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Original Article

HME-assisted formulation of taste-masked dispersible tablets of cefpodoxime proxetil and roxithromycin

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الملخص

أهداف البحث: المضادات الحيوية هي الأدوية الأكثر شيوعا بين المرضى الأطفال. ومع ذلك، في معظم الأحيان، يصبح إعطاء الجرعة الدقيقة للأطفال مشكلة بسبب مذاقه المر للغاية. يعد سيفبودوكسيم بروكسيتيل وروكسيثروميسين أحد المضادات الحيوية التي توصف غالبا للأطفال ولها طعم مرير. التركيبات المسوقة لهذه الأدوية هي معلق جاف و/أو أقراص. من المعروف أن طريقة التجفيد تتضمن خطوات مختلفة وبالتالي فهي تستغرق وقتا طويلا ومكلفة. كان الهدف من هذه الدراسة هو إخفاء الطعم المر لسيفبودوكسيم بروكسيتيل وروكسيثروميسين دون المساس بالذوبان وشكل إطلاق الدواء عند مقارنته بالتركيبات المسوقة. بالإضافة إلى التغلب على العيوب المرتبطة بتقنية التجفيد المستخدمة حاليا.

طريقة البحث: تم استخدام تقنية البثق بالذوبان الساخن لمعالجة سيفبودوكسيم بروكسيتيل وروكسيثروميسين بشكل فردي باستخدام بوليمر يودراجيت إيبو. تم تشخيص البثقات التي تم الحصول عليها بواسطة التحليل الطيفي للأشعة تحت الحمراء لتحويل فورييه، وقياس نمط الحيود للمواد البلورية وقياس السعرات الحرارية بالمسح التفاضلي. تمت صياغة البثقات المسحوقة كأقراص قابلة للتشتت وتم تقييمها من حيث كفاءة إخفاء الطعم داخل المختبر وفي الجسم الحي.

النتائج: أظهرت الأقراص المحضرة في هذه الدراسة ملامح ذوبان قابلة للمقارنة ولكن تم تعزيز كفاءة إخفاء الطعم بشكل كبير عند مقارنتها بالأقراص المسوقة من سيفبودوكسيم بروكسيل وروكسيثروميسين. وكانت نتائج تقييم إخفاء الطعم البشري داخل الجسم متفقة أيضا مع دراسات إخفاء التذوق داخل المختبر.

الاستنتاجات: وبالتالي فإن العمل الحالي قد قدم تكنولوجيا البثق بالذوبان الساخن الخالية من المذيبات والقابلة للتطوير والمستمرة لمعالجة مشكلات الطعم المر في سيفبودوكسيم بروكسيتيل وروكسيثروميسين. علاوة على ذلك، تم التغلب على العيوب المرتبطة بتقنية التجفيد المستخدمة حاليًا من خلال تطوير التركيبات باستخدام تقنية البثق بالذوبان الساخن.

الكلمات المفتاحية: إخفاء الطعم؛ أقراص قابلة للتشتت؛ البثق بالذوبان الساخن؛ يودراجيت إيبو؛ الذوبان

Abstract

Objectives: Antibiotics are the most commonly administered medications among pediatric patients. However most of the time, accurate dose administration to children becomes a problem due to the extremely bitter taste. Cefpodoxime proxetil (CP) and roxithromycin (ROX) are antibiotics often prescribed to the pediatric population and have a bitter taste. Marketed formulations of these drugs are dry suspension and/or tablets. The lyophilization method involves various steps and thus is time consuming and expensive. The objective of this study was to mask the bitter taste of CP and ROX without compromising the solubility and drug release profile compared to marketed formulations, as well as to overcome the disadvantages associated with the currently used lyophilization technique.

Methods: Hot melt extrusion (HME) technology was used to process CP and ROX individually with Eudragit E PO polymer. The extrudates obtained were characterized by Fourier transform infrared spectroscopy, powder

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X-ray diffraction, and differential scanning calorimetry. The powdered extrudates were formulated as dispersible tablets and evaluated for *in vitro* and *in vivo* taste-masking efficiency.

Results: The tablets prepared in this study showed comparable dissolution profiles but the taste-masking efficiency was significantly enhanced compared to the marketed tablets of CP and ROX. The results of *in vivo* human taste-masking evaluation were also in agreement with the *in vitro* taste-masking studies.

Conclusion: The current work presents solvent-free, scalable, and continuous HME technology for addressing the bitter taste issues of CP and ROX. The disadvantages associated with the currently used lyophilization technique were overcome by developing the formulations using HME technology.

Keywords: Dispersible tablets; Dissolution; Eudragit EPO; Hot melt extrusion; Taste masking

Introduction

Antibiotics are the most commonly administered medications in the pediatric population, and are reportedly prescribed to one in five pediatric patients.[1] The main problem associated with the administration of such medications is that they are very bitter in taste, making them aversive to children and in turn difficult for parents to administer the required dose. Additionally, some widely used antibiotics have low bioavailability due to their poor aqueous solubility. There are several techniques including cyclodextrin complexation, microencapsulation, granulation, formulation of beads, solid dispersion with polymers having pH-dependent solubility, and formulation of nanoparticles to address the bitter taste and solubility issues of drugs.[2–4] Among these techniques, solid dispersion is the most widely used due to its advantages such as conversion into amorphous form; improved surface area by particle size reduction; and improved wettability, porosity, and dispersion into an inert polymer or matrix, which in turn enhance the solubility and oral bioavailability of Biopharmaceutical Classification System (BCS) class II drugs. Furthermore, the dispersion of bitter tasting drugs into the polymer matrix also has taste-masking effects.[5] Solid dispersion of drug and polymer can be achieved by methods such as solvent, melting, melt extrusion, and lyophilization methods.

Cefpodoxime proxetil (CP) is a broad-spectrum third-generation cephalosporin antibiotic, which is a prodrug that is hydrolyzed to its active metabolite cefpodoxime. It acts by binding to the penicillin-binding proteins of bacteria, impairing bacterial cell wall synthesis. It is mainly prescribed for upper respiratory tract and urinary tract infections. CP is slightly alkaline, amorphous in nature, and absorbed from the gastrointestinal tract after oral administration. It has low bioavailability due to its poor aqueous solubility (0.103 mg/mL), gelation behavior in an acidic environment, and luminal metabolism.[6–11] Furthermore, CP is highly hygroscopic and unstable in water and hence it is given in the form of dry powder for reconstitutable suspension. The reconstituted suspension once produced, needs to be stored in the refrigerator and used within 1 week. It is well known that such reconstitutable suspensions are formulated by the lyophilization technique. Nevertheless, the lyophilization method has disadvantages, including extended handling and processing time, the necessity for a sterile diluent during reconstitution, the use of expensive equipment, and significantly, its batch nature, which leads to longer production times and higher costs for the final product due to reduced output for the manufacturing company.[12]

The second antibiotic roxithromycin (ROX) is a semi-synthetic macrolide derived from erythromycin containing a 14-membered lactone ring. It acts by binding to the 50S ribosome, thereby inhibiting protein synthesis in both gram-positive and gram-negative bacteria. ROX is extremely bitter in taste and has poor bioavailability due to poor aqueous solubility (0.187 mg/mL).[13–16] Hot melt extrusion (HME) is an emerging technology due to its scalable, continuous, and solvent-free process and multiple applications such as taste masking, stabilizing the active ingredients, solubility enhancement, delayed or controlled release formulations, and fabrication of implants. HME is a process that leads to formation of a homogeneous mixture of drug and polymer by the application of heat and pressure.[17] Furthermore, HME has been efficiently used for taste masking bitter drugs. CP and ROX used in the present study are bitter in nature.

The objective of the present study was to address the bitter taste and low aqueous solubility issues of CP and ROX using commercially viable HME technology. Furthermore, development of the HME processing technique for these two antibiotics individually would lead to a reduction in the processing cost associated with the currently used lyophilization technique and associated packaging. Considering the same, the preparation of dispersible tablets of CP and ROX individually using HME was attempted, which would provide ease of handling, taste-masking efficiency, and patient acceptability.

Materials and Methods

Materials

CP and roxithromycin were donated by Lupin Ltd. (Pradesh, India) and Century Pharmaceuticals Ltd. (Vadodara, India), respectively. Eudragit EPO (E-EPO) was obtained as a gift sample from Evonic India Pvt. Ltd. (Mumbai, India). All other excipients such as polyethylene glycol 6000 (PEG 6000), stearic acid, mannitol, crospovidone, silicon dioxide, magnesium stearate, and flavoring were purchased from Sigma Aldrich (St. Louis, MO, USA). All chemicals used were of analytical grade.

Methods

Preformulation studies

Drug excipient compatibility study using Fourier transform infrared spectroscopy. Fourier transform infrared spectroscopy (FTIR) spectra of CP, ROX alone, E-EPO, and their physical mixture were obtained using the Jasco IR Spectrophotometer (FT/IT-4100; Jasco Inc., Easton, MD, USA) to investigate if there was any interaction between the drug and excipients. FTIR spectrum of the extruded batch was also recorded to analyze the degradation of the drug molecules. The powder samples were triturated with potassium bromide and filled into the die of an equipment to examine the samples by infrared spectroscopy within the range of 400–4000 cm^{-1}.

Analytical method for CP

Analysis of CP for its assay, solubility, drug release, and *in vitro* taste-masking assessment was done with an ultraviolet (UV) spectrophotometer at different wavelengths. To study the assay, methanol was used as a solvent. Serial dilutions of CP in different media such as methanol, glycine buffer (pH 3), and simulated salivary media (pH 6.8) were prepared and the absorbance was recorded at λ_{max} of 235 nm for methanol and 259 nm for glycine buffer and simulated salivary media. The recorded absorbance was plotted against concentration to calculate the standard regression equation and regression coefficient (R^2).

High-performance liquid chromatography for roxithromycin

For the analysis of roxithromycin, high-performance liquid chromatography (HPLC) was used. The Jasco chromatographic system with a UV detector was used. The Kromasil C18 HPLC Column (150 × 4.6 mm; Kromasil, Bohus, Sweden) with the mobile phase consisting of acetonitrile and ammonium dihydrogen phosphate (4.8% w/v) buffer pH adjusted to 5.3 at a ratio of 3:7 was used. The UV detection wavelength was 205 nm. The column temperature was maintained at 25 °C.

Preparation methods

Optimizing the parameters for HME using placebo. Extrusion was done with only E-EPO and EPO with plasticizers in different concentrations to optimize the parameters such as barrel temperature, screw speed, feed rate, and amount of plasticizer to be added for obtaining clear, plastic, and uniform extrudates using a co-rotating twin screw extruder (10 mm, Steer omicron 10P; STEERLife India Pvt. Ltd., Bangalore, India). The barrel temperature was in the range of 80 °C–110 °C and the screw speed was in the range of 100–300 rpm while keeping the feed rate constant at 2 g/min. To reduce the processing temperature and obtain plastic extrudates, E-EPO was extruded with varying amounts of plasticizer PEG 6000 in varying ranges of 2%–10%.

Preparation of hot melt extrudates of CP

CP and E-EPO with PEG 6000 (5%) as a plasticizer was first blended using the geometric blending method in a polybag followed by passing the blend from sieve mesh #40. The drug-loading amount varied from 10% to 40%, keeping the quantity of plasticizer constant. The uniformly blended and mesh-passed mixtures of drug and polymer were extruded using a co-rotating twin screw extruder at 75 °C with a screw speed of 150 rpm. The extrudates were further milled using a ball mill and passed from sieve mesh #60 before further processing.

Preparation of hot melt extrudates of roxithromycin

Roxithromycin, E-EPO, PEG 6000, and stearic acid (5% each) were first blended using a geometric blending method in a polybag followed by passing the blend from sieve mesh #40. The drug-loading amount varied from 10% to 40%, keeping the quantity of plasticizer and stearic acid constant. The uniformly blended and mesh-passed mixtures of drug and polymer were extruded using a co-rotating twin screw extruder at 100 °C with a screw speed of 150 rpm. The extrudates were further milled using a ball mill and passed from sieve mesh #60 before further processing.

Optimizing drug loading using solubility studies

All of the batches processed in different concentrations were studied for solubility to finalize the drug loading. The solubility of CP and ROX was assessed in their standard prescribed media glycine buffer (pH 3) and phosphate buffer (pH 6), respectively. The excess quantity of samples of different batches was added to 100 mL of each dissolution media and kept in a mechanical shaker water bath maintaining the temperature of 37 ± 0.5 °C. Samples were collected at various time points of 15, 30, 60, 120, and 240 min, and 24 h. The filtered samples (0.45 µm syringe filter) were analyzed spectroscopically for CP and by HPLC for ROX.

Powder X-ray diffraction

The physical form of the drug (CP and ROX), excipients, their physical mixture, and milled extrudates was determined using powder X-ray diffraction (PXRD). The study was performed with the Thermo Scientific ARL EQUINOX 100 Powder X-ray Diffractometer (Thermo Fisher Scientific, Waltham, MA, USA) at room temperature using CuKα radiation at 15 mA and 30 kV, 4 °C min^{-1}. The samples were scanned in the range of diffraction angles (2θ) of 1–100°.

Differential scanning calorimetry

The physical state, thermal and melting behavior of active pharmaceutical ingredients (API) alone (CP and ROX), excipients, their physical mixtures, and milled extrudates were examined by differential scanning calorimetry (DSC) (Mettler-Toledo 823e; Mettler Toledo, Columbus, OH, USA). A small quantity of sample (2–3 mg) was placed in pierced aluminum pans and heated from 30 to 200 °C at a heating rate of 10 °C min^{-1} in a nitrogen atmosphere.

Preparation and evaluation of dispersible tablets

Flow properties of granules. Milled extrudates or granules were evaluated for their flow properties and compressibility. Micromeritic properties such as bulk density, tapped density, Hausner's ratio, Carr's compressibility index, and angle of repose of milled extrudates were investigated using the Electrolab Tap Density Tester ETD-1020X and Electrolab Manual Powder Flow Tester ETF-01 (Electrolab, Mumbai, India). All granules taken for the evaluation were passed through mesh #60. Bulk density (ρ_B) was calculated by the equation $\rho_B = M/V_B$, by placing 30 g (M = the mass of

granules) of the granules in a 100 mL graduated measuring cylinder to measure the bulk volume (V_B). Tap density (ρ_T) was calculated by the equation $\rho_T = M/V_T$, by placing 30 g of the granules in a 100 mL graduated measuring cylinder followed by tapping 100 times with the tap density apparatus, after which the volume (V_T)was recorded. Hausner's ratio was calculated with the formula ρ_T/ρ_B, while Carr's compressibility index was calculated with the formula $CI = (\rho_T - \rho_B)/\rho_T \times 100$.

Drug content

To determine the actual drug content in the respective extrudates, the assay was performed in a methanol and solvent mixture for CP and ROX, respectively, as given in the Indian Pharmacopoeia (IP). The solvent mixture for ROX was acetonitrile and ammonium dihydrogen phosphate (4.8% w/v) buffer pH adjusted to 5.3 at a ratio of 3:7. Then 333.33 and 500 mg milled extrudes or granules of fixed drug content equivalent to 100 mg were dissolved in their respective solvents, diluted appropriately, and analyzed for drug content using the previously reported analytical methods.

Preparation of dispersible tablets of CP and ROX

For the preparation of CP tablets, a 30% drug-loading batch was selected based on the solubility and taste-masking efficiency. Similarly, for ROX tablets, a 20% drug-loading batch was finalized. All tablets were prepared by the direct compression method. The quantity of milled extrudates was decided based on calculating % assay along with maintaining the standard dose of respective drugs (348.99 mg for CP and 387.37 mg for ROX). Other excipients such as crospovidone, silicon dioxide (aerosil), mannitol, magnesium stearate, and flavor were optimized by taking trials with varying concentrations of crospovidone in the range of 1%−5% and within the minimum required amount (Table 1). The uniformly mixed blend was passed through mesh #40, and tablets were punched with adjusting compression force as per the requirement (18−24 kN) in hardness, thickness, and disintegration time.

Tablet characterization

The prepared tablets were evaluated in different physical aspects such as hardness, thickness, friability, disintegration time, and uniformity of dispersion. Hardness was determined with the ERWEKA hardness tester (ERWEKA GmbH, Langen, Germany), the thickness was determined with a digital vernier caliper (Insize Co., Ltd., Suzhou, China), friability was determined with the Electrolab friabilator (Electrolab), and disintegration time was assessed with the Electrolab disintegration apparatus (Electrolab). For the uniformity of dispersion test, as per IP, two tablets of CP and ROX each were dispersed in 100 mL distilled water at 25 °C with gentle stirring until they were completely dispersed. A smooth dispersion was obtained, which was passed through sieve mesh #22.

In vitro *taste-masking evaluation*

To study the taste-masking efficiency of tablets *in vitro*, the amount of drug release in the simulated salivary fluid (pH 6.8) was recorded. Simulated salivary media was prepared according to the composition previously reported.[5] The test was performed at a temperature of 37 ± 0.5 °C, 50 rpm, and 150 mL media. The study was done for only 120 s considering the residence time in the mouth. The samples were collected at predetermined time intervals of 10, 20, 30, 60, 90, and 120 s and drug concentration was estimated using previously described analytical instruments.

In vivo *taste-masking evaluation*

For the confirmatory test of taste-masking efficiency, the CP and ROX tablets were analyzed *in vivo* with human taste panel studies. *In vivo* taste-masking evaluation of formulated and marketed tablets of both CP and ROX was performed according to the Code of Ethics of the World Medical Association (Declaration of Helsinki). Considering the *in vitro* taste-masking efficiency of the prepared tablets and the holding time of 60 s in the mouth, the study did not require approval; however, written consent from the participating volunteers was obtained. Six healthy volunteers were selected randomly within the same age group (18−45) of either sex (i.e., three males and three females). After properly training the volunteers, they were given the formulated tablets individually and told to hold them in their mouths for 60 s and then spit them out followed by rinsing their mouth with water. The taste-masking efficiency or bitterness was recorded by obtaining the score by volunteers from 1 to 5 (i.e., 1, 2, 3, 4, and 5 indicate bitterness of none, slightly bitter, moderately bitter, bitter, and strongly bitter, respectively). The same procedure was repeated for the marketed tablets to compare the bitterness.

In vitro *dissolution study of dispersible tablets*

The dissolution study of the tablets was conducted in 900 mL medium glycine buffer (pH 3.0) for CP and phosphate buffer (pH 6.8) for ROX tablets. The USP Type II Electrolab Dissolution Test Apparatus (Electrolab) was used with a media temperature of 37 ± 0.5 °C at 100 rpm for 120 min. The samples were withdrawn at time points of 5, 15, 30, 45, 60, 90, and 120 min and analyzed for their content with the Shimadzu UV Spectrophotometer (Shimadzu, Columbia, MD, USA) for CP and the Waters HPLC-UV system (Waters, Milford, MA, USA) for ROX. Sink conditions were maintained throughout the dissolution test.

Results

Preformulation studies

Polymer selection

To accomplish the primary objective of taste masking selected drugs, it was necessary that the polymer used release the minimum amount of drug in the mouth (i.e., saliva without compromising solubility at another gastric pH).[18] Considering the same from the literature survey, we pointed out that the E-EPO could be the polymer of choice to mitigate the set objective. Once theoretically finalized, it is important to analyze the compatibility of APIs and excipients before proceeding with formulation development. To this end, FTIR studies were performed.

Table 1: Composition of dispersible tablets.

Cefpodoxime proxetil			Roxithromycin		
Ingredients	Quantity (mg)	Quantity (%)	Ingredients	Quantity (mg)	Quantity (%)
CP Granules	385	84.4	ROX Granules	417	84.4
Crospovidone	20	4.38	Crospovidone	25	5.1
SiO_2	4	0.98	SiO_2	5	1
Mannitol	25	5.5	Mannitol	25	5.1
Flavor	20	4.35	Flavor	20	4
Mg. Stearate	2	0.49	Mg. Stearate	2	0.4
Total	456	100	Total	456	100

CP, cefpodoxime proxetil; Mg, magnesium; ROX, roxithromycin; SiO_2, silicone dioxide.

Drug excipient compatibility study using FTIR

The FTIR spectra of CP depicted % transmittance bands at wavelengths of 2988.16 cm^{-1} and 2938.02 cm^{-1} corresponding to C−H stretching, 1782.87 cm^{-1} for C=O stretching, 1677.77 cm^{-1} for N−H stretching, 1618.95 cm^{-1} for C=N vibration, 1531.2 cm^{-1} for N−O vibration, 1275.68 cm^{-1} for C−N vibration, and 1035.59 cm^{-1} for C−O vibration[19] (Figure 1). Similarly, the FTIR spectra of

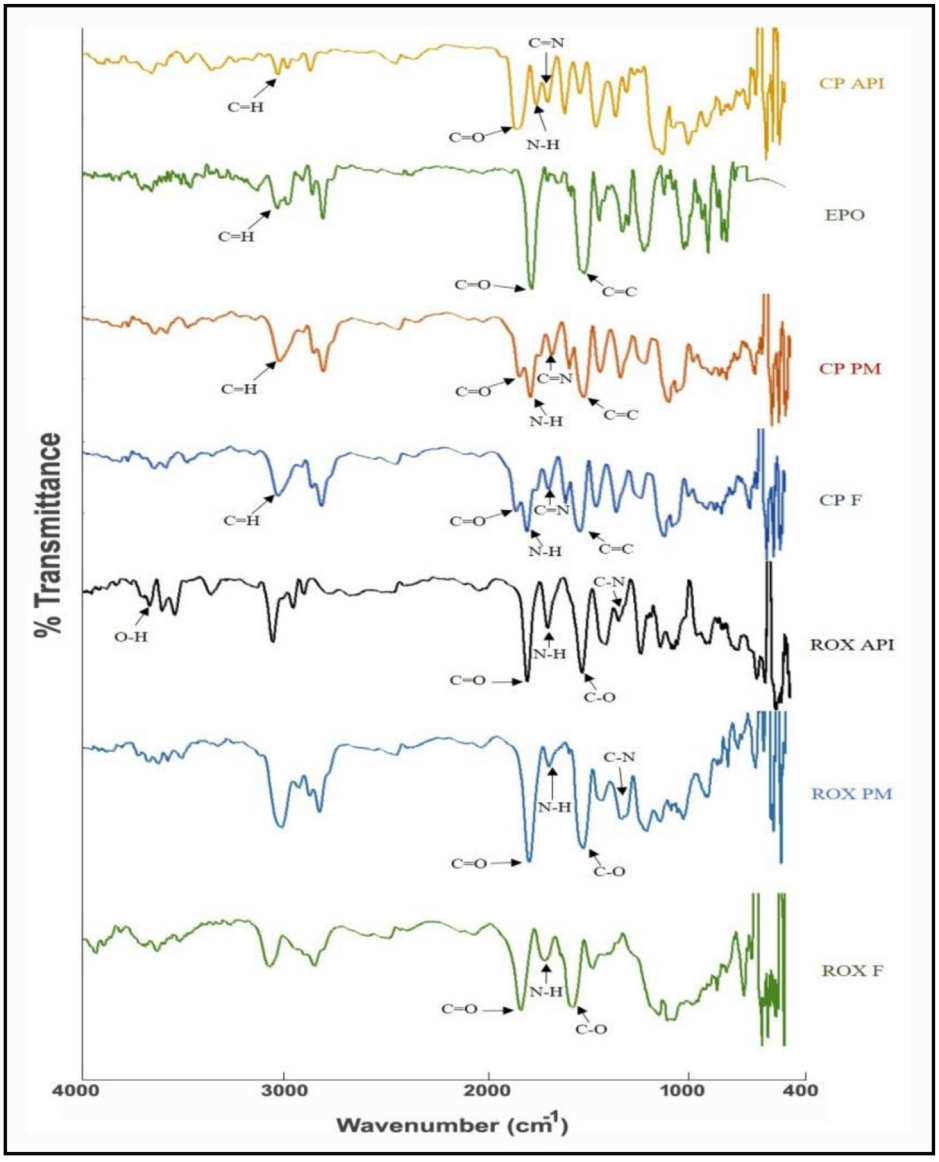

Figure 1: FTIR spectra of CP API, EPO, CP physical mixture (CP PM), CP formulation (CP-F), ROX API, ROX physical mixture (ROX PM) and ROX formulation (ROX F).

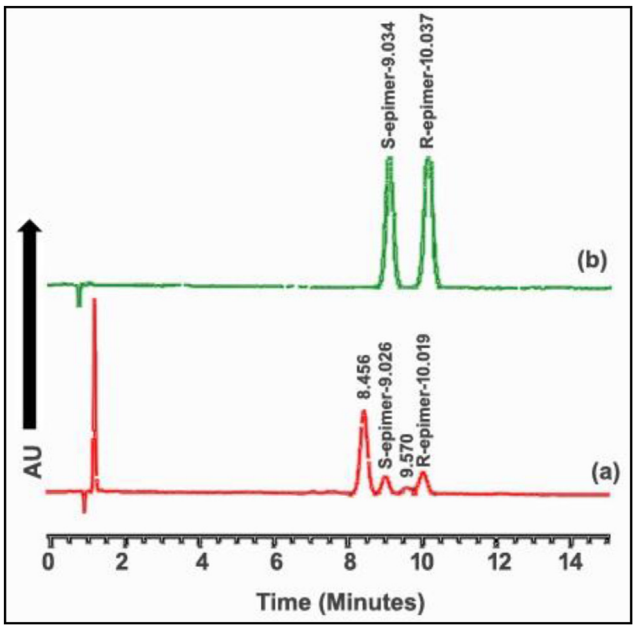

Figure 2: HPLC chromatogram of (a) degraded batch of CP (b) optimized batch of CP.

ROX showed characteristic bands at 3582.13 cm^{-1}, 3522.34 cm^{-1}, and 3460.63 cm^{-1} corresponding to free −OH groups and intramolecular hydrogen bonding between −OH groups, 1729.83 cm^{-1} (C=O stretching), 1630.52 cm^{-1} (N−H stretching), 1460.81 cm^{-1} (C−H bending), and 1282.43 cm^{-1} (C−N vibration).[20] FTIR spectra of E-EPO showed characteristic peaks at 1724.05 cm^{-1} (C=O stretching), 1463.71 cm^{-1} (C−H bending), 1272.79 cm^{-1} (C−N stretching), and 1062.59 cm^{-1} (C−O vibration).[21] To investigate the interaction (if any) between API and Eudragit, physical mixtures of CP and E-EPO and of ROX and E-EPO were prepared and subjected to FTIR spectroscopy. It was observed that all of the characteristic peaks associated with drug and polymer was retained in the FTIR spectra of the physical mixture, and no new peak was identified.

Analytical method for CP and ROX

The analytical methods used for CP were found to be linear in the concentration range of 10−20 ppm. The regression analysis of calibration curves generated standard equations with R^2 values nearer to 1 for CP in methanol, glycine buffer (pH 3), and simulated salivary media (pH 6.8). Similar results were recorded for ROX, which showed linearity in the range of 50−100 ppm in the solvent mixture, dissolution media, and simulated salivary media. The regression equations generated were used to compute drug content, assay, and *in vitro* drug release study (data not shown).

HME process

The processing parameters (temperature, screw speed, and feed rate) in the HME process were optimized using plain polymer E-EPO with varying ratios of plasticizers. The plasticizer content was optimized based on trials with an increase in its amount from 1% to 5% until an uninterrupted continuous extrusion process was observed with clear plastic extrudates at the desired temperature (minimum). Plastic extrudates made the further milling process easy and convenient. Elastic extrudates were obtained at a lower concentration of plasticizer, which could not be milled easily. Finally, 5% w/w plasticizer was optimized for the study. In the preliminary studies, we tried to optimize the extrusion temperature for both CP and ROX batches based on the extrusion process and morphology of the extrudates with HME parameters of 100 °C extrusion temperature, 300 rpm screw speed, and 2 g/min feed rate based on the clarity of extrudates, plasticity, and smooth flow through the extruder.

These parameters were then used for processing batches containing CP. The primary batches executed with CP were analyzed using UV spectroscopy to investigate the degradation of the drug (if any). Surprisingly, the UV spectroscopic analysis showed a shift in the characteristic λ_{max} of CP. To investigate this further, we performed HPLC analysis according to the reported method in IP to confirm if there was degradation of CP after HME processing. HPLC spectra showed characteristic peaks corresponding to S and R epimers of CP at Rt value of 9 and 10 min, respectively. However, HPLC analysis also showed an extra peak at Rt 8.456,

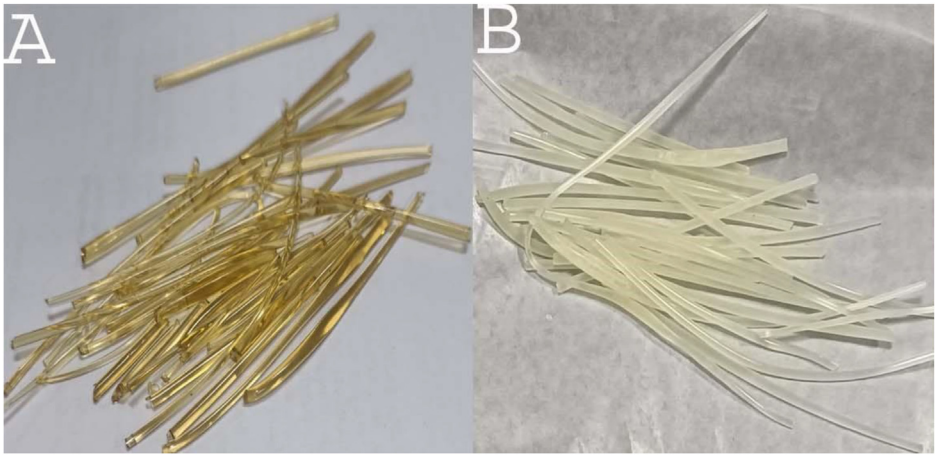

Figure 3: A) Extrudates of CP-F batch B) extrudates of ROX-F batch.

Table 2: Saturation solubility and torque value generated by the HME machine for CP and ROX tablets.

CP batches	Drug loading	Torque (Nm)	Solubility in glycine buffer pH 3.0	ROX batches	Drug loading	Torque (Nm)	Solubility in phosphate buffer pH 6.0
F1	10%	0.28 ± 0.02	0.19 ± 0.02	F1	10%	0.32 ± 0.03	0.24 ± 0.03
F2	20%	0.31 ± 0.03	0.21 ± 0.03	F2	20%	0.43 ± 0.02	0.31 ± 0.02
F3	30%	0.39 ± 0.01	0.25 ± 0.02	F3	30%	0.48 ± 0.03	0.27 ± 0.01
F4	40%	0.46 ± 0.02	0.22 ± 0.01	F4	40%	0.54 ± 0.04	0.25 ± 0.04

n = 3 Data are presented as the mean ± standard deviation.

which could be attributed to the degradation of CP and/or impurity compared with the HPLC spectra of the reference standard (Figure 2a). To address this issue, placebo batches were taken again by changing the plasticizer, their amount, and processing temperature. Finally, for CP, the HME process was set as plasticizer PEG 6000 (5%), extrusion temperature of 75 °C, and screw speed of 150 rpm, keeping the feed rate the same. The processing batch of CP with these optimized parameters showed characteristic peaks of CP of its S and R epimers (Figure 2b) with an absence of any extra peak confirming the prevention of CP degradation. Figure 3A depicts the CP extrudates obtained after processing with optimized parameters, which were used for further processing.

In the case of batches executed with ROX, we did not observe any degradation of ROX; however, in preliminary studies we observed lack of taste-masking efficiency. Thus, it was decided to process batches of ROX after the addition of stearic acid as a wax to coat the drug efficiently and to pass it easily from the oral cavity (tongue) minimizing taste sensation. Thus, the processing of ROX batches was done as per previously optimized parameters with the addition of 5% stearic acid. Figure 3B depicts the ROX extrudates obtained after processing with optimized parameters. The extrudates were cooled to room temperature, milled, and passed through sieve #60 for further evaluation.

Optimizing drug loading using solubility studies

It is known that while designing taste, masked formulation solubility of an API is of prime importance. In our case, there was no significant enhancement in the solubilities of both CP and ROX after the HME process (Table 2). Thus, we utilized the taste-masking efficiency to optimize the drug loading into final formulations along with the solubility data. In the case of CP, the taste masking was efficient up to the drug loading of 30%, whereas in the case of ROX, it was up to 20% after addition of stearic acid. Hence, based on these considerations CP drug loading was confirmed to be 30% and ROX 20% with stearic acid.

PXRD

The PXRD graphs of CP alone, CP Physical Mixture (CP PM), and CP Formulation (CP-F) showed broad diffraction peaks. Similarly, E-EPO also did not show sharp diffraction peaks (Figure 4A). In the case of ROX, ROX alone showed characteristic sharp diffraction peaks at $2\theta = 7.20°$, 10.92°, 11.76°, 12.83°, 13.52°, 18.8°, and 22.3°.[16] Furthermore, the PXRD graph of ROX PM showed all of the peaks of ROX (Figure 4B). However, PXRD analysis of ROX-F displayed a reduction in the intensity of ROX upon HME processing.

DSC

The DSC thermogram of CP alone showed a blunt peak at about 100 °C supporting our observation of its existence as an amorphous form (Figure 5A). Similar behavior was observed in the DSC thermogram of E-EPO. DSC thermograms of PEG 6000 and stearic acid showed sharp melting endotherms at temperatures of 62 °C and 71 °C, respectively. Similarly, the DSC thermogram of ROX alone showed a sharp melting endotherm at 120 °C (Figure 5B).[22]

Preparation and evaluation of disintegrating tablets

Flow properties of granules

The drug-loaded batch of CP (30% w/w) and ROX (20% w/w) with stearic acid was considered to be optimized, which

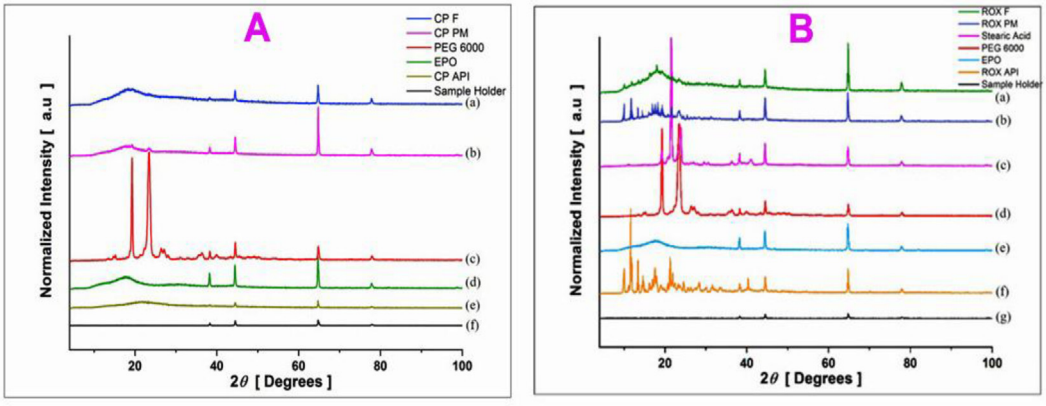

Figure 4: A) X-ray crystallographs of (a) CP formulation (b) CP PM (c) PEG 6000 (d) E-EPO (e) CP-API (f) sample holder. B) X-ray crystallographs of a) ROX formulation (b) ROX PM (c) stearic acid (d) PEG 6000 (e) E-EPO (f) ROX-API (g) sample holder.

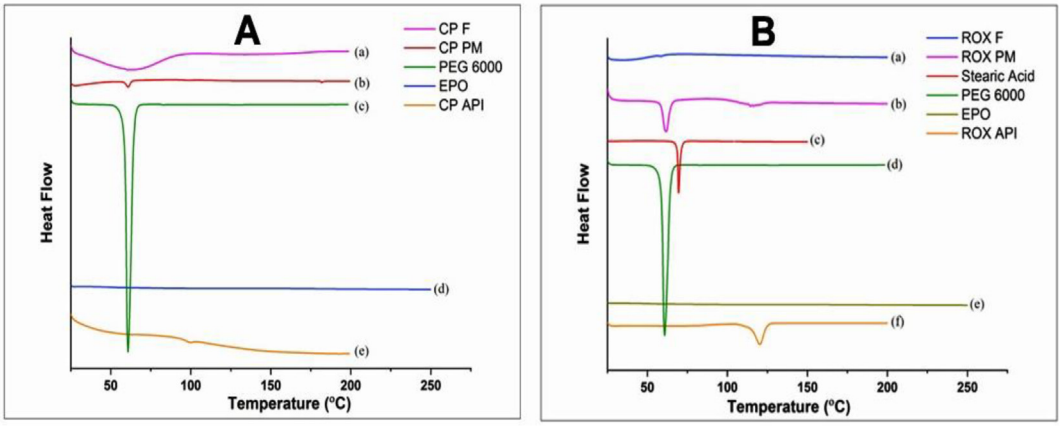

Figure 5: A) DSC thermograms of (a) CP formulation (b) CP PM (c) PEG 6000 (d) E-EPO (e) CP-API. B) DSC thermograms of (a) ROX formulation (b) ROX PM (c) stearic acid (d) PEG 6000 (e) E-EPO (f) ROX-API.

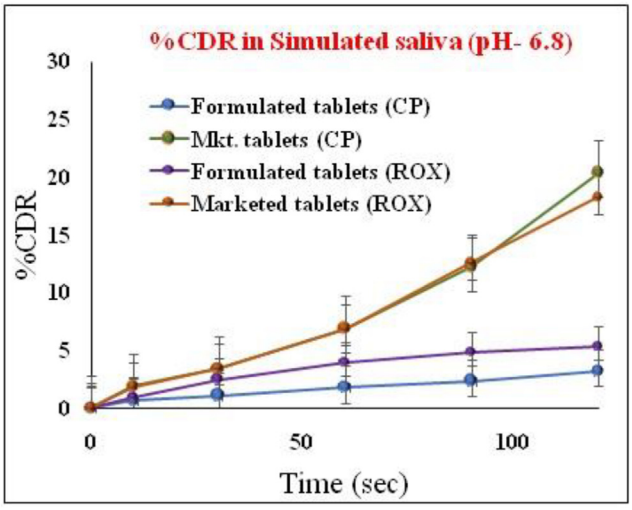

Figure 6: Comparative *in vitro* taste-masking evaluation study of formulated tablets with marketed tablets of CP and ROX.

was further processed by their milling and passing through sieve #60 to obtain uniform free-flowing granules. These granules were analyzed for flow properties with different evaluating parameters such as bulk density, tap density, Carr's index, Hausner's ratio, and angle of repose and those were found to be within the range of 0.55–0.58 g/mL, 0.48–0.5 g/mL, 12.2–15.5%, 1.14–1.18, and 31–33°, respectively, for both CP and ROX. The assessment of all parameters suggested that the prepared granules had good flow properties.

Drug content

The drug content of the granules of CP and ROX was investigated and found to be 95.3% ± 0.8% and 96.7% ± 1.3%, respectively. Considering these drug content values, the final amount of granules for processing into tablets with the desired dose was 100 and 75 mg for CP and ROX, respectively.

Tablet preparation and characterization

Dispersible tablets of CP and ROX were prepared and evaluated physically with parameters including hardness, thickness, disintegration time, friability, drug content, and uniformity of dispersion and the results were found to be within the range of 3–3.5 kg, 4.5–5 mm, 30–40 s, 0.74%–0.78%, 95%–105%, respectively, and the uniformity of dispersion test passed and complied as per IP.

In vitro *taste-masking evaluation*

In vitro taste-masking studies were performed for the prepared tablets of CP-F and ROX-F, which were compared with the marketed tablets OPOX DT and Roxid DT, respectively (Figure 6).[23,24] The prepared tablets showed 3.21% ± 0.6% of CP and 5.3% ± 0.8% of ROX release in simulated salivary media (pH 6.8) within the first 2 min. However, the marketed tablets OPOX DT and Roxid DT showed 20.35% and 18.25% of CP and ROX release, respectively. It is always preferred to evaluate the

Table 3: Bitterness score obtained from human volunteers.

Name of sample	Scores given by volunteers for respective samples						Average bitterness value
CP (F)	1	1	1	1	1	1	1
CP (M)	4	5	5	4	5	4	4.5
ROX (F)	1	1	2	1	2	1	1.33
ROX (M)	5	5	5	5	5	5	5

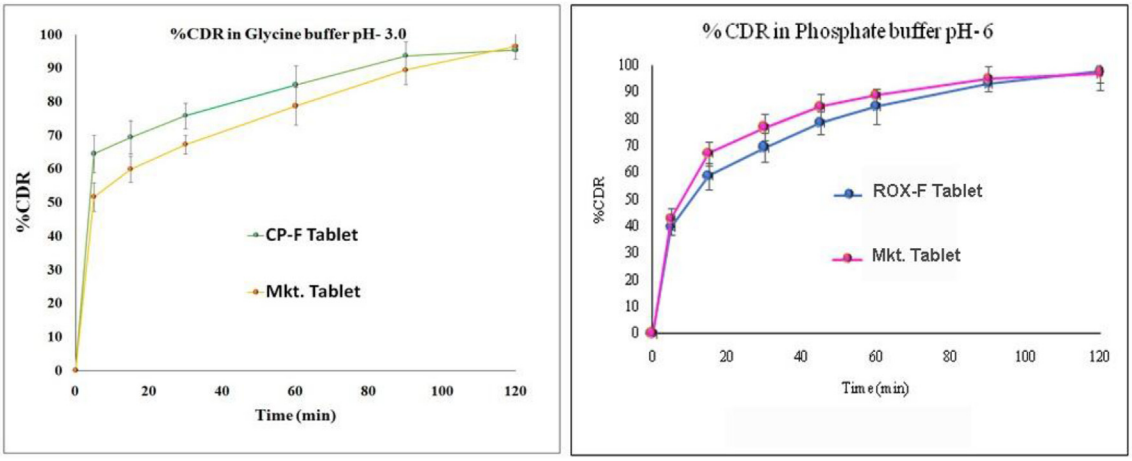

Figure 7: Comparative *in vitro* dissolution study of CP-F and ROX-F formulated tablets with marketed tablets.

formulation efficiency *in vivo*. Accordingly, the prepared tablets along with their marketed counterparts were evaluated in human volunteers for taste-masking efficiency.

In vivo *taste-masking evaluation*

From the data obtained from volunteers (Table 3), the average bitterness score of the prepared tablets of CP was found to be 1 and that for ROX was found to be 1.3.[25] Similarly, the bitterness scores of the marketed tablets of CP and ROX were found to be 4.5 and 5, respectively.

In vitro *dissolution study of dispersible tablets*

An *in vitro* dissolution study was performed in glycine buffer (pH 3) and phosphate buffer (pH 6) for the prepared and marketed tablets of CP and ROX, respectively.[26] Both (i.e., formulated and marketed) showed drug release in the range of 96–98% within 120 min (Figure 7). To evaluate whether the drug release profiles of prepared and marketed tablets were similar, F2 (similarity factor) values were evaluated. The prepared tablets of CP and ROX showed F2 values of 54.52 and 64.09, respectively, which suggested that the drug release profiles of the prepared tablets were similar.

Discussion

E-EPO is chemically a cationic copolymer consisting of dimethyl aminoethyl methacrylate, butyl methacrylate, and methyl methacrylate in a ratio of 2:1:1.[27] It displays pH-dependent solubility releasing most of the entrapped drug at an acidic pH below 5. E-EPO has a glass transition temperature (T_g) of 57 °C, which makes the extrusion process easy at lower temperatures. Additionally, there are reports highlighting the role of E-EPO in enhancing the aqueous solubility of poorly water-soluble drugs.[5,28] Moreover, E-EPO provides a moisture-protective coating and also creates a physical barrier to the drug toward taste buds, enhancing the taste-masking efficiency of the formulation.

FTIR studies confirmed the processing compatibility between drug (CP or ROX) and E-EPO, as there were no new peaks observed in the FTIR spectra of the physical mixtures and formulations of both drugs with the retention of all of the characteristic peaks of drug and polymer. As stated previously, formulating solid dispersion of drugs with EPO for taste-masking purposes also enhances their aqueous solubility as a result of strong intermolecular interactions such as hydrogen bonding or electrostatic interaction. The solid dispersion of mefenamic acid with E-EPO has been prepared using HME for taste masking wherein the authors claimed to significantly enhance the solubility of the drug due to the intermolecular interaction (hydrogen bonding) between the C=O group (proton-donating) of mefenamic acid and the amino alkyl group (proton-accepting) from E-EPO as per the FTIR spectra of the formulation.[5] In our case, there were no such intermolecular interactions observed between the drug and polymer (Figure 1), which might be the reason for no change in the solubility of CP and ROX after HME processing.

It is well known that the amorphous form of solids do not show sharp diffraction peaks in PXRD. Thus, in the present work, the amorphous nature of CP was confirmed by PXRD and it was retained even after HME processing. The reduction in the peak intensities of ROX-F as reflected by PXRD patterns suggests the possibility of its partial amorphization.[29] DSC studies confirmed the crystalline nature of ROX. Surprisingly, DSC thermograms of CP PM, CP-F, ROX PM, and ROX-F did not show melting endotherms for CP and ROX. This could be due to the solubilization of drugs in the already molten mass of excipients. Such results have previously been reported. The *in vitro* drug release study of CP-F and ROX-F tablets in the acidic medium showed a delay in the drug release in the initial time period, which could be attributed to the magnesium stearate that was used as a lubricant during compression of the tablet. It has been reported in the literature that magnesium stearate delays the drug dissolution rate from a tablet in acidic medium, due to the fact that stearic acid released by the magnesium stearate in acidic medium has detrimental effects on the drug release characteristics of dispersible tablets.[30] Furthermore, the results of *in vitro* taste-masking studies have confirmed that the prepared tablets have better taste masking compared to marketed tablets. The pH of media used for the test was 6.8; however, as stated earlier, E-EPO reportedly releases the drug below pH 6 due to its pH-dependent solubility characteristics. This could be the reason for better taste-masking efficiency by the prepared tablets compared to marketed

ones. Additionally, ROX tablets have stearic acid, which might have retarded ROX release and thus displayed taste-masking efficiency over its marketed counterpart. Moreover, the results of *in vivo* studies were in agreement with the *in vitro* taste-masking efficiency studies, confirming the accomplishment of the set objective of the present work.

Conclusion

To conclude, taste-masked dispersible tablets of CP and ROX were successfully prepared with E-EPO for pediatric administration using HME technology. The current work presented solvent-free, scalable and continuous HME technology to address the bitter taste issues of CP and ROX. Furthermore, the disadvantages associated with the currently used lyophilization technique were overcome by developing the formulations using HME technology.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

There is no ethical issue with the study performed in the present work.

Authors contributions

PP and SS performed the work and characterization of the prepared formulation as described in the manuscript. SP conceptualized the idea and wrote the manuscript. AP reviewed the written draft of the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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