higher average weight in comparison with ODF strips developed using PVA (P1–P4) (Table 3). Since the molecular weight of HPMC E5 is higher than PVA, which may be one of the possible reasons for the slightly higher average weight for the ODFs based on HPMC E5. The ODFs based on HPMC E5 and PVA without crospovidone in their composition were recorded with the lowest average weight of 0.094±0.004 mg and 0.087±0.007 mg respectively, whereas the highest average weight of 0.174±0.001 mg and 0.165±0.006 mg was recorded for H4 and P4 which had a maximum concentration of crospovidone i.e., 6% w/v. To analyse the effect of crospovidone concentration in the developed ODF strips of HPMC E5 and PVA i.e., H1–H4 and P1–P4 one-way ANOVA followed by Tukey's multiple comparison test was applied. The data indicated that the increase in the concentration of crospovidone significantly increased the weight of developed ODF strips (p<0.05), as well as the ODF strips without crospovidone i.e., both H1 and P1, showed statistically significant differences in average weight from the rest of the formulations containing crospovidone (Figure 3A and 3B).

The average thickness for the developed ODF strips of HPMC E5 and PVA were recorded between 0.062±0.0005 mm to 0.140±0.003 mm and 0.048±0.0005 mm to 0.103±0.005 mm respectively (Table 3). The statistical assessment of the data by one-way ANOVA followed by Tukey's multiple comparison test confirmed that an increase in the concentration of crospovidone from 2% w/v to 6% w/v was producing a statistically significant change in the thickness of developed ODFs in both HPMC E5 and PVA polymers (Figure 3C and 3D). It also confirmed that

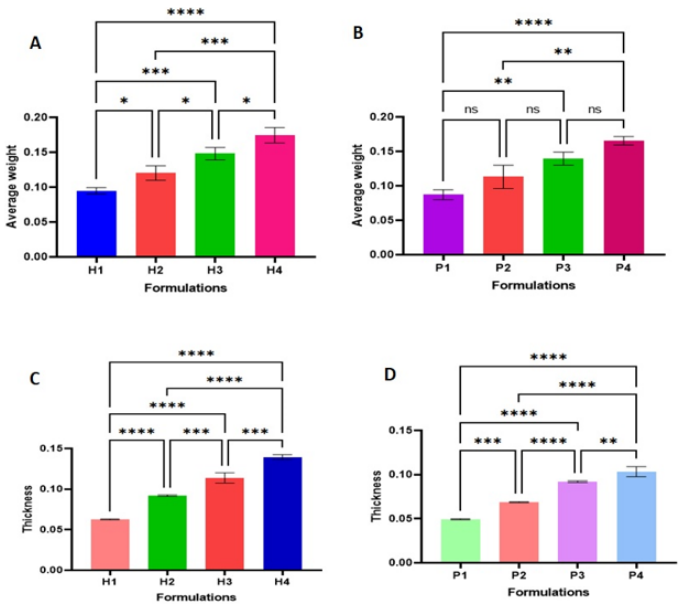

Figure 3: Comparison of the average weight 4A (H1–H4), 4B (P1–P4); thickness 4C (H1–H4), 4D (P1–P4); and folding endurance 4E (H1–H4), 4F (P1–P4) of the developed ODF strips. (*p*-value; 0.0332[*], 0.002[**], 0.0001[***], <0.0001[****]).

there was a statistically significant difference between ODFs without super disintegrant (H1 and P1) and ODFs containing superdisintegrant, which strongly suggested the influence of crospovidone concentration over the thickness of MA-βCD ODF strips. A similar trend was observed in a study conducted by Heer D *et al.*,[24] The folding endurance of developed ODF i.e., both HPMC E5 and PVA ranged between 54.6±0.57 to 299±1 (Table 3). The ODF with PVA i.e., P1–P4 was having comparatively higher folding endurance than the HPMC E5–based ODFs. The ODFs H1 and P1 i.e., without superdisintegrant were reported with higher folding endurance. The influence of crospovidone on the folding endurance was statistically analysed using the one-way ANOVA with Tukey's *post hoc* test indicated that an increase in the concentration of crospovidone significantly reduced the folding endurance (HPMC E5–based ODF reduced from 121±1 to 54.6±0.57 and for PVA based ODF, it was reduced from 299±1 to 150.6±0.33) (Figure 3E and 3F). The previous investigations also suggested that the thickness of ODF has an indirect relationship with folding endurance and results from the study supported a similar observation.[24] This further proved that the influence of crospovidone was producing a significant effect on the folding endurance of ODFs developed during the investigation.

The pH of the developed ODFs i.e., both HPMC E5 and PVA based (H1–H4 and P1–P4) ranged between 6.55±0.20 to 6.71±0.03 (Table 3). The pH obtained for the developed ODFs was closer to the pH of the oral cavity i.e., 6.8. This suggested that all the developed ODF may be safer for usage in the paediatric population in terms of pH. The statistical assessment of the data by one-way ANOVA reveals that the change in concentration of superdisintegrant could not produce any influence on the pH of the developed ODF ($p>0.05$).

The percentage moisture loss and percentage moisture uptake for the developed ODFs of MA (H1–H4 and P1–P4) were measured and reported between 1.06±0.21 to 1.90±0.18 and 1.21±0.11 to 1.99±0.15 respectively (Table 3). Since both parameters indicate the overall stability of ODFs, the data obtained during the investigation were within acceptable limits. The statistical analysis of the data by one-way ANOVA reported with $p>0.05$ suggested that the change in percentage moisture loss and percentage moisture uptake was not statistically significant, which further confirmed that crospovidone concentration was not producing any significant influence over percentage moisture loss and percentage moisture uptake in any of the developed batches i.e., H1–H4 and P1–P4.

Drug content estimation for oral dispersible film strips

The developed ODF strips i.e., H1 to H4 and P1 to P4 had MA ranging between 88.85±1.11% to 93.35±1.25% and 92.44±2.15% to 95.46±0.93% respectively (Table 3). The data obtained during the investigation suggested that the measured drug content between the batches was within the acceptable limit and they were uniform (85%-115% with a standard deviation ≤ of 6%).[25] To further confirm, the data was statistically analysed using the one-way ANOVA method, the $p>0.05$ indicated no statistically significant difference observed in drug content between the developed batches. This indicated that the methodology and conditions adopted for the formulation development were appropriate, and developed ODFs maintained consistency.

In vitro disintegration time of oral dispersible film strips

The *in vitro* disintegration time for the developed ODF strips of both HPMC E5 and PVA i.e., H1–H4 and P1–P4 ranged between 26.3±1.52 sec to 120±2.64 sec (Table 3). The data indicated that the addition of crospovidone showed improvement in the *in vitro* disintegration of the developed ODF. This was further supported by the data obtained for H1 and P1 formulations (without superdisintegrant) which took a maximum disintegration time of 120±2.64 sec and 45.0±1 sec in comparison with ODF strips containing superdisintegrant (Figure 4). The data also suggested an improvement in the disintegration process with an increase in the concentration of crospovidone in the formulation i.e., 2% w/v to 6% w/v. A similar trend was reported in peer–reviewed literature published on similar formulations.[25] The ideal disintegration time recommended for ODF is less than 60 ses.[26] When the *in vitro* disintegration data for the developed ODF strips were investigated, the formulation with PVA i.e., P1–P4 falls under the prescribed limit, whereas HPMC E5–based formulation H1, as well as H2, had *in vitro* disintegration time beyond the prescribed limit of 60 sec. The presence of crospovidone at 4%w/v and 6% w/v could reduce the *in vitro* disintegration time

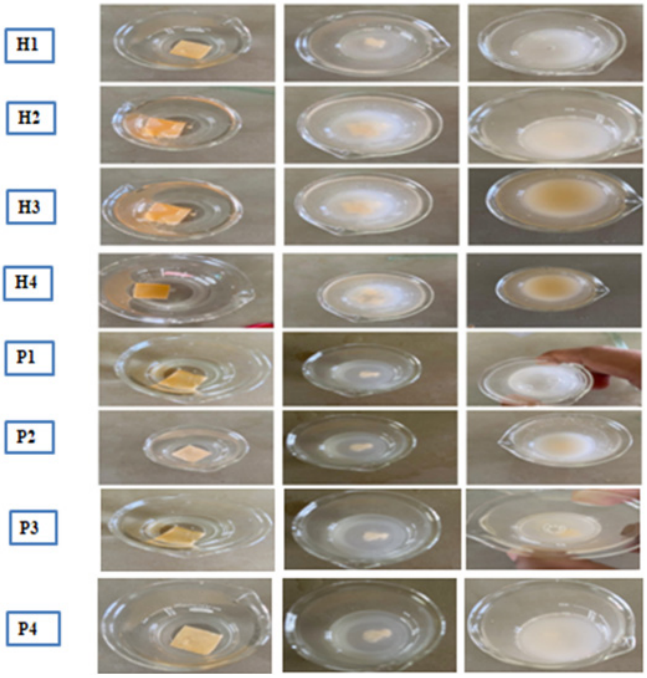

Figure 4: *In vitro* disintegration study of the developed ODF strips.

considerably to 45.33±0.57 sec and 48±1 sec respectively for H3 and H4. This suggested the importance of superdisintegrant in the MA ODF prepared using HPMC E5.

The PVA–based ODF formulations P1–P4 were recorded with a disintegration time of fewer than 60 sec. The crospovidone could further improve the disintegration time and bring it down to as low as 28 sec. When the comparison was made between ODFs of HPMC E5 and PVA, all PVA–based ODFs were having a faster *in vitro* disintegration process. The P1 without any superdisintegrant was able to disintegrate at almost the same time duration as that of the HPMC E5–based H3 formulation containing 4% w/v of crospovidone. Hence, polymer selection may be an important parameter along with the superdisintegrant for the development of ODF.

The statistical analysis by one-way ANOVA followed by *post hoc* analysis indicated that there was a statistically significant difference ($p<0.05$) in disintegration time exist between formulations without crospovidone i.e., H1 and P1 and those with crospovidone (H2–H4 and P2–P4) (Figure 5A and 5B). Further interpretation of the data suggested that formulations containing 2% w/v of crospovidone i.e., H2 and P2 were having a statistically significant difference in their disintegration time when compared to formulations containing 4% w/v and 6% w/v of crospovidone (H3–H4 and P3–P4). The interpretation revealed that the formulation H3–H4 and P3–P4 with 4% w/v and 6% w/v of crospovidone did not show any statistically significant difference in the *in vitro* disintegration time. This indicated that increasing the crospovidone concentration did not result in a substantial improvement in the *in-vitro* disintegration time. Hence it may be concluded that beyond 4% w/v crospovidone may not influence

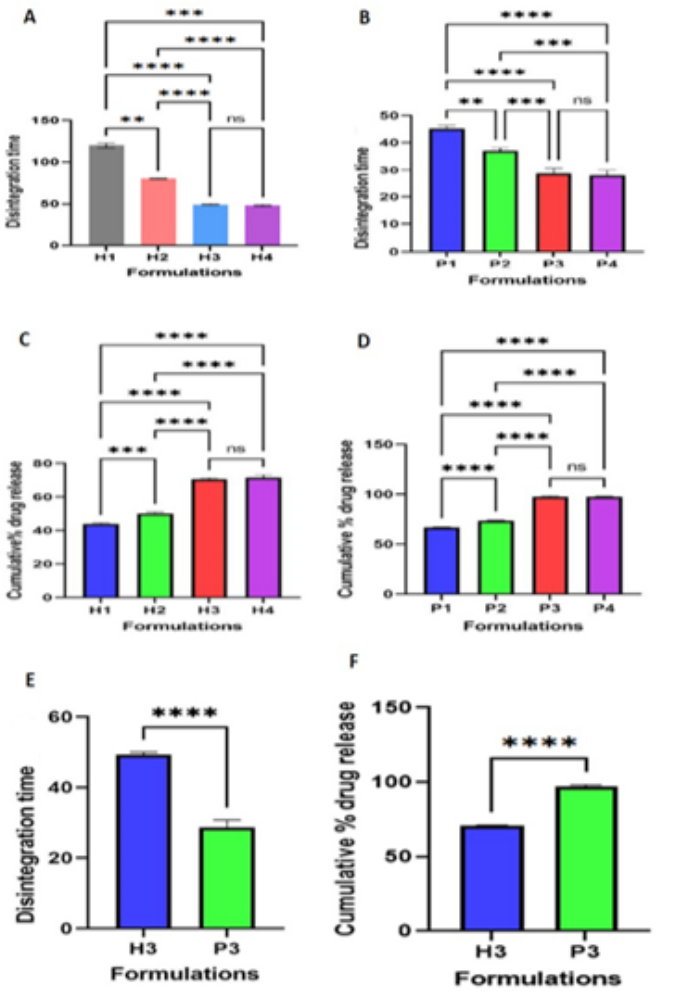

Figure 5: Comparison of the *in vitro* disintegration time 6A (H1–H4), 6B (P1–P4); cumulative percentage drug release 6C (H1–H4), 6D (P1–P4); *in vitro* disintegration time 6E (H3 and P3), cumulative percentage drug release 6F (H3 and P3) of the developed ODF strips (*p*-value; not significant[ns], 0.002[**], 0.0001[***], <0.0001[****]).

the disintegration process of an MA ODF prepared using HPMC E5 and PVA.

In vitro drug release study of the oral dispersible film strips

The percentage cumulative drug release obtained for MA ODF with HPMC E5 (H1–H4) and PVA (P1–P4) was illustrated in Figure 6. The MA ODF without superdisintegrant (H1) released 78.58±0.14% of MA after the completion of 300 sec. The H2 to H4 ODF strips developed using HPMC E5 i.e., 2% w/v to 6% w/v crospovidone could release MA at a higher percentage after 300 s i.e., 91.80±0.30%, 97.85±0.52%, and 98.31±0.31% respectively. The formulations H2, H3, and H4 could produce much faster drug release than H1 throughout *in vitro* drug release study. More than 50% of the loaded MA was released from H2, H3, and H4 within 180 sec, whereas H1 (without superdisintegrant) took almost 240 sec to cross 50% drug release. But at a similar time interval, formulations H3 and H4 could release more than 95% of loaded MA. This improved drug release profile H2–H4 indicated

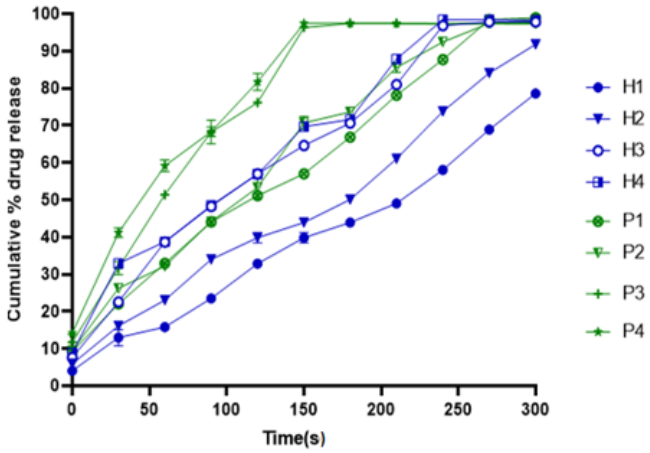

Figure 6: *In vitro* drug release study of the developed ODF strips.

the influence of crospovidone as a superdisintegrant selected for the formulation.

The ODFs with PVA (P1–P4) had a much faster drug release profile when compared with H1–H4 at all measured time intervals. At the 300th sec, the formulation of PVA (P1–P4) could release more than 95% of loaded MA. Formulation P3 and P4 with 4% w/v and 6% w/v crospovidone released more than 50% of loaded MA within 60 sec whereas formulation P1 without any super disintegrant took almost 120 sec to cross 50% drug release. This was a trend observed even with the ODFs developed using HPMC E5. This further supported the inclusion of superdisintegrant in ODFs. The previous study reports supported the claim made during this investigation.[24,25]

The comparison between ODFs of HPMC E5 and PVA in percentage Cumulative drug release indicated a difference i.e., P1–P4 was showing a superior drug release profile than H1–H4 at any measured time interval. The reason for the improved drug release from the PVA–based ODF may be due to its high moisture–holding capacity as compared to HPMC E5.[27] The drug release is also affected by the polymer concentration to develop a stable ODF. As the concentration of polymer increases, the drug release from the ODF may decrease.[18] The polymer concentration in PVA–based ODF strips (2% w/v) is less as compared to HPMC E5–based ODF strips (3% w/v). This may be a reason behind the enhanced drug release from the PVA–based ODF as compared to HPMC E5–based formulation. The faster disintegration time reported for PVA–based ODFs was further substantiated by the faster drug release profile observed in ODFs P1–P4.

The statistical analysis of the data at 180 sec by one-way ANOVA followed by Tukey's multiple comparison test reveals the statistically significant difference in the data ($p<0.05$), which may be due to the influence of superdisintegrant in the formulation, as well as the formulations without superdisintegrant i.e., both H1 and P1, were having a drug release profile which had a statistically significant difference from the rest of the developed formulations (H2–H4 and P2–P4) (Figure 5C and 5D). It also revealed that the ODF formulations H3–H4 and P3–P4 (4% w/v and 6% w/v crospovidone) were having a drug release profile that had a statistically significant difference from H2 and P2 with 2% w/v crospovidone. But when the drug release profile was compared between the formulations with 4% w/v and 6% w/v crospovidone (H3–H4 and P3–P4), there was no statistical difference identified. Irrespective of polymer change, this trend was similar in HPMC E5 and PVA. This indicated a possibility that crospovidone concentration beyond 4% w/v may not produce a significant change in the drug release profile for a MA ODF prepared using either HPMC E5 or PVA. The findings of the *in vitro* drug release study supported the observation from the *in vitro* disintegration study. Hence 4% w/v may be the ideal concentration of crospovidone as a super disintegrant to provide an enhanced release profile for MA ODF prepared using HPMC E5 or PVA.

Statistical optimization of developed MA oral dispersible film strips

Based on the above discussion, increasing the concentration of crospovidone beyond 4% w/v may not produce a significant effect on the *in vitro* disintegration time and *in vitro* drug release of the developed MA ODF. This trend was common for the ODFs developed using HPMC E5 and PVA. Hence, H3 and P3 i.e., HPMC E5 and PVA–based MA ODF with 4% w/v crospovidone may be an optimised formulation among the selected polymers. For the further comparison between H3 and P3, the *in vitro* disintegration and *in vitro* drug release data were subjected to one-way ANOVA, which suggested that change in the polymer had a statistically significant effect on disintegration time and drug release($p<0.05$). The *post hoc* analysis using Tukey's test confirmed that the ODF formulation P3 had a statistically highly significant ($p<0.001$) difference from the H3 formulation based on *in vitro* disintegration time and percentage cumulative drug release (Figure 5E and 5F). The statistical analysis of the data demonstrated that a PVA–based formulation with 4% w/v of crospovidone may be the best MA ODF developed during the investigation.

Drug release kinetics

To determine the mechanism of MA release from the ODF formulation P3, the *in vitro* MA release data were fitted into zero–order, first–order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell models. It was observed that the R^2 value for zero–order was 0.794 and the first order was 0.854, which indicated that the drug release data for P3 formulation showed the best fit in first–order kinetics. The data plot of the Higuchi model showed an R^2 value of 0.925, and the release exponent (n) value in the Peppas model for P3 formulation was found to be 0.465. The regression value obtained in the Hixson–Crowell model was higher (0.855).

Table 4: Stability study of P3 ODF packed in aluminium foil.

Parameters	Initial	After 30 days		
		18°C±2°C	30°C±2°C/ 70%RH±5%RH	40°C±2°C
Physical appearance	Light orange, Smooth, opaque, and homogenous	No change		
Folding endurance	255±0.33	253.6±0.56	251±0.89	250±0.89
Percentage moisture uptake	1.36±0.09%	1.30±0.25%	1.34±0.51%	1.32±0.41%
Percentage moisture loss	1.39±0.27%	1.35±0.23%	1.36±0.33%	1.38±0.56%
In vitro disintegration time	28.10±2.01sec	27.99±1.99sec	28.95±1.68sec	28.05±1.68sec
Drug content	95.66±1.96%	95.00±2.01%	94.99±1.80%	92.99±1.80%
Cumulative percentage drug release (After 3 min)	97.41±2.06	97.02±1.35	97.58±1.58	98.58±1.58

*Values SD. Samples taken in triplicates (n=3), p>0.05.

Table 5: Stability study of P3 ODF packed in polyethylene ziplock.

Parameters	Initial	After 30 days		
		18°C±2°C	30°C±2°C/ 70%RH±5%RH	40°C±2°C
Physical appearance	Light orange, Smooth, opaque, and homogenous	No change		
Folding endurance	255±0.33	253.6±0.56	251±0.89	250±0.89
Percentage moisture uptake	1.36±0.09%	1.30±0.25%	1.34±0.51%	1.32±0.41%
Percentage moisture loss	1.39±0.27%	1.35±0.23%	1.36±0.33%	1.38±0.56%
In vitro disintegration time	28.10±2.01sec	28.99±1.99sec	28.95±1.68sec	28.05±1.68sec
Drug content	95.66±1.96%	94.99±2.01%	93.90±1.80%	92.89%
Cumulative % drug release (After 3 min)	97.41±2.06	97.02±1.35	96.99±1.58	96.58±1.58

*Values SD. Samples taken in triplicates (n=3), p>0.05.

Based on drug release kinetics, it may be concluded that the P3 formulation followed the first–order, Quasi–Fickian diffusion–controlled release profile and the study also revealed that change in surface area of developed MA ODF with the progressive dissolution of a matrix was with respect to time.[10,16]

Comparison of in vitro drug release profile against a marketed suspension

The percentage cumulative drug release obtained for optimised MA ODF i.e., P3 and MS Figure 6 depicted that, P3 released 97.14±0.12% of MA and MS could release 96.60±0.21% of MA after the completion of 3 min. The MA-βCD inclusion complex, crospovidone and inherent property of PVA might have played a significant role in enhancing the drug release from the MA ODF, which had comparable results as that of available marketed products. The statistical assessment by one-way ANOVA at a 95% confidence interval revealed that optimised MA ODF i.e., P3 have a dissolution profile similar to marketed MS (p>0.05). Hence the ODF of MA may be an effective alternative formulation to marketed oral liquid dosage forms in the paediatric population for the management of fever.

Stability studies

The stability study of the best MA ODF strips i.e., P3 was performed under in-house testing conditions. The samples were evaluated for physical appearance, folding endurance, percentage moisture uptake, percentage moisture loss, *in vitro* disintegration time, drug content and cumulative percentage drug release after 30 days (Table 4, 5). The data collected indicated that the samples packed in aluminium foil and polyethylene ziplock stored at different temperature conditions had no major stability issues after the completion of 30 days. The colour and texture of the product remained unchanged throughout the study period at different temperature conditions. The data were subjected to one-way ANOVA, and when compared with the initial readings, there was no statistically significant change after 30 days in the folding endurance, percentage moisture uptake, percentage moisture loss, *in vitro* disintegration time, drug content and cumulative percentage drug release (after 3 m) in all testing conditions. The stability study indicated that the developed MA ODF using polyvinyl alcohol i.e., P3 was a stable product when packaged in both aluminium foil and polyethylene ziplock.

CONCLUSION

The study suggested the significance of inclusion complexes of βCD in enhancing the solubility profile of MA. The MA-βCD inclusion complexes may be ideal for loading fast–dissolving oral films with an optimised composition. The film–forming polymer PVA at 3% w/v with 4% w/v crospovidone as a superdisintegrant was recommended for the improved release profile for MA from oral dispersible films. Based on the findings, it is concluded that the MA oral dispersible films are an excellent alternative to existing marketed paediatric formulations. However, further *in vivo* evaluations may be required to substantiate the findings reported during the *in vitro* studies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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