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ORIGINAL ARTICLE

Taste Masking of Steroids for Oral Formulations

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ABSTRACT

Objectives: Oral steroids are commonly prescribed to children. Steroids have a strong bitter taste that limits their oral acceptance in children. The objective of this study was to formulate a pediatric-friendly and palatable oral dosage form of steroids.

Materials and Methods: Solid dispersions of dexamethasone were prepared using polyethylene glycol, pectin, and Eudragit as carrier polymers, and chocolate as a flavoring agent. Taste masking efficiency was evaluated by healthy volunteers to select the best formula. The selected formula was pressed into chewable tablets with varying amounts of sweeteners. Chewable tablets were evaluated for palatability, hardness, and chewing index. The typical application of the taste masking approach was confirmed using prednisolone.

Results: Eudragit-based solid dispersions were effective in dexamethasone taste masking. Using 40% mannitol resulted in palatable tablets with acceptable hardness and chewing difficulty. The effectiveness of the taste masking approach was successfully used to prepare prednisolone chewable tablets. However, an increase in the carrier: drug ratio and a change in the flavor to pineapple were necessary to achieve maximum palatability of prednisolone chewable tablets.

Conclusion: Eudragit solid dispersion is an effective method for the taste masking highly bitter steroids. The solid dispersion was successfully pressed into a palatable, easy-to-chew, and pediatric-friendly chewable tablet dosage form. The carrier: drug ratio and the choice of flavoring agent are crucial factors in improving tablet palatability.

Key words: Solid dispersion, taste masking, steroids, dexamethasone, eudragit

INTRODUCTION

Oral steroids are widely used in children in liquid dosage forms for the treatment of asthma, virus-associated wheezing, Crohn's disease, and others.[1] While liquid dosage forms occupy the largest share of pediatric medicines and present the most widely acceptable dosage form,[2] they come with a fair share of problems such as dose accuracy issues due to differences in measured dose and the need for elaborate patient instructions on proper dose measurements. Additionally, some children refuse to take liquid medicines.[3] In contrast, chewable tablets grant ease of administration in toddlers and young children, dose accuracy over liquid preparations, and enhanced stability.[4] Compared to medicated gummies, chewable tablets can be produced into scored tablets that can further allow dose adjustment and flexibility, and they have been suggested to be associated with less misuse.[5] As such, there is an expanding interest in formulating pediatric medicines in chewable tablet dosage form.[6]

An important consideration in drug formulations that release the drug in the mouth is palatability.[7,8] Chewable tablets mandate the release of the drug in the oral cavity, resulting in an immediate sense of the drug taste. This renders chewable tablets not suitable for medicines of non-pleasant taste, including steroids. Consequently, adequate taste masking is required to formulate medicines into chewable tablets, which have been the focus of several studies.[9-12] Although the use of different sweeteners and flavoring agents has been widely used, several medicines have a strong unpleasant taste that dominates over all other additives incorporated in the formulation. More effective taste masking approaches include solid dispersion, complexing with taste masking excipients, coating of medicine through micro- or nanoencapsulation, and the use of ion-exchange resins.[13-16]

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Solid dispersions, defined as the dispersion of one or more active ingredients in an inert carrier in the solid state, have been successfully used for taste masking purposes in the formulation of different oral dosage forms.[16,17] Different techniques have been used to prepare solid dispersions with hot melt, solvent evaporation, and solvent-melt methods being the most employed methods. The solvent evaporation method involves solubilizing the drug and the polymer in a common solvent and then evaporating the solvent.[18] This method offers several advantages, including ease of preparation and avoidance of heat that can lead to thermal instability of the drug.[19]

The objective of this study was to formulate a pediatric-friendly and palatable oral dexamethasone and prednisolone dosage form. There have been few reports of taste-masked steroid formulations. One study reported orally disintegrating tablets of dexamethasone.[20] However, the taste evaluation was not reported clearly to allow full evaluation of the taste masking efficiency. Another study reported microparticle-based orodispersible films and tablets of prednisolone.[21]

This study aimed to develop, optimize, and characterize a taste-masking formulation of dexamethasone on a chewable tablet formulation. The study employed solid dispersion using three different polymers: polyethylene glycol (PEG), film-forming pectin, and pH-dependent solubility Eudragit®. Solid dispersions were prepared using the solvent evaporation method and incorporating different flavoring agents. The prepared solid dispersion was pressed into chewable tablets that were characterized for palatability and chewing difficulty, among other attributes. The expanded applicability of the taste masking method was demonstrated using prednisolone, another steroid commonly prescribed for children.

MATERIALS AND METHODS

Materials

Dexamethasone and prednisolone from Hangzhou Hyper Chemical Ltd. (China), Eudragit E PO from Xi'an Sonwu Biotech Co. Ltd. (China) were purchased. D-Sorbitol was obtained from Thomas Baker Chemicals (India), while Avicel® PH102 was purchased from FMC, Belgium. PEG 4000 and 6000 from BDH Chemical Ltd. (England), mannitol from Gerhard Buchmann (Germany), and HMPC 15 cps (hydroxy propyl methyl cellulose) from HI Media (India) were obtained. All solvents and reagents used were of analytical grade.

Dexamethasone solid dispersion preparation and characterization

Solid dispersion preparation

A dexamethasone solid dispersion was prepared by the solvent evaporation method. In brief, predetermined amounts of dexamethasone and carrier polymer(s) were accurately weighed. For PEG/HPMC solid dispersions, PEG was dissolved in ethanol in a mortar and then HPMC was added gradually. Dexamethasone stock solution at a concentration of 20 mg/mL was added, and the mixture was poured into a petri dish to allow solvent evaporation. The solid dispersion was collected and sieved through a 40-mesh sieve. Eudragit® E PO solid dispersions were prepared as previously described.[22] Briefly, Eudragit® E PO was freshly dissolved in 96% ethanol with continuous stirring. Dexamethasone solution was added and the solution was left on a magnetic stirrer until a thick gel consistency was observed. The solidified gel was triturated and sieved through a 40-mesh sieve. For pectin-containing formulations, pectin was dissolved in water at a concentration of 40 mg/mL at 40 °C and used fresh. When indicated, chocolate (at 40-50% of formulation weight) was melted and thinned in ethanol to obtain a pourable slurry that was added to the polymer solution prior to adding dexamethasone solution. A liquid flavoring agent (caramel, grapes or hazelnut) was added to the polymer solution before adding the dexamethasone solution. When required, oven drying was employed for solid dispersion formulations containing aqueous flavoring agents. A full description of all formulations assessed in this study is summarized in Table 1.

When required, blank Eudragit® E PO solid dispersion was prepared using the same method without the addition of dexamethasone.

Percentage yield

The collected solid dispersion granules were weighed, and the weight (W_{SD}) was divided by the total weight of the drug and polymer (and chocolate when applicable), W_T. The percentage yield was calculated using equation 1.

$$percent\ yield = \left[\frac{W_{SD}}{W_T}\right] x\ 100 \quad (1)$$

Drug content

An accurately weighted amount of the solid dispersion was dissolved in 96% ethanol on a magnetic stirrer for 3 h, after which the solution was filtered using a filter paper. Drug content was determined spectrophotometrically at 241 nm. A sample of blank solid dispersion was treated in parallel.

Differential scanning calorimetry

Five milligrams of dexamethasone, Eudragit® E PO, dexamethasone: Eudragit® E PO physical mixture, dexamethasone solid dispersion, and blank Eudragit® E PO solid dispersion were placed in a sealed aluminum pan and heated at a scanning rate of 10 °C/min over a temperature range of 25-300 °C in a nitrogen atmosphere at a flow rate of 100 mL/min. Thermal analyses were performed using Shimazu DSC.

Taste masking effectiveness of solid dispersion

All seventeen dexamethasone solid dispersion formulations described in Table 1 were evaluated for their effectiveness in masking the bitter taste of the drug by healthy volunteers. Volunteers were asked to place a small amount of the formulation on their tongues and score the solid dispersion bitterness on a scale of 0-10, where 10 is very bitter and zero is not bitter. Volunteers were instructed to expel the solid dispersion and not to sallow it and to rinse their mouths after each taste evaluation. Ten volunteers evaluated each solid dispersion formulation.

Preparation and characterization of dexamethasone chewable tablets

Preparation of dexamethasone chewable tablets

Chewable tablets were prepared according to the formulations presented in Table 2. The accurately weighed ingredients were sieved and mixed geometrically. Tablet mixtures were characterized for flowability by calculating the angle of repose using the fixed funnel method.[23] Carr's index was calculated by measuring bulk and tapped densities using a Copley JV 2000 tapped density tester, UK. Carr's index was calculated according to equation 2.

Carr's index = (Tapped density-Bulk density / Tapped density) x 100 (2)

To prepare the chewable tablets, the tablet blend was compressed into tablets using an 8-mm flat punch tablet press.

Chewable tablet evaluation

Hardness test: Six randomly selected tablets were evaluated using a YD-2 hardness tester (Sinopharm, China). Hardness was expressed as kilopond (kp).

Ease of chewing: Ease of chewing was evaluated using the chewing difficulty index (CDI) and volunteers' rating of chewing difficulty. CDI was calculated according to equation 3, where F_h is the tablet breaking force under diametral compression and H is tablet thickness.[24]

$$CDI = F_h H \quad (3)$$

In addition, healthy volunteers assessed the ease of tablet chewing. Volunteers were asked to chew the tablet and rate tablet chewing as easy, medium or hard. Five to six volunteers assessed each formula. Volunteers were instructed to discard chewed tablets and rinse their mouths after expelling the tablets.

In vitro disintegration: The *in vitro* disintegration time was determined using the disintegration test apparatus as *per* USP specifications. Briefly, one tablet was placed in each of the six vessels of the apparatus basket. 0.1 N HCl (900 mL) was used as the disintegration medium, and the temperature was kept at 37 ± 2 °C. The apparatus was operated for 30 min, and the time required for complete tablet disintegration was recorded.

In vitro dissolution: The dissolution profile of the prepared dexamethasone tablets was determined using USP dissolution apparatus II (paddle method) and according to USP specifications.[25] The dissolution study was performed using 0.1 N HCl as the dissolution media at a 37 ± 0.5 °C and 100 rpm. A 5 mL sample was withdrawn at 0, 5, 15, 20, 30, and 45 min. Samples were filtered through 45 µm Millipore filter. Samples were extracted with three 15 mL portions of chloroform. Chloroform was evaporated from the combined extracts and the residue was dissolved in 20 mL of ethanol and analyzed spectrophotometrically at 241 nm. The amount released in mg was calculated using equation 4, where C is the dexamethasone concentration and V is the volume of the aliquot extracted with chloroform. Drug release was considered satisfactory, if not less than 2.8 mg (70%) dexamethasone was released in 45 min portion of dexamethasone dissolved.

Table 1. Formulation of the dexamethasone solid dispersion (expressed as *w/w*)

Formulation	Dexamethasone	PEG 6000	HMPC	Pectin	Eudragit® EPO	Flavoring agent
F1	0.1	1.5				Chocolate
F2	0.1	3.0				Chocolate
F3	0.1	1.5	0.75			/
F4	0.1	1.5	1.5			/
F5	0.1	1.5	1.5			Caramel/chocolate
F6	0.1	1.5	1.5			Grape
F7	0.1	3.0	1.5			Chocolate
F8	0.1	3.0	1.5			Hazelnut/chocolate
F9	0.1	3.0	3.0			Caramel/chocolate
F10	0.1			0.1		Hazelnut/chocolate
F11	0.1			0.2		Hazelnut/chocolate
F12	0.1			0.2		Caramel/chocolate
F13	0.1	1.5	1.5	0.1		Caramel/chocolate
F14	0.1				0.2	Chocolate
F15	0.1				0.4	Chocolate
F16	0.1				0.8	Chocolate
F17	0.1				0.4	/

Table 2. Chewable tablet formulation of the model steroids employed in this study

Ingredient	A Dexamethasone			B Prednisolone		
Notation	**D1**	**D2**	**D3**	**P1**	**P2**	**P3**
SD, weight (drug dose)	40 (4 mg)	40 (4 mg)	40 (4 mg)	95 (5 mg)	95 (5 mg)	45 (5 mg)
Flavor	Chocolate	Chocolate	Chocolate	Chocolate	Chocolate	Pineapple
Avicel, weight (%)	80 (40%)	80 (40%)	60 (30%)	150 (30%)	150 (25%)	150 (30%)
PEG 4000, weight (%)	20 (10%)	20 (10%)	20 (10%)	50 (10%)	50 (8%)	50 (10%)
Sorbitol, weight (%)	60 (30%)					
Mannitol, weight (%)		60 (30%)	80 (40%)	205 (41%)	305 (51%)	255 (51%)
Final weight (mg)	**200**	**200**	**200**	**500**	**600**	**500**

SD: Standard deviation

(in mg) = 10(C/V)(Au/*(As)* (4)

Tablet palatability: Five healthy volunteers were asked to evaluate the palatability of the tablet and report their acceptance of the chewable tablet on a scale of 1-5 with one being very unpalatable and five being very palatable. The volunteers were instructed to chew the tablet, expel it, and rinse their mouths after each taste.

Applicability of the taste masking technique for other steroids

Solid dispersion preparation

Prednisolone solid dispersion was prepared using Eudragit® E PO at drug: polymer ratios of 1:4, 1:6, and 1:8 using the same method described for dexamethasone. The flavors used included chocolate and pineapple. Healthy volunteers evaluated the taste masking efficiency of the prepared solid dispersions, similar to the procedure described for dexamethasone solid dispersion. Each formulation was assessed by five volunteers.

Chewable tablet preparation and characterization

Chewable tablets of prednisolone were prepared according to the formulations presented in Table 2B. The accurately weighed ingredients were sieved and mixed geometrically. The tablet mixture was compressed into tablets using a 12-mm flat punch tablet press for prednisolone tablets. Chewable tablets were characterized for hardness, chewing index, ease of chewing, and palatability, as described earlier for dexamethasone chewable tablets.

Statistical analysis

When indicated, data were analyzed by the non-parametric Kruskal-Wallis test followed by Dunn's multiple comparison test. Differences were considered significant at an adjusted p value < 0.05. statistical analyses were conducted using GraphPad Prism 7.04.

Compliance with ethical standards

The study proposal was approved by the ethical committee of the institution (approval number: RECAUBCP-31102020B).

RESULTS AND DISCUSSION

Dexamethasone solid dispersion preparation and characterization

Seventeen solid dispersion formulations were successfully prepared for dexamethasone using three types of polymers, namely PEG, pectin, and Eudragit® E PO (Table 1). Successful preparation indicates the ability to grind the solid dispersion mass into fine particles that can be used for tablet preparation. Percent yield for all seventeen formulas ranged from 80 to 98%, with lower yield for pectin-containing formulas (F10-F13) and formulas F5-F6 and higher yield for formulas F1-F4 (PEG 6000). All seventeen formulas were characterized for taste masking efficiency, which was the goal of the solid dispersion preparation. For PEG-based solid dispersions, F1-9, volunteers reported highly variable results, with the general trend being failure of the solid dispersion to mask the bitter taste of dexamethasone (Figure 1). Similar incomplete taste masking by PEG 6000 was reported for arbidol hydrochloride.[16] PEG 6000 was selected based on its oral safety, relative ease of handling and processing in solid dispersion preparation, and low affinity for ethanol, which further enhances solid dispersion preparation.[26] Additionally, it is superior to the lower molecular weight PEG in dissolution rate enhancement.[27] Formulation F6 showed the best outcome among PEG-based formulations. This was the only formulation that used a grape flavoring agent. However, this formulation consistently had a lower yield (about 81%) and required extended oven drying due to the large volume

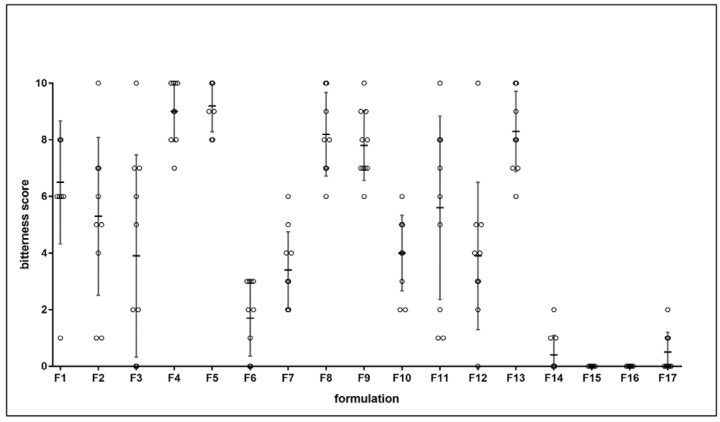

Figure 1. Taste masking efficiency of different solid dispersion formulations. Bitterness level is expressed as a scale of 0-10 with 0 is not bitter and 10 is very bitter. Data are expressed as mean ± SD, n: 10

SD: Standard deviation

of aqueous flavoring agent required. Therefore, no further modifications to improve this formulation were attempted.

The other polymer used for taste masking was pectin. Pectin is a natural polymer that is abundant and safe. Pectin has been suggested to have good taste masking properties and has been used as a carrier for solid dispersion.[28] It is hypothesized to limit drug release in the mouth because it is specifically hydrolyzed by colon bacteria,[29,30] thereby reducing or masking the bitter taste of the drug. Pectin-based solid dispersions, F10-F13, resulted in variable outcomes for taste masking efficiencies comparable to those obtained for the PEG-based formulation (Figure 1). Additionally, solid dispersion yield and processing were not highly reproducible due to the tendency of pectin to form plastic-like sheets that are difficult to pulverize.[30] Pectin has been used to limit drug release in acidic media.[31] In this study, we displayed the technical limitations of using pectin as a sole carrier for solid dispersions. In addition, the combination of PEG and pectin failed to efficiently mask the bitter taste of dexamethasone, F13 (Figure 1). Higher amounts of pectin than those used in F13 resulted in a sheet-like material, and the solid dispersion was rated as a failed formulation (data not shown).

On the other hand, all three Eudragit® E PO-based formulations showed promising outcomes even with a lower drug: polymer ratio of 1:2 in F14 (Figure 1). A further increase of the ratio to 1:4 in F15 resulted in complete taste masking of the bitter dexamethasone taste. Eudragit® are acrylic-based polymers with varying solubility properties that allow the control of the rate of drug release.[32] The Eudragit® E family are soluble in pH below 5, which is below saliva pH[32] making it suitable for taste masking applications.[8,22] To evaluate the need for chocolate for taste masking, a 1:4 solid dispersion was prepared without chocolate. Taste masking evaluation indicated a better performance of the chocolate containing solid dispersion (Figure 1), F15 *vs.* F17. These results agree with previous reports on flavor-free taste-masked microparticles that were largely rated "tasteless" but not pleasant.[33] Chocolate flavoring had been shown to be effective for taste masking of bitter drugs[34,35] and has been used to improve the palatability and acceptability of dexamethasone oral formulations.[36] Additionally, chocolate represents an excellent flavoring agent for pediatric dosage forms due to its high acceptability among children and even adults.[37,38] Besides palatability improvement, chocolate has been suggested to offer several health benefits, including antioxidant effects, cardiovascular effects, and possible cognitive effects.[39,40] As such, chocolate containing Eudragit® E PO solid dispersion with a dexamethasone:polymer ratio of 1:4 was used for further evaluation.

Selected solid dispersion formulation characterization

Before chewable tablet preparation, the chocolate containing 1:4 Eudragit® E PO-based solid dispersion was evaluated for yield, drug content, and thermal analysis. A percent yield by weight of 92.88 ± 3.50% was obtained across the different batches prepared. The dexamethasone content of the solid dispersion was found to be 97.91 ± 2.21% of the initial drug used in the preparation. These results confirm the technical suitability of the prepared solid dispersion for further formulation into a pharmaceutical dosage form. DSC analyses were conducted to confirm the formation of solid dispersions. The DSC thermogram of pure dexamethasone presented an endothermic peak at 257.41 °C and Eudragit® E PO thermogram showed two peaks one at 227.48 °C and another broad peak at 86.48 °C (Figure 2A, B). A dexamethasone peak was evident in the physical mixture

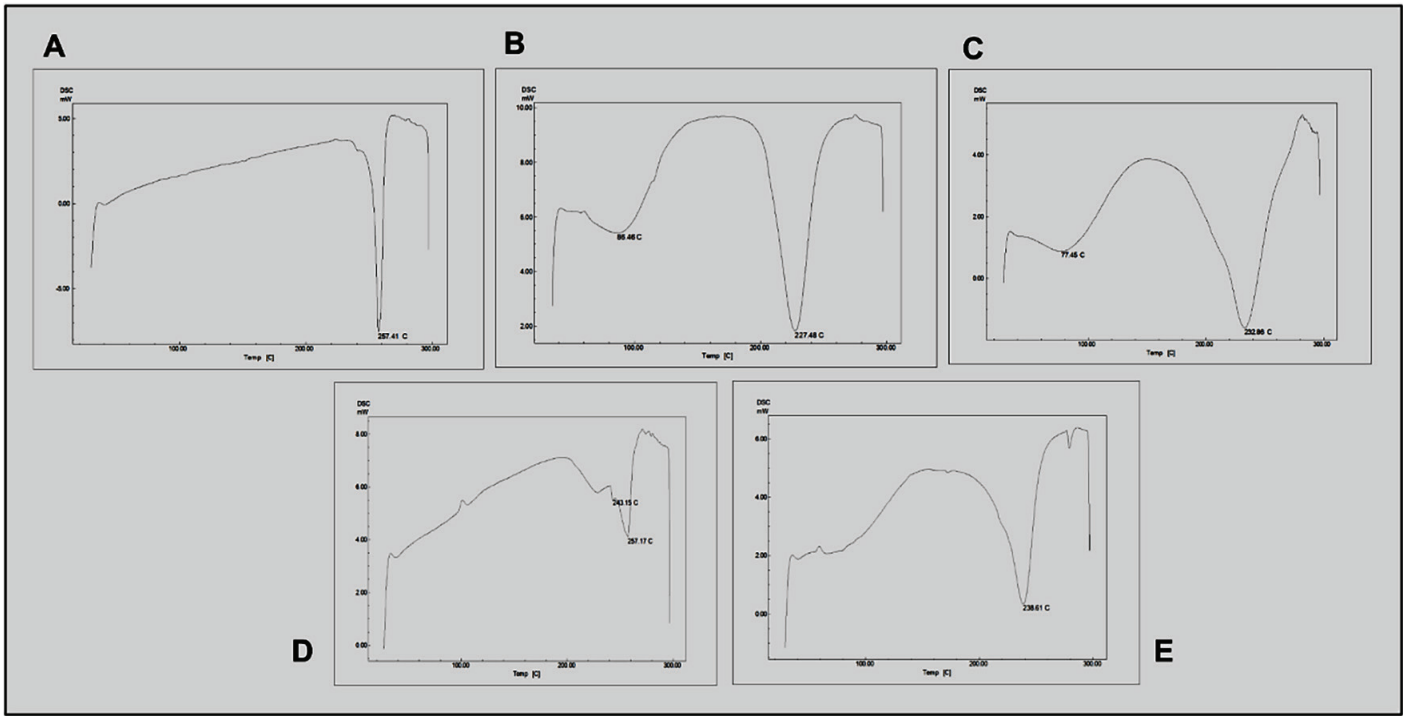

Figure 2. DSC profile of A: dexamethasone, B: Eudragit® EPO only, C: 1:4 solid dispersion, D: 1:1 physical mixture, and E: blank solid dispersion

but absent in the solid dispersion thermogram, confirming solid dispersion formation and indicating drug polymer miscibility and possible drug solubility in the polymer liquid phase (Figure 2C, D).[41,42]

Preparation and characterization of dexamethasone chewable tablets

Dexamethasone solid dispersion was developed into chewable tablets for optimal delivery to patients. Tablets were developed according to the mixtures presented in Table 2. The tablet blend contained basic constituents required for tablet compression such as binders and diluents. Because chewable tablets are intended mainly for children, the tablet blend was limited to essential excipients.[43] Sweeteners at different weight percentages were incorporated to improve tablet palatability. The change of sorbitol to mannitol resulted in a marginal non-significant reduction in tablet blend flow properties (Table 3). Such results are expected because of the poorer flow properties and compressibility of mannitol compared with sorbitol. However, tablet blend flow properties remained well. Thus, it was used without further adjustments.

Chewable tablets should have palatable taste, be easy to chew, compressed into acceptable size and shape, and readily disintegrate.[44] The tablet blend used in this study was compressed into 8-mm chewable tablets with 2-mm thickness. The use of 30% sorbitol as a sweetener resulted in a moderately palatable tablet. The use of mannitol at the same concentration resulted in an improved palatability that was significantly improved by further increasing the mannitol content in the tablet blend to 40% (Figure 3A). Sorbitol and mannitol are both naturally occurring sugar alcohols (polyols) that are used as bulk sweeteners in pharmaceutical preparations. They have comparable sweetness, and both are less sweet than sucrose. Mannitol and sorbitol are non-caloric, non-hyperglycemic, and do not cause dental decay, which makes them attractive for pharmaceutical dosage forms compared with sucrose. Mannitol specifically is commonly used in chewable tablets because of its high negative heat of solution, which boosts its cooling effect.[45,46] Even though the tablets were evaluated by adult participants, the chocolate component and sweet taste from mannitol are expected to enhance tablet acceptance by pediatric patients.

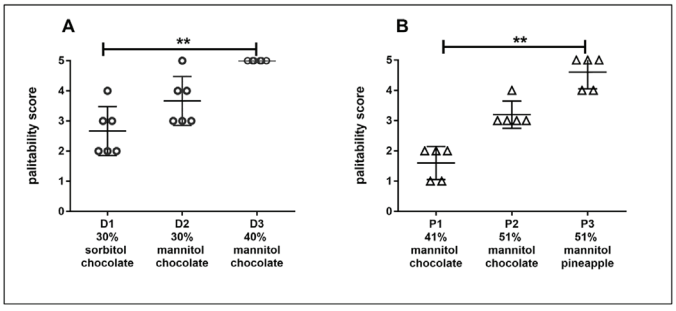

Figure 3. Palatability of steroids chewable tablets. A: Dexamethasone chewable tablets, B: Prednisolone chewable tablets. Data are expressed as mean ± SD, n: 5-6. **: $p < 0.01$

SD: Standard deviation

Table 3. Precompression characterization of the chewable tablet powder blend

		Angle of repose	Carr's index	Flow properties
Solid dispersion		17.14 ± 1.33		Excellent
Tablet blend	D1	28.57 ± 0.99	10.86 ± 0.16	Excellent and good
	D2	31.80 ± 1.96	11.58 ± 0.58	Good and good
	D3	30.78 ± 0.88	11.45 ± 1.11	Good and good

Values are expressed as mean ± SD, n: 3
SD: Standard deviation

In addition to palatability, dexamethasone chewable tablets were evaluated for hardness and chewing difficulty. Chewable tablets are intended to be chewed completely by the patients and they are largely intended for pediatric patients.[47] Excessive tablet hardness might lead to incomplete chewing by the patient which can cause serious side effects, including choking and intestinal obstruction. A CDI has been described and is recommended by the FDA in quality attribute guidance for chewable tablets.[44] The index relates tablet hardness measured under diametral loading and tablet thickness, and it provides a direct estimate of the force required to break the tablets in the mouth.[24] As *per* FDA guidance, the hardness of small chewable tablets should not exceed 12 kp to avoid serious side effects. Dexamethasone tablets for all three formulations showed comparable results in terms of hardness and CDI with no significant differences (Table 4). The hardness of the three different formulations was below 12 kp, and they were rated easy to chew by volunteers, suggesting a successful chewable tablet formulation.

A major consideration in chewable dosage forms is the need for mechanical stress provided by chewing to initiate drug release. However, it is possible that the patient will swallow the tablet or inadequately chew it. Consequently, disintegration and dissolution tests were conducted to ensure tablet performance compliance with USP specifications if tablets were swallowed by the patient without chewing. Chewable tablets from all three formulations passed the disintegration test according to the USP specifications for plain tablets. The disintegration time for all three formulations was comparable with no significant differences (Table 4). The dissolution profile for the optimal chewable tablet formulation showed more than 70% dexamethasone release within 45 min, which suggests that the chewable tablet has passed the USP tolerance limit for the dissolution test (Figure 4).

Applicability of the taste masking technique to other steroids

To demonstrate the applicability of the prepared solid dispersion for taste masking of other steroids, the same method was applied to prepare prednisolone chewable tablets. Initially, chocolate containing Eudragit® E PO solid dispersion was prepared according to the method described for dexamethasone. The use of a drug: polymer ratio of 1:2 was not sufficient to mask the bitter taste of prednisolone and an increase up to 1:8 was

required to reduce the bitter taste as rated by the volunteers. These results agree with the previously reported taste masking efficiency of Eudragit® E PO microbeads.[48] Additionally, a pineapple-flavored solid dispersion was prepared, and it was rated nearly non-bitter by the volunteers (data not shown). Chewable tablet blends were prepared like the dexamethasone optimal blend starting with 41% mannitol, which was increased to 51%. However, 51% mannitol was insufficient to produce sufficiently palatable tablets, Figure 3B. In contrast, the use of pineapple as a flavoring agent with 51% mannitol (P3) enhanced the palatability of the prednisolone pineapple-flavored chewable tablets compared with both chocolate-flavored tablet formulations (P1 and P2), Figure 3B. While chocolate flavoring was reported to be optimal for bitter drug taste masking,[49] it is possible that the taste masking effect of the chocolate-based solid dispersion was disrupted by the tablet compression force, which resulted in premature drug release, causing non-palatable tablets.[50] This speculation is based on the fact that a lower amount of mannitol was sufficient to produce palatable tablets in the pineapple flavored tablets (Table 2). Additionally, for some bitter medications, a high content of the flavoring agent is needed to mask the bitter taste,[35,49] which was not possible for the chocolate-containing chewable tablets prepared in this study to avoid a larger tablet size that renders the tablet no longer suitable for pediatric patients.

Prednisolone chewable tablets were rated easy to chew by all participants, except for the chocolate-containing tablet compressed with 51% mannitol (P2), which was rated moderate to chew by 3/6 participants. Tablet hardness and chewability index were within the accepted level, indicating successful tablet formulation (Table 5).

Study limitations

Stability studies should be conducted to confirm the long-lasting taste masking efficiency of the developed formulation.

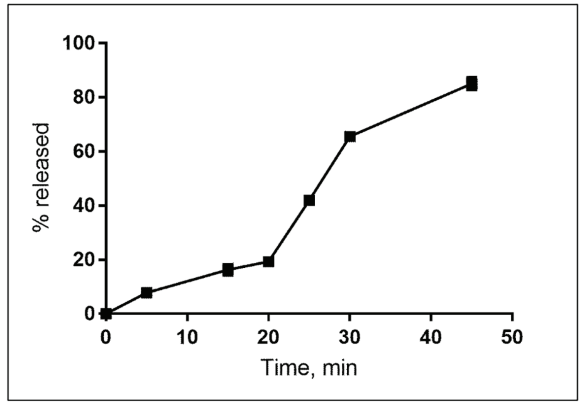

Figure 4. Dissolution profile of dexamethasone chewable tablets. Tablets were prepared according to formulation D3. The dissolution test was conducted in 0.1 N HCl. Data are plotted as mean ± SD, n: 3

SD: Standard deviation

Table 4. Characterization of the dexamethasone chewable tablets

Parameter	Formulation			Statistical differences
	D1 30% sorbitol	D2 30% mannitol	D3 40% mannitol	
Weight uniformity (mg)	199 ± 1	197 ± 2	200 ± 4	NA
Hardness (kp)	4.4 ± 0.4	4.7 ± 0.1	4.6 ± 0.3	ns
Chewing difficulty index (Nm)	0.87 ± 0.08	0.94 ± 0.03	0.92 ± 0.05	ns
Ease of chewing	Easy	Easy	Easy	NA
Disintegration time (sec)	18.6	22.1	18.9	ns

Samples are presented as mean ± SD, n: 6, NA: Not applicable, ns: Non-significant
SD: Standard deviation

Table 5. Characterization of the dexamethasone chewable tablets

Parameter	Formulation			Statistical differences
	P1 41% mannitol chocolate	P2 51% mannitol chocolate	P3 51% mannitol pineapple	
Tablet thickness (mm)	1	1.2	1	NA
Weight uniformity (mg)	493 ± 9	604 ± 12	496 ± 11	NA
Hardness (kp)	7.3 ± 0.7	6.6 ± 0.7	6.8 ± 0.6	ns
Chewing difficulty index (Nm)	0.7 ± 0.1	0.8 ± 0.1	0.7 ± 0.1	ns
Ease of chewing	Easy	Easy/moderate	Easy	NA

Samples are presented as mean ± SD, n: 6, NA: Not applicable; ns: Non-significant
SD: Standard deviation

Evaluation of optimal taste masking in the targeted population (pediatric patients) was not feasible due to ethical considerations.

CONCLUSION

A chewable tablet formulation was developed with improved palatability and taste masking of bitter steroids. The chewable tablets contained the bitter steroid in a taste-masking flavored solid dispersion employing Eudragit® E PO polymer. The drug: carrier ratio and the flavor choice impacted the palatability of the chewable tablets. The chewable tablets were within acceptable levels of hardness and were easy to chew as rated by healthy volunteers. The chewable tablet formulation is expected to improve compliance in pediatric patients and allow dosing flexibility, when prepared as scored tablets. Further studies are required to assess the long-term stability of the prepared tablet.

Ethics

Ethics Committee Approval: The study proposal was approved by the ethical committee of the institution (approval number: RECAUBCP-31102020B).

Informed Consent: Volunteers were informed about the content of the sample and possible side effects.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.K.A., H.J.K., Design: K.K.A., H.J.K., Data Collection or Processing: K.K.A., H.J.K., I.J.A.R., Z.S.A., Analysis or Interpretation: K.K.A., H.J.K., Literature Search: K.K.A., Z.S.A., Writing: K.K.A., H.J.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

1. Ferrara G, Petrillo MG, Giani T, Marrani E, Filippeschi C, Oranges T, Simonini G, Cimaz R. Clinical use and molecular action of corticosteroids in the pediatric age. Int J Mol Sci. 2019;20:444.
2. Alessandrini E, Brako F, Scarpa M, Lupo M, Bonifazi D, Pignataro V, Cavallo M, Cullufe O, Enache C, Nafria B, Claverol J, De Taeye L, Vermeulen E, Preston J, Tuleu C. Children's preferences for oral dosage forms and their involvement in formulation research *via* EPTRI (European Paediatric Translational Research Infrastructure). Pharmaceutics. 2021;13:730.
3. Herziger B, Jeschke S, Müller RM, Neininger MP, Bertsche T, Bertsche A. Drug-handling problems and expectations of the ideal pediatric drug-reported by children and their parents. Eur J Pediatr. 2022;181:2161-2171.
4. Michele TM, Knorr B, Vadas EB, Reiss TF. Safety of chewable tablets for children. J Asthma. 2002;39:391-403.
5. Lopez FL, Ernest TB, Tuleu C, Gul MO. Formulation approaches to pediatric oral drug delivery: benefits and limitations of current platforms. Expert Opin Drug Deliv. 2015;12:1727-1740.
6. Karavasili C, Gkaragkounis A, Fatouros DG. Patent landscape of pediatric-friendly oral dosage forms and administration devices. Expert Opin Ther Pat. 2021;31:663-686.
7. Samprasit W, Opanasopit P, Akkaramongkolporn P, Ngawhirunpat T, Wongsermsin K, Panomsuk S. Preparation and evaluation of taste-masked dextromethorphan oral disintegrating tablet. Pharm Dev Technol. 2012;17:315-320.
8. Alotaibi HF, Elsamaligy S, Mahrous GM, Bayomi MA, Mahmoud HA. Design of taste masked enteric orodispersible tablets of diclofenac sodium by applying fluid bed coating technology. Saudi Pharm J. 2019;27:354-362.
9. Suzuki H, Onishi H, Hisamatsu S, Masuda K, Takahashi Y, Iwata M, Machida Y. Acetaminophen-containing chewable tablets with suppressed bitterness and improved oral feeling. Int J Pharm. 2004;278:51-61.
10. Zhu Y, You X, Huang K, Raza F, Lu X, Chen Y, Dhinakar A, Zhang Y, Kang Y, Wu J, Ge L. Effect of taste masking technology on fast dissolving oral film: dissolution rate and bioavailability. Nanotechnology. 2018;29:304001.
11. Sugiura T, Uchida S, Namiki N. Taste-masking effect of physical and organoleptic methods on peppermint-scented orally disintegrating tablet of famotidine based on suspension spray-coating method. Chem Pharm Bull (Tokyo). 2012;60:315-319.
12. Shishu, Kamalpreet, Kapoor VR. Development of taste masked oral formulation of ornidazole. Indian J Pharm Sci. 2010;72:211-215.
13. Felton LA. Use of polymers for taste-masking pediatric drug products. Drug Dev Ind Pharm. 2018;44:1049-1055.
14. Aibani N, Bajaj A, Singh K. *In vivo* evaluation of taste masking for developed chewable and orodispersible tablets in humans and rats. Pharm Dev Technol. 2014;19:290-295.
15. Preis M, Grother L, Axe P, Breitkreutz J. *In-vitro* and *in-vivo* evaluation of taste-masked cetirizine hydrochloride formulated in oral lyophilisates. Int J Pharm. 2015;491:8-16.
16. Wang L, Sun Y, Kuang C, Zhang X. Preparation and evaluation of taste masked oral suspension of arbidol hydrochloride. Asian J Pharm Sci. 2015;10:73-79.
17. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971;60:1281-1302.
18. Sapkal SB, Adhao VS, Thenge RR, Darakhe RA, Shinde SA, Shrikhande VN. Formulation and characterization of solid dispersions of etoricoxib using natural polymers. Turk J Pharm Sci. 2020;17:7-19.
19. Bhujbal SV, Mitra B, Jain U, Gong Y, Agrawal A, Karki S, Taylor LS, Kumar S, Tony Zhou Q. Pharmaceutical amorphous solid dispersion: a review of manufacturing strategies. Acta Pharm Sin B. 2021;11:2505-2536.
20. Soroush H, Ghorbani-Bidkorbeh F, Mortazavi SA, Mehramizi A. Formulation optimization and assessment of dexamethasone orally disintegrating tablets using Box-Behnken design. Iran J Pharm Res. 2018;17:1150-1163.
21. Brniak W, Maślak E, Jachowicz R. Orodispersible films and tablets with prednisolone microparticles. Eur J Pharm Sci. 2015;75:81-90.
22. Abdulqader A, Bekir E. Formulation and evaluation of fast dissolving tablets of taste-masked ondansetron hydrochloride by solid dispersion. Iraqi J Pharm Sci. 2017;26:50-60.
23. Beakawi Al-Hashemi HM, Baghabra Al-Amoudi OS. A review on the angle of repose of granular materials. Powder Technol. 2018;330:397-417.
24. Gupta A, Chidambaram N, Khan MA. An index for evaluating difficulty of chewing index for chewable tablets. Drug Dev Ind Pharm. 2015;41:239-243.

25. Dexamethasone Tablets USP-NF. Rockville, MD2021. https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/dexamethasone-tabs-pending-20230127.pdf
26. Okubo Y, Takeuchi Y, Mizuno H, Matoba H, Tahara K, Takeuchi H. Statistical analyses for the preparation of taste-masking granules using a pH-dependent polymer. J Drug Deliv Sci Technol. 2019;53:101124.
27. Tekko IA, Ali OM, Hatahet T, Chehna MF. Polyethylene glycol-based solid dispersions to enhance eprosartan mesylate dissolution and bioavailability. Arch Phar & Pharmacol Res. 2019;2:1-11.
28. Kumar S, Gupta S. Mango peel pectin as a carrier for solid dispersions. Polim Med. 2013;43:231-233.
29. Mura P, Maestrelli F, Cirri M, Rodríguez M, Rabasco AM. Development of enteric-coated pectin-based matrix tablets for colonic delivery of theophylline. J Drug Target. 2003;11:365-371.
30. Freitas CMP, Coimbra JSR, Souza VGL, Sousa RCS. Structure and applications of pectin in food, biomedical, and pharmaceutical industry: a review. Coatings. 2021;11:922.
31. Kamble D, Singhavi D, Tapadia S, Khan S. Investigation of pectin-hydroxypropyl methylcellulose-coated floating beads for pulsatile release of piroxicam. Turk J Pharm Sci. 2020;17:542-548.
32. Nikam V, Kotade KB, Gaware VM. Eudragit a versatile polymer: a review. Pharmacologyonline. 2011;1:152-164.
33. Hassan N, Latif S, Afzal H, Abbas N, Naheed S, Khokar R, et al. Taste masking of levofloxacin by microparticulate system using emulsion solvent evaporation technique. Indian J Pharm Sci. 2019;81:843-850.
34. Truong S, Tang EKY, Khan RN, Nguyen MN, von Ungern Sternberg BS, Yeo AWY, Lim LY. Prior administration of chocolate improves the palatability of bitter drugs: the choc-with-med study. J Paediatr Child Health. 2021;57:1267-1273.
35. Naqvi RF, Khan A, Umer MF, Malik O, Shahwani NA. Design and optimization of novel taste-masked medicated chocolates of dextromethorphan with *in vitro* and *in vivo* taste evaluation. J Pharm Innov. 2022;17:376-390.
36. Synaridou MS, Andriotis EG, Zacharis CK, Fatouros DG, Markopoulou CK. Solid dosage forms of dexamethasone sodium phosphate intended for pediatric use: formulation and stability studies. Pharmaceutics. 2020;12:354.
37. Martir J, Flanagan T, Mann J, Fotaki N. Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review. J Pharm Pharmacol. 2016;69:384-397.
38. Karavasili C, Gkaragkounis A, Moschakis T, Ritzoulis C, Fatouros DG. Pediatric-friendly chocolate-based dosage forms for the oral administration of both hydrophilic and lipophilic drugs fabricated with extrusion-based 3D printing. Eur J Pharm Sci. 2020;147:105291.
39. Katz DL, Doughty K, Ali A. Cocoa and chocolate in human health and disease. Antioxid Redox Signal. 2011;15:2779-2811.
40. Cova I, Leta V, Mariani C, Pantoni L, Pomati S. Exploring cocoa properties: is theobromine a cognitive modulator? Psychopharmacology (Berl). 2019;236:561-572.
41. Sharma A, Jain CP, Tanwar YS. Preparation and characterization of solid dispersions of carvedilol with poloxamer 188. J Chil Chem Soc. 2013;58:1553-1557.
42. Bikiaris D, Papageorgiou GZ, Stergiou A, Pavlidou E, Karavas E, Kanaze F, Georgarakis M. Physicochemical studies on solid dispersions of poorly water-soluble drugs: evaluation of capabilities and limitations of thermal analysis techniques. Thermochim Acta. 2005;439:58-67.
43. Khan D, Kirby D, Bryson S, Shah M, Rahman Mohammed A. Paediatric specific dosage forms: patient and formulation considerations. Int J Pharm. 2022;616:121501.
44. FDA - Quality Attribute Considerations for Chewable Tablets Guidance for Industry. In: U.S. Department of Health and Human Services FaDA, Center for Drug Evaluation and Research (CDER), editor. USA2018.
45. Strickley RG, Iwata Q, Wu S, Dahl TC. Pediatric drugs-a review of commercially available oral formulations. J Pharm Sci. 2008;97:1731-1774.
46. Bunlung S, Nualnoi T, Issarachot O, Wiwattanapatapee R. Development of raft-forming liquid and chewable tablet formulations incorporating quercetin solid dispersions for treatment of gastric ulcers. Saudi Pharm J. 2021;29:1143-1154.
47. Nyamweya N, Kimani S. Chewable tablets: a review of formulation considerations. Pharm Technol N Am. 2020;44:38-44.
48. Lopalco A, Denora N, Laquintana V, Cutrignelli A, Franco M, Robota M, Hauschildt N, Mondelli F, Arduino I, Lopedota A. Taste masking of propranolol hydrochloride by microbeads of EUDRAGIT® E PO obtained with prilling technique for paediatric oral administration. Int J Pharm. 2020;574:118922.
49. Bierwirth JE, Oftedal KN, Civille GV, Fahey JW. Flavor misattribution: a novel approach to improving compliance and blinding in food-based clinical interventions. NFS Journal. 2015;1:24-30.
50. Kolter K, Dashevsky A, Irfan M, Bodmeier R. Polyvinyl acetate-based film coatings. Int J Pharm. 2013;457:470-479.