

# Taste Masking of Steroids for Oral Formulations

**Short Title in English: Palatable Steroids Chewable Tablets**

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## Abstract

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

**Method:** Solid dispersions of dexamethasone were prepared using PEG (polyethylene glycol), pectin and Eudragit as the carrier polymers and chocolate as a flavoring agent. Taste masking efficiency was evaluated by healthy volunteers to select the best formula. 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. The use of 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 of carrier: drug ratio and a change of flavor to pineapple was necessary to achieve maximum palatability of prednisolone chewable tablets.

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

**Keywords:** solid dispersion, taste masking, steroids, dexamethasone, Eudragit

## Introduction

Oral steroids are widely used in children for the treatment of asthma, virus associated wheezing, Crohn's disease, and others.<sup>(1)</sup> Oral steroids for children are available in liquid dosage forms. While liquid dosage forms occupy the biggest share of pediatric medicines and present the most widely acceptable dosage form<sup>(2)</sup>, they come with a fair share of problems like 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.<sup>(3)</sup> In contrast, chewable tablets grant ease of administration in toddlers and young children, dose accuracy over liquid preparations, and enhanced stability.<sup>(4)</sup> Compared to medicated gummies, chewable tablets can be produced into a scored tablets that can further allow dose adjustment and flexibility and they have been suggested to be associated with less misuse.<sup>(5)</sup> As such, there is an expanding interest in formulating pediatric medicines as a chewable tablet dosage form.<sup>(6)</sup> An important consideration in drug formulations that release the drug in the mouth is palatability.<sup>(7, 8)</sup> Chewable tablets mandate the release of the drug in the oral cavity resulting in 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.<sup>(9)</sup> Taste masking of strong-tasting medicines has been the focus of several studies.<sup>(10-12)</sup> While the use of different sweeteners and flavoring agents have been widely used, several medicines have 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 excipient, coating of medicine through micro- or nanoencapsulation, and the use of ion-exchange resins.<sup>(13-16)</sup>

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

The objective of this study is to formulate a pediatric-friendly palatable oral dexamethasone and prednisolone dosage form. There have been few reports of taste-masked steroids formulations. One study reported orally disintegrating tablets of dexamethasone.<sup>(20)</sup> However, the taste evaluation was not reported clearly to allow full evaluation of the taste masking efficiency. Another study reported microparticles based orodispersible film and tablet of prednisolone.<sup>(21)</sup>

The study aims at developing, optimizing, and characterizing a taste masking formulation of dexamethasone pertaining to a chewable tablet formulation. The study employed solid dispersion using three different polymers: polyethylene glycol (PEG), film forming pectin, and pH-dependent solubility Eudragit®. The 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 as another steroid commonly prescribed for children.

## **Materials and methods**

### **Materials**

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

### ***Dexamethasone solid dispersion preparation and characterization:***

#### ***Solid dispersion preparation:***

Dexamethasone solid dispersion was prepared by the solvent evaporation method. Briefly, a 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 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. Solid dispersion was collected and sieved through a 40-mesh sieve. Eudragit® E PO solid dispersions were prepared as previously described<sup>(22)</sup>. Briefly, Eudragit® E PO was freshly dissolved in 96% ethanol with continuous stirring. Dexamethasone solution was added, and the solution was left on 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 freshly. 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. Liquid flavoring agent (caramel, grapes, or hazelnut) was added to the polymer solution prior to adding dexamethasone solution. When needed, 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 needed, 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 drug and polymer (and chocolate when applicable),  $W_T$ . Percent yield was calculated using equation (1).

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

#### ***Drug content***

An accurately weighted amount of the solid dispersion was dissolved in 96% ethanol on a magnetic stirrer for 3 hours 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 Shimadzu, Japan DSC.

#### *Taste masking effectiveness of the 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 tongue and score the solid dispersion bitterness on a scale of zero -10 where ten is very bitter and zero is not bitter. Volunteers were instructed to expel the solid dispersion and not to swallow it and to rinse their mouth 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 formulations presented in Table 2A. Accurately weighed ingredients were sieved and mixed geometrically. Tablet mixture was characterized for flowability by calculating the angle of repose using the fixed funnel method.<sup>(23)</sup> Carr's index was calculated through measuring bulk and tapped densities using Copley JV 2000 tapped density tester, UK. Carr's index was calculated according to equation (2)

$$\text{Carr's index} = ((\text{Tapped density} - \text{Bulk density}) / \text{Tapped density}) \times 100 \quad (2)$$

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

##### *Chewable tablet evaluation*

**Hardness test:** Six randomly selected tablets were evaluated on 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 and volunteers' rating of chewing difficulty. Chewing difficulty index (CDI) was calculated according to equation (3) where  $F_h$  is tablet breaking force under diametral compression and  $H$  is tablet thickness<sup>(24)</sup>

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

Additionally, 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 tablet and rinse their mouth after expelling the chewed tablet.

**In vitro disintegration:** The in vitro disintegration time was determined using disintegration test apparatus as per USP specifications. Briefly, one tablet was placed in each of the six vessels of the apparatus basket. A 900 ml 0.1 N HCl was used as the disintegration medium, and the temperature was kept at  $37^\circ\text{C} \pm 2$ . The apparatus was operated for 30 minutes, 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<sup>(25)</sup> The dissolution study was performed using 0.1 N HCl as the dissolution media at a  $37^\circ\text{C} \pm 0.5$  and 100 rpm. A 5-ml sample was withdrawn at 0, 5, 15, 20, 30, and 45 min. Samples were filtered through 45µm 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 ethanol and analyzed spectrophotometrically at 241 nm. Portion released in mg was calculated using equation (4) where  $C$  is dexamethasone concentration and  $V$  is the volume of aliquot extracted with chloroform. Drug release was considered satisfactory if not less than 2.8 mg (70%) dexamethasone is released in 45 minutes.

$$10(C/V)(Au/As) \quad (4)$$

**Tablet palatability:** Five to six 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 mouth after each tasting.

#### **Applicability of 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. Flavors used included chocolate and pineapple. Healthy volunteers evaluated taste masking efficiency of the prepared solid dispersions like procedure described for dexamethasone solid dispersion. Each formulation was assessed by five volunteers.

#### *Chewable tablet preparation and characterization*

Prednisolone chewable tablets were prepared according to formulations presented in Table 2B. Accurately weighed ingredients were sieved and mixed geometrically. Tablet mixture was compressed into tablets using 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 non-parametric Kruskal Walls test followed by Dunn's multiple comparison test. Differences were considered significant at 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 at 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 utilized 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 F 5- 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<sup>(16)</sup>. 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.<sup>(26)</sup> Additionally it is superior to the lower molecular weight PEG in dissolution rate enhancement.<sup>(27)</sup>

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 lower yield (about 81%) and required extended oven drying due to the large volume of aqueous flavoring agent needed. As such, 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 abundantly available and safe. Pectin has been suggested to have good taste masking properties and has been used as a carrier for solid dispersion<sup>(28)</sup> Pectin is hypothesized to limit drug release in the mouth as it is specifically hydrolyzed by colon bacteria<sup>(29, 30)</sup> thereby reduce or mask 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 PEG-based formulation, Figure 1. Additionally, solid dispersion yield and processing was not highly reproducible due to the tendency of pectin to form plastic-like sheets that are difficult to pulverize.<sup>(30)</sup> Pectin has been used to limit drug release in acidic media.<sup>(31)</sup> In this study we showed the technical limitations in using pectin as a sole carrier for solid dispersions. Additionally, the combination of PEG and pectin failed to efficiently mask the bitter taste of dexamethasone, F13, Figure1. Higher amounts of pectin greater 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 the lower drug: polymer ratio attempted 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 allows the control of the rate of drug release.<sup>(32)</sup> The Eudragit® E family are soluble in pH below 5 which is below saliva pH<sup>(32)</sup> making it suitable for taste masking applications.<sup>(8, 22)</sup> To evaluate the need of 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 as “tasteless” but not pleasant<sup>(33)</sup> Chocolate flavoring had been shown to be effective for taste masking of bitter drugs<sup>(34, 35)</sup> and was used to improve palatability and acceptability of dexamethasone oral formulations<sup>(36)</sup> Additionally, chocolate represents an excellent flavoring agent for pediatric dosage forms due to its high acceptability among children and even adults<sup>(37, 38)</sup>. Besides palatability improvement, chocolate has been suggested to offers several health benefits including its antioxidant effect, cardiovascular effects, and possible cognitive effects.<sup>(39, 40)</sup> As such, chocolate containing Eudragit® E PO solid dispersion with dexamethasone: polymer ratio of 1:4 was used for further evaluation.

### ***Selected solid dispersion formulation characterization.***

Prior to 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  $92.88 \pm 3.50$  % was obtained across the different batches prepared. Dexamethasone content of the solid dispersion was found to be  $97.91 \pm 2.21$  % of 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. DSC thermogram of the pure dexamethasone showed an endothermic peak at  $257.41^\circ\text{C}$  and Eudragit® E PO thermogram showed two peaks one at  $227.48^\circ\text{C}$  and another broad peak at  $86.48^\circ\text{C}$ , Figure 2A-B. Dexamethasone peak was evident in the physical mixture 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<sup>(41, 42)</sup>

### ***Preparation and characterization of dexamethasone chewable tablets***

Dexamethasone solid dispersion was formulated into chewable tablets for optimal delivery to patients. Tablets were formulated according to mixtures presented in Table 2A. Tablet blend contained basic constituents required for tablet compression like binders and diluents. Since the chewable tablets are intended mainly for children, the tablet blend was limited to essential excipient<sup>(43)</sup> Sweeteners at different weight percent 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 due to the poorer flow properties and compressibility of mannitol compared to sorbitol. However, tablet blend flow properties remained good 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.<sup>(44)</sup> The tablet blend 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 percent resulted in an improved palatability that was significantly improved by further increase of 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 to sucrose. Mannitol specifically, is commonly used in chewable tablets due to its high negative heat of solution which boosts its cooling effect.<sup>(45, 46)</sup> 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. Besides 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.<sup>(47)</sup> Excessive tablet hardness might lead to incomplete chewing by the patient which can cause serious side effects including choking and intestinal obstruction. A chewing difficulty index has been described and is recommended by FDA in quality attribute guidance for chewable tablets.<sup>(44)</sup> 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.<sup>(24)</sup> 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 chewing difficulty index with no significant differences, Table 4. The hardness for the three different formulations were below 12 Kp and they were rated as easy to chew by volunteers suggesting successful chewable tablet formulation.

A major consideration in chewable dosage form is the need of 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 USP specifications for plain tablets. Disintegration time for all three formulations was comparable with no significant differences, Table 4. Dissolution profile for the optimal chewable tablet formulation showed more than 70% dexamethasone release within 45 minutes which suggests that the chewable tablet has passed the USP tolerance limit for 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 1:2 drug: polymer ratio was not sufficient to mask the bitter taste of prednisolone and an increase up to 1:8 was required to ameliorate the bitter taste as rated by the volunteers. These results

agree with previously reported taste masking efficiency of Eudragit® E PO microbeads.<sup>(48)</sup> Additionally, a pineapple flavored solid dispersion was prepared, and it was rated as nearly non-bitter by the volunteers (data not shown). Chewable tablet blends were prepared like dexamethasone optimal blend starting with 41% mannitol that was increased to 51%. However, 51% mannitol was not sufficient 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 as compared to both chocolate flavored tablet formulations (P1 and P2), Figure 3B. While chocolate flavoring was reported to be optimal for bitter drug taste masking<sup>(49)</sup>, 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<sup>(50)</sup>. This speculation is based on the fact that less 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<sup>(35, 49)</sup> which was not possible for the chocolate containing chewable tablets prepared in this study to avoid bigger tablet size that renders the tablet no longer suitable for pediatric patients. Prednisolone chewable tablets were rated as easy to chew by all participants apart from chocolate containing tablet compressed with 51% mannitol (P2) that was rated moderate to chew by 3/6 participants. Tablet hardness and chewability index was within the accepted level indicating successful tablet formulation, Table 5.

### **Study limitations**

Stability studies should be conducted to confirm long-lasting taste masking efficiency of the developed formulation. Evaluation of optimal taste masking in targeted population (pediatric patients) was not feasible due to ethical consideration.

### **Conclusions**

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. Drug: carrier ratio and the flavor choice impacted the chewable tablet palatability. 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.

**Conflict of interest:** The authors report no conflict of interest

### **References**

1. Ferrara G, Petrillo MG, Giani T, Marrani E, Filippeschi C, Oranges T, et al. Clinical Use and Molecular Action of Corticosteroids in the Pediatric Age. *Int J Mol Sci.* 2019;20(2):444.
2. Alessandrini E, Brako F, Scarpa M, Lupo M, Bonifazi D, Pignataro V, et al. Children's Preferences for Oral Dosage Forms and Their Involvement in Formulation Research via EPTRI (European Paediatric Translational Research Infrastructure). *Pharmaceutics.* 2021;13(5).
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(5):2161-71.
4. Michele TM, Knorr B, Vadas EB, Reiss TF. Safety of chewable tablets for children. *J Asthma.* 2002;39(5):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(11):1727-40.
6. Karavasili C, Gkaragkounis A, Fatouros DG. Patent landscape of pediatric-friendly oral dosage forms and administration devices. *Expert Opin Ther Pat.* 2021;31(7):663-86.
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(3):315-20.
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 Pharmaceutical Journal.* 2019;27(3):354-62.
9. Suzuki H, Onishi H, Hisamatsu S, Masuda K, Takahashi Y, Iwata M, et al. Acetaminophen-containing chewable tablets with suppressed bitterness and improved oral feeling. *Int J Pharm.* 2004;278(1):51-61.
10. Zhu Y, You X, Huang K, Raza F, Lu X, Chen Y, et al. Effect of taste masking technology on fast dissolving oral film: dissolution rate and bioavailability. *Nanotechnology.* 2018;29(30):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(3):315-9.
12. Shishu, Kamalpreet, Kapoor VR. Development of taste masked oral formulation of ornidazole. *Indian J Pharm Sci*. 2010;72(2):211-5.
13. Felton LA. Use of polymers for taste-masking pediatric drug products. *Drug Dev Ind Pharm*. 2018;44(7):1049-55.
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*. 2013;19.
15. Preis M, Grother L, Axe P, Breitzkreutz J. In-vitro and in-vivo evaluation of taste-masked cetirizine hydrochloride formulated in oral lyophilisates. *Int J Pharm*. 2015;491(1-2):8-16.
16. Wang L, Sun Y, Kuang C, Zhang X. Preparation and evaluation of taste masked oral suspension of arbidol hydrochloride. *Asian Journal of Pharmaceutical Sciences*. 2015;10(1):73-9.
17. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. *J Pharm Sci*. 1971;60(9):1281-302.
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(1):7-19.
19. Bhujbal SV, Mitra B, Jain U, Gong Y, Agrawal A, Karki S, et al. Pharmaceutical amorphous solid dispersion: A review of manufacturing strategies. *Acta Pharm Sin B*. 2021;11(8):2505-36.
20. Soroush H, Ghorbani-Bidkoreh F, Mortazavi SA, Mehrmizi A. Formulation Optimization and Assessment of Dexamethasone Orally Disintegrating Tablets Using Box-Behnken Design. *Iran J Pharm Res*. 2018;17(4):1150-63.
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(2):239-43.
25. Dexamethasone Tablets USP-NF. Rockville, MD2021.
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. *Journal of Drug Delivery Science and Technology*. 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(3).
28. Kumar S, Gupta S. Mango peel pectin as a carrier for solid dispersions. *Polim Med*. 2013;43:231-3.
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;11:365-71.
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(8):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(5):542-8.
32. Nikam V, Kotade KB, Gaware VM. Eudragit a versatile polymer: A review. *Pharmacologyonline*. 2011;1:152-64.
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.
34. Truong S, Tang EKY, Khan RN, Nguyen MN, von Ungern Sternberg BS, Yeo AWY, et al. Prior administration of chocolate improves the palatability of bitter drugs: The Choc-with-Med study. *J Paediatr Child Health*. 2021;57(8):1267-73.
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(2):376-90.
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(4).

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(4):384-97.
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. *Antioxidants & Redox Signaling*. 2011;15(10):2779-811.
40. Cova I, Leta V, Mariani C, Pantoni L, Pomati S. Exploring cocoa properties: is theobromine a cognitive modulator? *Psychopharmacology (Berl)*. 2019;236(2):561-72.
41. Sharma A, Jain CP, Tanwar YS. Preparation and characterization of solid dispersions of carvedilol with poloxamer 188. *Journal of the Chilean Chemical Society*. 2013;58:1553-7.
42. Bikiaris D, Papageorgiou GZ, Stergiou A, Pavlidou E, Karavas E, Kanaze F, et al. Physicochemical studies on solid dispersions of poorly water-soluble drugs: Evaluation of capabilities and limitations of thermal analysis techniques. *Thermochim Acta*. 2005;439(1):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(5):1731-74.
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(10):1143-54.
47. Nyamweya N, Kimani S. Chewable Tablets: A Review of Formulation Considerations. *Pharmaceutical Technology North America*. 2020;44:38-44.
48. Lopalco A, Denora N, Laquintana V, Cutrignelli A, Franco M, Robota M, et al. 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, Civiile 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(2):470-9.

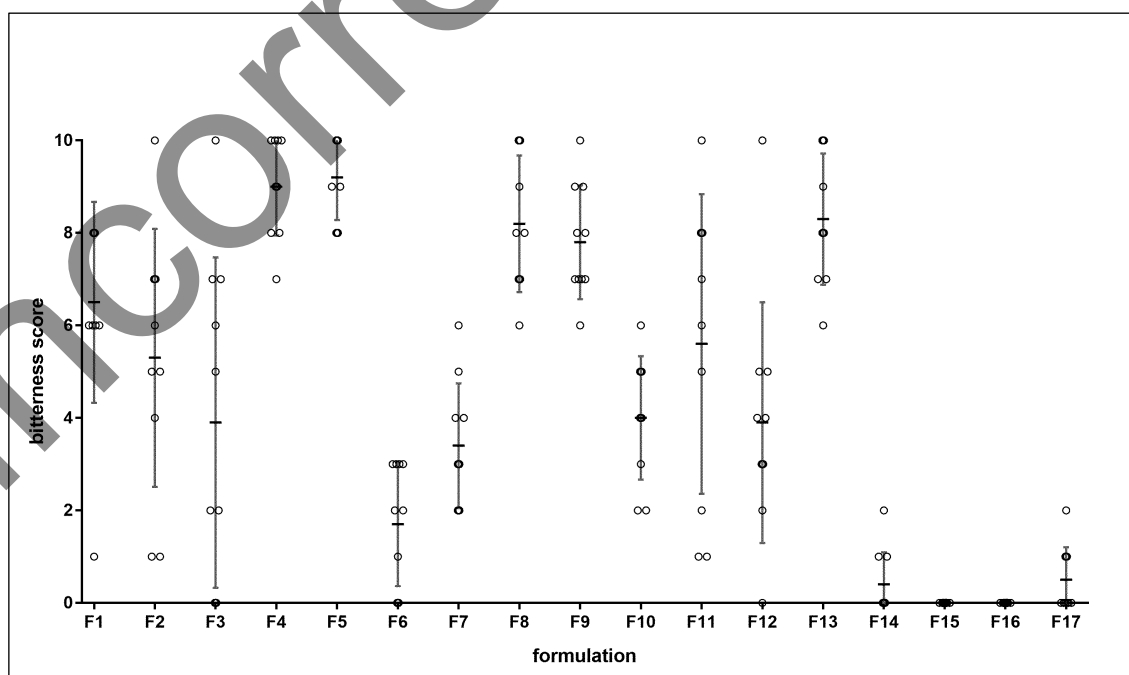




Figure 1: Taste masking efficiency of the different solid dispersion formulations. Bitterness level is expressed as a scale of 0 – 10 with 0 is not bitter and 10 is very bitter, data are expressed as mean  $\pm$  SD, n-10.

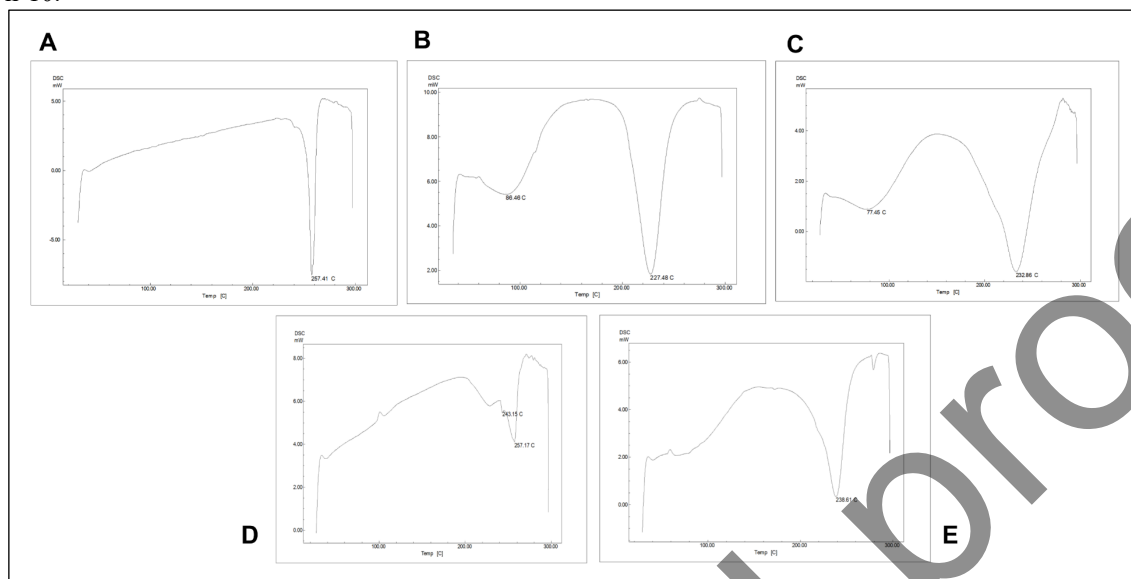


Figure 2: DSC profile of A: dexamethasone, B: Eudragit® EPO only, C: 1:4 solid dispersion, D: 1:1 physical mixture, and E: blank solid dispersion

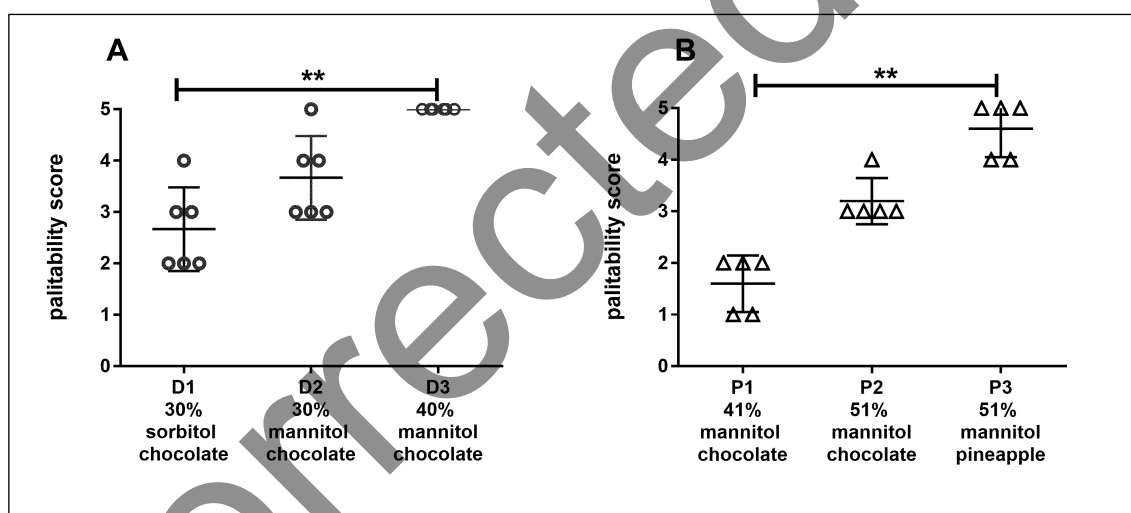


Figure 3: Palatability of steroids chewable tablets. A: dexamethasone chewable tablets, B: prednisolone chewable tablets. Data are expressed as mean  $\pm$  SD, n = 5-6. \*\*:  $p < 0.01$ .

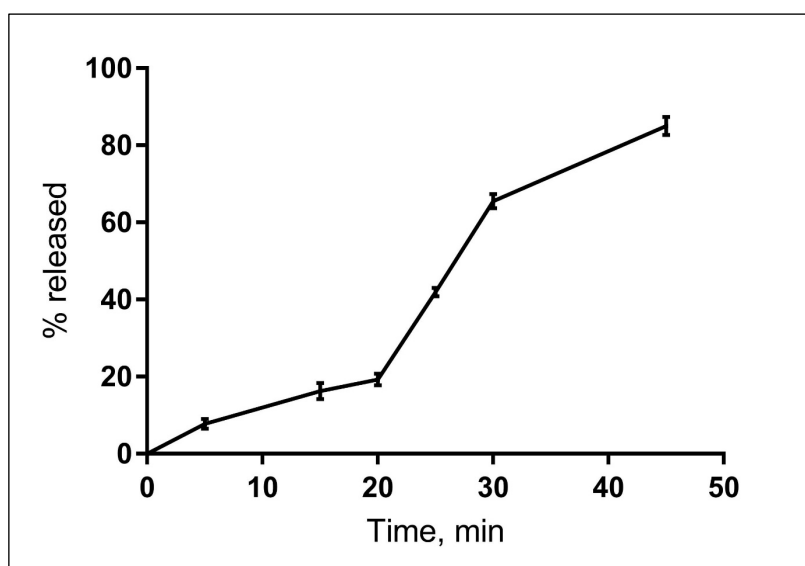


Figure 4: Dissolution profile of dexamethasone chewable tablets. Tablets were prepared according to formulation D3. Dissolution test was conducted in 0.1N HCl. Data are plotted as mean  $\pm$  SD, n=3.

Table 1: Formulation of 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 model steroids employed in this study.

Ingredient	A Dexamethasone			B Prednisolone		
	D1	D2	D3	P1	P2	P3
SD, wt. (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, wt. (%)	80 (40%)	80 (40%)	60 (30%)	150 (30%)	150 (25%)	150 (30%)
PEG 4000, wt. (%)	20 (10%)	20 (10%)	20 (10%)	50 (10%)	50 (8 %)	50 (10%)
Sorbitol, wt. (%)	60 (30%)					
Mannitol, wt. (%)		60 (30%)	80 (40%)	205 (41%)	305 (51%)	255 (51%)
Final weight, mg	200	200	200	500	600	500

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

Table 4: Characterization of 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

Table 5: Characterization of 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

Uncorrected proof