

Original Article

TASTE MASKING BY HOT MELT EXTRUSION WITHOUT LOSS OF BIOAVAILABILITY FOR PEDIATRICS

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ABSTRACT

Objective: The aim of present work was to develop a platform technology for the pediatric dosage form to mask the bitter taste of Furosemide (FUR) and prepare a flexible solid oral dosage form.

Methods: Excipient compatibility study was carried out by using Fourier-transform infrared spectroscopy (FTIR). Taste masking was done by hot melt extrusion (HME) technology. Eudragit EPO and Soluplus were used as a taste masking and solubilizing polymers respectively. The prepared solid dispersion and tablets were evaluated for their physicochemical parameters such as hardness, friability, disintegration, *in vitro* drug release.

Results: Experimental data revealed that physical integrity, brittleness of granules, conversion of a drug in amorphous form was improved by combining Eudragit EPO with Soluplus. Plasticizer helped to complete HME at 80 °C. Less than 10% drug release in pH 6.8 medium revealed that release would be extremely limited in the saliva and thus avoiding bitterness. Animal study data revealed that bioavailability has been increased by 30%. Differential scanning calorimetry (DSC) and x-ray diffraction (XRD) tests confirmed the existence of molecularly dispersed drug. Fourier-transform infrared spectroscopy (FTIR) confirmed the unchanged functional groups of FUR after HME processing.

Conclusion: Proposed platform technology masked the bitter taste and enhanced the bioavailability of FUR in D: P ratio of 1:2.

Keywords: Hot Melt Extrusion, Solubility, Dissolution, Pediatric dosage, Taste Masking

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INTRODUCTION

Different options are regularly used to make unavailable drugs available for pediatric patients and to adjust doses according to an individual patient's requirement. Such choices are a modification of administration routes (eg. oral use of parenteral formulations), manipulation of adult dosage forms (eg. diluting liquid formulations), segmenting tablets and suppositories, cutting patches, and dispersing capsule content or crushed tablets in water, liquid, or food, or spontaneous dispensing (compounding medicines from ingredients within pharmacies) [1].

Disadvantages of oral pediatric dosage forms are the requirement of dose-measuring devices, chances of incorrect dosing, shaking requirement for dose accuracy in the liquid dosage form and the ability to swallow intact dosage form, a risk of chewing and choking, limited dose flexibility, taste masking requirements, less stability of liquid dosage form.

The solid oral dosage form is one of the most preferred dosage forms in adults. The main challenges in the development of solid oral dosage form for pediatrics are palatability and acceptance of dosage form due to their bitter taste, obnoxious odor, unattractive finished product appearance, handling and dose measurement/accuracy issues, and many others [1, 2].

There may be no single oral dosage form which is ideal for pediatric patients of all ages [3].

The present research work aimed to mask the bitter taste of FUR and prepare chewable dispersible tablet which can overcome all above-mentioned challenges and disadvantages, and accomplishes the desired features.

FUR was selected as a model drug which is bitter in taste and belongs to the biopharmaceutics classification system (BCS) class IV [4] and has a pH-dependent solubility [5]. The pediatric dose and

minimum dose of FUR is 2 mg/kg and 20 mg respectively [6]. The presence of an amine as a functional group make drugs like FUR bitter in taste however if the functional groups are blocked the bitterness of the drug reduces drastically [7]. FUR is a loop diuretic act primarily by inhibiting chloride and sodium reabsorption over the entire length of the thick ascending limb of the loop of henle, it is widely used for the symptomatic treatment of heart failure and fluid retention in chronic kidney disease [8].

Various types of taste masking methods are available which involve multiple steps with scale-up challenges. So, hot melt extrusion (HME) method was selected as taste masking technique due to its unique advantages like easy to scale up and reproducibility [9].

HME technology is an innovative technology which can be used for taste masking of bitter drugs with a unique advantage over other available technologies [10, 11]. Different polymer(s) can be used alone or in combination for taste masking of bitter drugs to get desired results, examples are copovidone (kollidon VA 64), polymethacrylic acid copolymer (eudragit EPO), polyvinyl caprolactam (soluplus), ethyl cellulose, etc. Additionally, these polymers can be used for solubility enhancement of poorly soluble drugs [12-14].

In the present work, eudragit EPO is selected as taste masking polymer as it's the only polymer having reverse enteric properties (pH-dependent solubility). It is soluble below pH 5 and swellable and permeable above pH 5 [15]. It is a cationic copolymer based on dimethylamino-ethyl methacrylate, butyl methacrylate, and methyl methacrylate which is insoluble above pH 5 [16]. Soluplus is selected to enhance the solubility of the drug and used in combination with eudragit EPO. Soluplus is polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer which is freely water-soluble [16]. These polymers were selected to have a rapid gastric release of FUR in the stomach. By using these two polymers we intend to examine the correlation between *in vitro* drug release and taste masking efficiency. Possible taste masking mechanism would be intermolecular ionic

interactions between an amine and carboxylic groups of active pharmaceutical ingredients (API) and eudragit EPO respectively [17].

In the present study plasticizers like polyethylene glycol (PEG) and polysorbate were used as plasticizer and para glycoprotein (Pgp) as inhibitors/surfactant [18, 19] respectively and their impact on solubility and permeability was evaluated.

MATERIALS AND METHODS

Materials

Furosemide of Ralington Pharma (India), Eudragit EPO of Evonik Pharma, Soluplus of BASF, Crospovidone of Ashland, Mannitol of Roquette, Sodium Stearyl Fumarate of JRS Pharma, Colloidal silicon dioxide of Evonik, Iron oxide red of Neelikon food dyes and chemicals, Raspberry flavor by Kerry, were used in present research work.

Methods

An analytical method for calibration curve of FUR

Maximum wavelength of FUR was found to be 274 nm using UV visible spectroscopy (Make: Shimadzu, Model: 1800). Stock solution (100 µg/ml) was prepared with 0.01N HCL with 2 % sodium lauryl sulfate (SLS). Aliquots of stock solution ranging from 1.0 to 7.0 ml were transferred into 10 ml volumetric flask and were diluted up to the mark with 0.01N HCL with 2 % SLS to get concentrations of 10, 20, 30, 40, 50, 60, 70 µg/ml. The Absorbance of each solution was measured at 274 nm against 0.01N HCL with 2 % SLS. A plot of

concentration of drug versus absorbance was plotted. The linear regression analysis was applied. The standard regression equation for FRU obtained was $Y = 0.2019X - 0.1726$ with a coefficient of regression (R^2) of 0.9993. The Same procedure was followed to generate the calibration curve in pH 6.8 phosphate buffer where the standard regression equation for FRU obtained was $Y = 0.1910X - 0.1686$ with a coefficient of regression (R^2) of 0.9982.

Determination of the drug: polymer ratio (solubilization capacity)

Different solvents like methanol, ethanol and distilled water were used for determination of the solubility of the drug and polymers. Drug and polymers were observed to be soluble in methanol, hence selected for further study. For optimization, different ratio of drug and polymer like 1:1 to 1:3 were used. The proportionate amount of drug and polymer was dissolved in methanol and these liquid samples were poured into the Petri dishes. The pure drug was also dissolved in methanol and used as a control sample. The solvent in the samples was evaporated by the evaporation method and appearance of samples was recorded for clearness and transparency at the initial stage and after 24 h storage at room temperature [20].

Preparation and evaluation of SD granules prepared by HME technology

FUR, eudragit EPO, soluplus, polysorbate and silicon dioxide (table 1) were sifted through #30 sieve and mixed in a polybag for 10 min. Liquid PEG mixed in dry powder to get a uniform blend. Obtained blend was screened through # 18 sieve and used for HME process.

Table 1: Composition of chewable dispersible tablets

Formulation Ingredients	D: P (1:1)			D: P (1:2)			D: P (1:3)		
	F2	F2	F3	F4	F5	F6	F7	F8	F9
	Quantity								
	HME granules part								
FUR (mg)	20	20	20	20	20	20	20	20	20
Eudragit EPO (mg)	20	20	20	40	40	40	60	60	60
Soluplus*	25	25	25	25	25	25	25	25	25
Polyethylene glycol*	5	10	15	5	10	15	5	10	15
Polysorbate*	5	10	15	5	10	15	5	10	15
Silicon dioxide*	1	1	1	1	1	1	1	1	1
Total (mg)	47.2	49.2	51.2	74.4	78.4	82.4	101.6	107.6	113.6
	Extragranular excipient part								
	qs	qs	qs	qs	qs	qs	qs	qs	qs
Total (mg)	101.7	106.0	110.3	160.3	169.0	177.6	219.0	232.0	244.8

HME: Hot melt extrusion, D: FUR, P: Eudragit EPO, F: Formulation, %w/w of eudragit quantity

HME was carried out using Pharma 11 model of Thermo scientific. It was twin-screw extruder with 11 mm screw diameter and 440 mm in length. Screw diameter to length ratio was 1:40. There were 8 heating zones out of which 2 were mixing zones and others were conveying zones. Screws were co-rotating at the speed of 80-100 rpm; the processing temperature of different zones was set in increasing order and 80 °C was set in mixing zones. The Powder blend was slowly added to a hopper. Screw speed and feed rate were optimized to get torque in the range of 40-70 % and residence time less than 1 min for smooth processing. The extrudates were collected as strands with a diameter of approximately 2 mm and further milled and sifted through #40 sieve to get final taste masked granules. HME granules were evaluated for saturation solubility, FTIR, DSC and XRD tests as given below.

Saturation solubility

An excess amount of pure drug and HME granules were added to 0.01N hydrochloric acid (HCL) with 2% SLS and was kept for shaking up to 48 h (Orbital shaking incubator, Make: Remi) at 37±0.5 °C with intermittent vigorous shaking. Filtration of the suspension was done using a 0.45 µ membrane filter, followed by measuring the absorbance of filtrate using UV visible spectrophotometer to determine the concentration of drug [21].

Fourier transform infrared spectroscopy (FTIR)

FTIR was carried out to find out and ensure the presence and no change in functional groups of the drug before and after HME

processing using FTIR spectrophotometer (Make: Jasco, Model: V538). Samples were triturated with potassium bromide (KBr), which were further used to form a pellet. Scanning was done in the range of 400-4000 wavelength (cm⁻¹).

Differential scanning calorimetry (DSC)

Thermal behavior, physical state and melt endotherm of the drug were examined by DSC. The thermographs of each powder sample were obtained by using a Mettler Toledo-DSC 1. DSC was also used to confirm the conversion of a crystalline form of drug into amorphous form after HME processing. The sample was accurately weighed (5-10 mg) and was placed into the suitable aluminum pan and heated from 50 to 250 °C at the scanning rate of 10 °C/min in a nitrogen atmosphere (purging of 50 ml/min). FTIR and DSC were also used as identification tests.

Powder X-Ray diffraction (PXRD)

XRD was carried out at room temperature using a D/max 2500VL/PC powder X-ray diffractometer (Rigaku mini flex, Japan) operating at 40kV and 40mA to determine the presence of crystals in HME granules. Samples were scanned over a 2θ range of 3-40 ° with a step size of 0.02 ° and a step time of 0.3 s.

Tablet preparation and evaluation

Extra granular excipients screened through # 40 sieve and mixed HME granules in a polybag for 10 min. Tablets equivalent to a 20 mg

dose of FUR were prepared by 7.0 mm round shape punch using 8 stations single rotary compression machine (Make: CIP machineries, Model: CIP D8 Lab Press). The prepared tablets were evaluated for friability (Make: Electrolab, Model: EF-2) according to United States pharmacopeia (USP) general chapter 1216 [22]. The diametral compression test defined by Fell and Newton [23] was used to determine the tensile strength T, using the formula:

$$T = \frac{2P}{\pi Dt}$$

Where P (kP) is the applied stress, D (cm) is the diameter of the tablet, and t (cm) is the tablet thickness. Tablets were also evaluated for disintegration time and dissolution.

Disintegration time (DT)

DT of tablets was determined as per the process mentioned in USP general chapter 701[24].

Dissolution (simulation of drug release in the oral cavity)

Dissolution testing was conducted in 900 ml of two different media (i.e. 0.01N HCL with 2 %w/w SLS and pH 6.8 phosphate buffer) for 45 min (at an interval of 5, 15, 30, 45 min) using USP Type II apparatus (Make: Electrolab, Model: TDT-06L) at 50 rpm and temperature 37 °C±0.5 °C. At every time point, 10 ml aliquots were withdrawn, filtered through membrane filter paper (Whatman 0.45 µ) and checked for content by measuring the absorbance at 274 nm using UV visible spectrophotometer.

An equal volume of fresh medium pre-warmed at the same temperature was replaced in the dissolution medium after each sampling to maintain constant volume throughout the test. Each test was performed on three tablets, and release curves were plotted using calculated mean values of cumulative drug release. Dissolution in 0.01N HCL with 2 % w/w SLS and pH 6.8 buffer was required to predict release in the stomach and oral cavity respectively (*in vitro* taste masking efficiency) [25].

Stability study

Tablets (F6) were packed in heavyweight high-density polyethylene (HDPE) bottle with 2 g of silica gel canister with cotton filler and closed with a child-resistant closure (CRC). These samples were stored in the stability chamber (Make: Thermo lab scientific equipment) at accelerated (40 °C±2 °C and 75 %±5 %RH), intermediate (30 °C±2 °C and 65 %±5 %RH) and long term (25 °C±2 °C and 60 %±5 %RH) stability conditions up to 6 mo. Stability samples were analyzed after 3 and 6 mo for physical appearance, DT, dissolution XRD and FTIR [26].

Animal study

Due permission was obtained from the animal ethical committee and study was completed as per protocol No. SGRS/IAEC/ 12/2018-19.

Healthy male and female rats of Wistar strain, weight 200±15 g were obtained from the in house animal store of SGRS college of Pharmacy, Saswad, Pune and used to carry out the procedure. The rats were kept in environmentally controlled rooms at temperatures of 23 ±2 °C. The relative humidity was at least 40% in rooms and a 12-hr light/dark cycle was maintained. The animals were kept in suspended steel cages with wire-mesh fronts and floors and were given water and stock diet.

The rats have fasted overnight with free access to water before administration of drugs. Suspension of FUR was prepared in 1 % Carboxymethyl Cellulose (CMC) solution. After a single oral administration of 20 mg/kg of Frusemide blood samples were collected from the retro-orbital plexus sinus at different time-points (15 min, 30 min, 1 h, 2 h and 5 h). Blood samples were transferred in pre-treated tubes with anticoagulant and centrifuged at 3500

rotations/min for 10 min in a cooling centrifuge at a constant temperature of 4 °C. The separated plasma was transferred in Eppendorf microtubes and kept on-20°C until analyzed. All the samples of the same animal were analyzed on the same day to avoid variation among analysis. Sample plasma concentration was determined by High-Pressure Liquid Chromatography (HPLC). An HPLC (Shimadzu, SPD 20A, UV visible detector) and RP-C18 column (5 µm particle size) was used. The RP-HPLC system was equipped with LC CHROM software for data processing. The method was developed using a HIQ SIL, C18 (250×4.6 mm, µm) column. The mobile phase was used for the preparation of drug samples throughout the analysis. For preparing the mobile phase 50 mmol phosphate buffer (pH adjusted to 3.0) and acetonitrile were mixed together in the ratio of 50:50% v/v. It was filtered before use through 0.45 µ membrane filter and then degassed ultrasonically for 15 min. Flow rate employed was 1.0 ml/min. Detection was carried out at 283 nm at 25 °C.

RESULTS AND DISCUSSION

Determination of the drug: polymer ratio

Drug: Polymer ratio optimization study showed opaqueness in pure FUR sample after storage for a period of 24 h at room temperature indicating the occurrence of recrystallization during storage. This was possibly due to the free movement of FUR molecules during storage leading to nucleation and recrystallization. Whereas samples containing drug: polymer in the ratio of 1:1 to 1:3 observed clear after storage. It designates the importance of selected polymers to hold the solubilized form of FUR during storage. FUR was found stable and solubilized in all polymer ratios of 1:1 to 1:3.

Evaluation of SD granules

The recommended dissolution media for FUR tablet is pH 5.8 phosphate buffer [27]. As eudragit EPO is soluble below pH 5, saturation solubility was determined in 0.01N HCL with 2% SLS instead of water. The solubility of all SD was observed about 0.15±1.2 mg/ml compared to 18±1.5 µg/ml of pure FUR.

Saturation solubility of all solid dispersions was increased compared to pure FUR. All three drug: polymer ratios revealed a similar improvement in saturation solubility, so 1:2 ratio was finalized for further development. 1:1 and 1:3 ratios were not finalized due to the processing risk and pill burden due to the increased weight of tablets respectively. The probable reason for solubility enhancement was the formation of a solid solution and conversion of the drug into an amorphous form.

When the HME process was tried at 70 °C the high % torque (More than 70%) and friction noise of the screw was observed. So, HME processing was completed at increased temperature by 10 °C i.e. 80 °C which gives optimum % torque (less than 60%) and no noise of screws. As the concentration of plasticizer increases the % torque and screw friction noise decreases.

DSC and XRD data of all SD samples shows the absence of a sharp peak mostly observed due to crystalline form. FTIR values of samples were similar to that of pure drug. Comparative DSC, XRD thermograms and FTIR values of FUR and SD are presented in fig. 1, 2 and table 2 respectively.

Soluplus is polymeric solubilizer with an amphiphilic chemical structure, which is particularly developed for solid solutions. Due to its bifunctional character, it is able to act as a matrix polymer for solid solutions and is capable of solubilizing poorly soluble drugs in aqueous media [28].

Additionally, specific interactions of the polymer with itself, the drug, and the aqueous medium can result in a range of solubilizing structures, including micelles, colloids, and ionic complexes. Examples of such solubilizers include soluplus (BASF), affinisol (Dow), eudragit E, and eudragit L 100-55 (Evonik) [29].

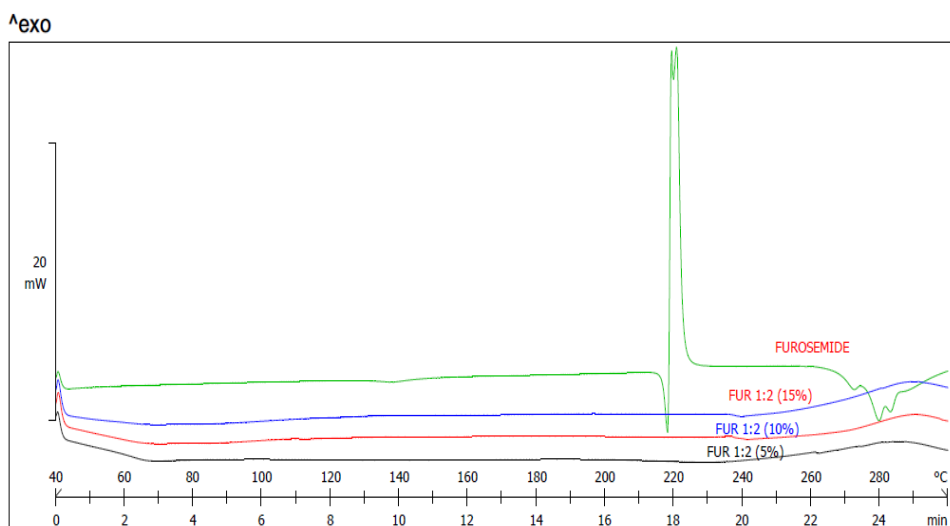


Fig. 1: DSC thermograms of pure FUR (drug), HME formulations of drug: polymer ratio 1:2 (5%, 10%, 15% PEG)

DSC study enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic or exothermic phase transformations). DSC thermogram of FUR shows its melting at 218 °C as presented in fig. 1.

Thermograms showed a clear, sharp and symmetric peak of FUR. HME granules of D: P 1:2 ratio with 5, 10 and 15 % of plasticizers showed single Tg with no other peak in thermograms endorsed the complete conversion of crystalline form to amorphous due to its solubilization in a polymeric matrix.

Glass transition temperature (T_g) of eudragit EPO and soluplus were 48 °C and 71 °C respectively [13, 15]. Due to lower T_g of both polymers, they melted easily at 80 °C which was the minimum possible processing temperature. FUR was solubilized and distributed uniformly in the molten mass with the help of rotating screws and mixing zone assembly of hot melt extruder. The possibility of FUR degradation during HME processing was minimized as it was exposed to a temperature for a short duration of time.

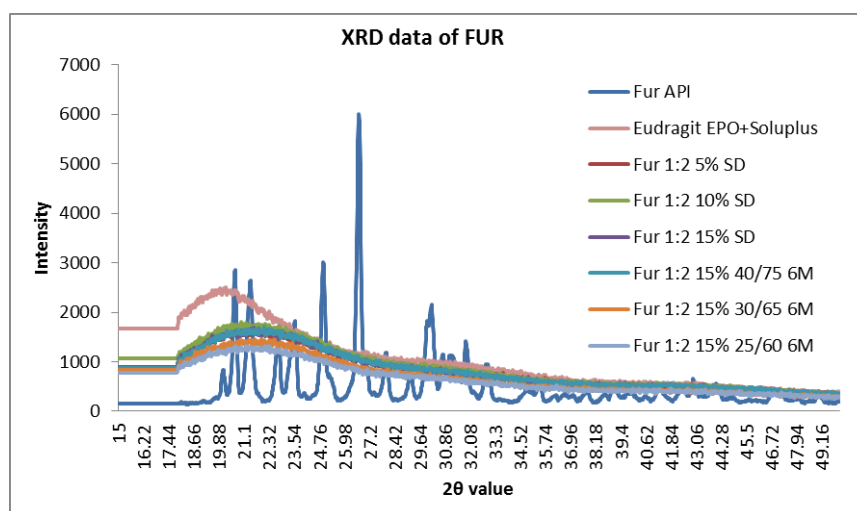


Fig. 2: XRD of pure FUR (drug), a mixture of polymers, HME formulations of drug:

Polymer ratio 1:2 (5%, 10%, 15% PEG and polysorbate) and stability samples of F6 at 6-mo time point

XRD is a fundamental technique used to detect a crystalline form of substance and data shows that FUR was in crystalline form. The absence of sharp peaks in the polymer sample confirmed their amorphous nature. In fig. 2, XRD data shows sharp peaks of FUR and absence of peaks in SD samples confirmed the amorphous form of FUR after HME.

FTIR has been used to assess the interaction between the carrier and guest molecules in the solid state. During the SD preparations, there may be a peak band shift in the absorption spectrum of the guest. However, some of the changes are very subtle, requiring careful interpretation of the spectrum [30]. FTIR spectra of FUR showed

similar peaks like its standard values as mentioned in table 2. This study was conducted to explore any interaction or incompatibility between drug and excipients. Data shown in table 2 indicates that there was no change in key functional groups of FUR even after HME processing at 80 °C compared to pure drug. FTIR spectrum of FUR and formulations showed similar characteristic peaks as per the standard values so confirmed the absence of chemical interaction between drug and excipients during and after HME processing. The important aspect of HME process was to set the minimum possible temperature to avoid any chemical change in functional groups and chemical degradation. FTIR data assured that 80 °C was the desired temperature to run the HME process smoothly without any chemical change in FUR. Moreover, all the spectra showed no peaks other than those assigned for FUR and polymers.

Table 2: FTIR values of pure FUR and optimized HME formulations (F6)

Chemical group	The standard range of absorbance bands (cm ⁻¹)	Reference no*.	Absorbance band values of FUR (cm ⁻¹)	Observed absorbance band in a formulation (cm ⁻¹)			Absorbance band (cm ⁻¹) of formulation F6 (6M stability)		
				F4	F5	F6	25 °C and 60%RH	30 °C and 65%RH	40 °C and 75%RH
N-H bending	1591		1592.91	-	-	1610.27	1613.16	1614.13	1610.27
S=O stretching of sulfonamide	1140, 1318		1144.55, 1324.86	1154.19, 1333.53	1148.4, 1332.57	1159.97, 1333.53	1164.79, 1338.36	1149.37, 1338.36	1155.15, 1338.36
Stretching vibrations of SO ₂ NH ₂	3260	31	3285.14	3241.75	3219.58	3231.15	3236.93	3214.75	3237.9
Non bonded aromatic amino group and a sulfonyl amide group	3500-3200		3285.14, 3351.68, 3400.85	3241.75	3219.58	3231.15	3236.93	3214.75	3237.9
Bending vibration of the amino group	1665		1674.87	1677.77	1671.23	1675.84	1681.62	1681.62	1681.62

*Reference no. mentioned belongs to the standard range of absorbance of different chemical, groups of FUR

Tablet evaluation

Table 3: Tablet evaluation data

Parameters	Hardness (kp/cm ²)	Friability* (%w/w)	Disintegration (min)	% drug release at 45 min in 0.01N HCL with 2% SLS	% drug release at 15 min in pH 6.8 phosphate buffer
F4	5.95±1.8	0.54	2.3	99±3.5	3.2±2.5
F5	5.80±2.2	0.45	2.4	102±4.2	2.8±3.8
F6	6.0±2.5	0.60	2.1	103±3.3	3.8±4.2
F6 (S1)	6.2±3.5	0.50	2.3	98±3.8	4.2±4.5
F6 (S2)	6.0±4.1	0.48	5.8	97±4.0	3.8±3.5
F6 (S3)	5.9±3.8	0.52	6.0	99±3.7	4.0±3.6

All values expressed as mean±SD, where n=3, *n=20, S1=storage condition 25 °C±2 °C and 60 %±5 %RH, S2=storage condition 30 °C±2 °C and 65 %±5 %RH, S3= storage condition 40 °C±2 °C and 75 %±5 %RH.

All compression parameters were satisfactory and well within the limit. The weight of the tablet was targeted as mentioned in table 1. The tensile strength of all formulations was targeted about 6.0 kp/cm² to achieve the desired disintegration time of less than 3 min and friability of less than 1% w/w as shown in table 3.

Tablets were disintegrated by erosion mechanism where it didn't swell but disintegrated rapidly. All formulations complied the fineness of dispersion test as well [32].

All three formulations irrespective of the different concentration of plasticizers showed more than 85 % release in 45 min, whereas

marketed formulation showed more than 85 % release in 60 min in 0.01N HCL with 2%SLS. Drug release of test formulations in pH 6.8 buffer was observed less than 10% release in 15 min, whereas marketed formulation showed about 85 % release. Restricted drug release of test formulations in pH 6.8 buffer assured the masking of bitter taste compared to the marketed formulation.

As pH of saliva is about 6.75-7.00 [33] drug release in pH 6.8 phosphate buffer utilized to estimate bitter taste inpatient. As a restricted drug release observed in this buffer, no bitter taste will be experienced by patients.

Table 4: Comparative PK parameters of FUR pure API and its HME granules (F6)

	T _{max} (h)	C _{max} (µg/ml)	AUC _{last} (h*µg/ml)	AUC _{inf,obs} (h*µg/ml)
Pure FUR				
Mean	0.50	8.10	16.70	22.00
SD	0.00	0.20	0.50	1.10
CV%	0.00	2.00	3.00	5.00
HME Granules				
Mean	0.50	10.90	21.60	25.20
SD	0.00	0.20	0.70	1.10
CV%	0.00	1.90	3.00	4.00

All values expressed as mean±SD, where n=6

Stability study

When tablets stored in the accelerated and intermediate storage condition DT of tablets increased up to 6 min compared to initial results of less than 3 min. Samples of long term storage condition disintegrated in 2.3 min. Dissolution of all samples was satisfactory. Tablets showed more than 85 % drug release in 0.01N HCL with 2 % SLS at 45 min.

XRD study of stability samples shown in fig. 2 revealed the absence of sharp peaks of a crystalline drug and recrystallization even after 6 mo of storage conditions. FTIR data shown in table 2 confirmed no change in chemical groups of FUR during stability study. At accelerated and intermediate stability conditions (3 mo and 6 mo), due to low T_g of eudragit EPO, HME granules might have melted

partially to make tablets harder and less porous, which lead to increased DT however targeted dissolution in 0.01N HCL with 2 % SLS was achieved in 45 min. Based on stability data it was concluded that the formulation was stable at long term condition, so the product's proposed storage condition would be "Store below 25 °C" [34].

Animal study

The retention time of FUR was observed at 4.11 min. A Linear equation used for calculation was $Y = 6916.1X + 6497.8$.

All pharmacokinetic (PK) parameters as the outcome of the animal study presented in table 4 and fig. 3.

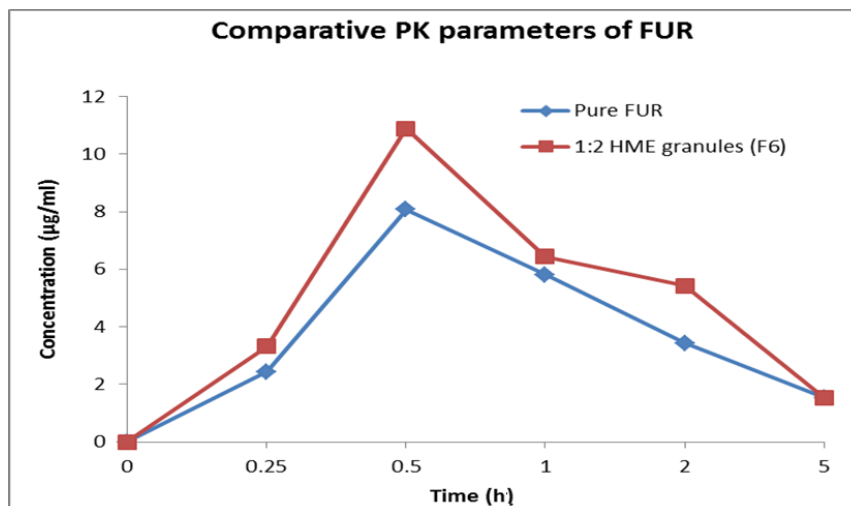


Fig. 3: Comparative PK parameters of FUR pure API and HME granules (F6)

Faster and increased absorption of FUR from HME granules were observed in the animal study. HME granules contained an amorphous form of FUR embedded in the polymer matrix of eudragit EPO and soluplus. Additionally, surfactants used in the HME process. Surfactant like Polysorbate 80 also exhibits Pgp inhibition activity. A cumulative effect of all these factors resulted in increased absorption of FUR at a fast rate. As per literature FUR exhibit about 60-70 % of oral bioavailability [35]. The total absorption of FUR from HME granules was enhanced by about 30 % compared to pure FUR. In humans, FUR is more rapidly absorbed from the upper gastrointestinal (GI) tract following dissolution in the stomach. In case of animal study rapid absorption is observed when administered to the stomach, but slower when administered to the small intestine. The most rapid absorption occurred after administration to the stomach at a pH of 3 [4].

CONCLUSION

The present study demonstrated the designing and manufacturing of an age-independent pediatric dosage form using HME technology. FUR was hot melt extruded and embedded within a eudragit EPO and soluplus polymer matrix. D: P 1:2 ratio was adequate to convert the FUR into amorphous form and hold it during storage and stability study. A unique property of eudragit EPO restricts the release of bitter FUR in pH 6.8 phosphate buffer and allows fast and complete release in 0.01N HCL with 2 % w/w SLS. Proposed packing configuration protected the dosage form from moisture during stability study.

Prepared flexible chewable dispersible tablets can be swallowed intact or administered by dispersing in a sufficient quantity of water or converted into the syrup with the use of a small amount of water (less than 5 ml). This technology minimizes the challenges of oral dosage form like dose adjustment, accuracy in dose measurement, ease of administration, the requirement of dose administration tools, acceptance of the dosage by pediatric patients. This proposed dosage form achieved all the desired features of pediatric drug delivery.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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