ORIGINAL RESEARCH ARTICLE

Oral Disintegrating Tablets of Analgesic Drugs alone and in Combination for Pain Management

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Abstract

Oral disintegrating tablet (ODT) is the highly accepted oral drug delivery system due to its patient compliance. Pain is an unpleasant sensory and emotional experience usually treated with an analgesic. As the rapid onset of action is desirable with analgesic drugs, the present research work was attempted to develop individual and combination ODTs of lornoxicam (LX) and paracetamol (PCM). Bitterness of PCM was masked by co-grinding with Eudragit EPO whereas the taste of LX was masked either by forming inclusion complex with beta-cyclodextrin induced circular dichroism or by solid dispersion with Eudragit E100. ODTs were prepared by direct compression method using croscarmellose sodium, crospovidone and low substituted hydroxy propyl cellulose as disintegrants. *In vitro* drug release studies of ODTs were performed in simulated salivary fluid, 0.1 N HCl and modified dissolution media. Selected formulations were assessed for *in vivo* disintegration time and taste masking in healthy human volunteers. The optimized formulation was characterized by differential scanning calorimetry and by powder X-ray diffraction. As indicated by the above findings, the goal of the present study of developing a patient friendly, taste-masked, rapid pain relieving formulations amenable to large scale manufacture has been successfully achieved.

Key words: Beta-cyclodextrin, Eudragit E, lornoxicam, oral disintegrating tablets, paracetamol

INTRODUCTION

Though drug and dosage form development are going toward new dimensions, the immediate release dosage form still keeps its glance due to its instant therapeutic response and patient compliance. Among the immediate release dosage forms orally disintegrating dosage forms stimulated generic companies and researchers to develop new drug moieties into oral disintegrating tablets (ODTs) and converting already existing drugs into patient compliant ODTs. Using ODT technology, the generic companies can extend the patent life and market exclusivity of an established drug boosts the value of a brand, fending off generic erosion and thereby increasing revenues. ODT releases the medicament in the mouth for absorption through local or mucosal tissue and through pregastric, gastric and postgastric segments of the gastrointestinal tract.[1,2]

Lornoxicam (LX), a congener of tenoxicam, is a new nonsteroidal anti-inflammatory drugs (NSAIDs) belonging to the oxicam class. It is a strong analgesic and anti-inflammatory NSAID as compared to other NSAIDs. It is used in musculoskeletal and joint disorders and other painful conditions including postoperative pain.[3] LX is already available as immediate release film-coated tablets (4 mg and 8 mg) and injections (8 mg). Paracetamol (PCM) is widely and effectively used analgesic to reduce pain and fever. General Dosing Guidelines for PCM is orally or rectally 325–650 mg every 4–6 h or 1000 mg every 6–8 h.

The combination of LX and PCM gives complete relief from pain and associated inflammation by two different mechanisms and ensures quick onset of action and longer duration of action. Thus, the combination of LX with PCM is synergistic, safe and well-tolerated.[4] LX and PCM combination tablets are available in Indian market as

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immediate release tablets and not as ODT. The present study was aimed at development of ODT of the analgesic that may prove more useful in expediting its onset of action.

The various strategies tried in taste making include sweeteners, inclusion complexes or solid dispersions with polymers.[5,6] The bitter taste of substances can be reduced, or even completely eliminated if they form inclusion complexes of sufficient stability with the selected cyclodextrin.[7] An acid-soluble polymer Eudragit E (EE) is a cationic copolymer suitable for taste-making.[8] EE, having dimethyl aminoethyl methacrylate as its functional unit forms, is swellable and permeable at pH 5 or higher, yet insoluble, but dissolves rapidly at acidic pH values lower than 5 by forming salts. Consequently, EE will mask the taste of bitter drugs in mouth, and complete drug release would be possible in stomach as the polymer dissolves in acidic pH.

EXPERIMENTAL

Materials

Lornoxicam was the gift sample obtained from Glenmark Pharmaceuticals Ltd., Navi Mumbai, India. Beta–cyclodextrin (BCD) (Kleptose), Poly (butyl methacrylate, (2-dimethylaminoethyl) methacrylate, methyl methacrylate (Eudragit E 100 and EPO), Mannitol (Pearlitol SD 200), Microcrystalline Cellulose (Avicel PH112), Crospovidone (Polyplasdone XL-10), Croscarmellose Sodium (Acdisol), Low Substituted Hydroxypropyl Cellulose (L HPC-LH11), sucralose were generously gifted by Par Pharmaceuticals, Chennai. High-performance liquid chromatography (HPLC) grade methanol and acetonitrile were procured from Fisher Scientific. Distilled deionized water was used for all purposes. All other reagents and chemicals used were of analytical reagent grade.

Drug-excipient compatibility study

Fourier transform infrared spectroscopy (FTIR) for pure drugs, polymers used and blends were performed to test the compatibility between drug and excipients. FTIR spectra of samples were recorded on KBr disk method using FTIR-8400S Spectrophotometer with IR solution software (Shimadzu, Japan). Sample powder was thoroughly mixed, triturated with potassium bromide in a glass mortar with pestle and compressed into KBr disks in a hydraulic press (Technosearch Instruments, India). FTIR spectra of all the samples were recorded over a spectral region from 4700/cm to 400/cm using 20 scans with 4/cm resolution.

Taste masking of lornoxicam

Preparation of inclusion complex

Drug/BCD inclusion complex at weight ratios (1:1 g) and molar ratio (1:1 molar) were prepared by kneading method. Kneaded products were obtained by triturating LX and BCD in a glass mortar with the pestle by adding a small volume of purified water. The slurry obtained was kneaded for 45 min and then dried in vacuum oven at 35°C. Dried complex was passed through #60 ASTM sieve.

Preparation of solid dispersion

Solid dispersion was prepared by common solvent method by dissolving Eudragit E100 (30%w/w of drug) in a small volume of acetone and homogenized in a mechanical stirrer (RQ-122, Remi Motors Ltd., Mumbai, India) until complete dissolution occurred, to which LX was added and further stirred for 20 min, dried in vacuum oven at 35°C. Dried complex was passed through #60 ASTM sieve.

Taste masking of paracetamol

Taste-making strategy followed for PCM was by triturating it with Eudragit EPO in a glass martor with pestle for 15 min. The co-grind mixture was then sifted through #40 ASTM sieve.

Preparation of oral disintegrating tablet

Oral disintegrating tablet of LX was formulated with pure drug (F1) or BCD complex with 1:1 g ratio (F2) or BCD complex with 1:1 molar ratio (F3) or Eudragit solid dispersion (F4) equivalent to 4 mg of LX. PCM ODT was prepared with co-grind mixture of PCM and Eudragit EPO equivalent to 325 mg of PCM. Combination ODT was formulated with core formula of PCM ODT and solid dispersion of LX with Eudragit E100 equivalent to 4 mg of LX. ODTs were prepared by direct compression method. Drug/co-grind mixture of PCM/co-grind mixture of PCM and solid dispersion of LX was weighed and mixed with Pearlitol SD 200, Avicel PH 112, L HPC-LH11, Acdisol/Polyplasdone XL-10, Sucralose, Peppermint flavor and Aerosil 200. Mixed ingredients were sifted through ASTM sieve #40 and lubricated with magnesium stearate that was presifted through ASTM sieve #60. Compositions of different batches of LX ODT, PCM ODT are given in Tables 1 and 2, respectively.

The prepared blend was evaluated for bulk density, tapped density, compressibility index, Hausner ratio and angle of repose. ODTs were compressed on a 12 station multi tooling R&D tablet press machine GMP model (CEMACH Machineries Ltd., Gujarat, India). Lornoxicam ODT was compressed using 8 mm concave punches, upper punch embossed with "c" whereas PCM ODT and combination ODT were compressed using 12 mm FFBE tooling with break line on one side and plain on the other side.

Evaluation of oral disintegrating tablet

The compressed ODTs were evaluated for in process parameters like weight variation (Shimatzu Electronic Balance, Japan), thickness (Digital Vernier Caliper, Aerospace, China), hardness (Monsanto hardness tester, Magumps,

Table 1: Composition of LX ODT

Ingredients	mg/tablet
LX	4*
Mannitol (Pearlitol SD 200)	63.5
Microcrystalline cellulose (Avicel PH 112)	15
Hydroxy propyl cellulose, low substituted (L HPC-LH11)	3
Croscarmellose sodium (AcDiSol)	7.5
Sucralose	3
Peppermint flavor	2
Colloidal silicon dioxide (Aerosil 200)	1
Magnesium stearate	1

*For ODT with beta-cyclodextrin inclusion complex and ODT with solid dispersion of Eudragit E100, quantity equivalent to 4 mg of LX was taken and average weight adjusted to 100 mg by reducing the weight of mannitol. LX: Lornoxicam, ODT: Oral disintegrating tablet

Table 2: Composition of PCM ODT

Ingredients	mg/tablet
PCM	325.0
Poly (butyl methacrylate, (2-dimethyl aminoethyl) methacrylate, methyl methacrylate (Eudragit EPO)	65.0
Mannitol (Pearlitol SD 200)	30.0
Microcrystalline cellulose (Avicel PH 112)	15.0
Crospovidone (Polyplasdone XL-10)	15.0
Hydroxypropyl cellulose, low substituted (L HPC-LH11)	15.0
Colloidal silicon dioxide (Aerosil 200)	5.0
Sucralose	15.0
Peppermint flavor	10.0
Magnesium stearate	5.0

PCM: Paracetamol, ODT: Oral disintegrating tablet

Mumbai, India), friability (PSM Industries, Bengaluru, India) disintegration time (digital tablet disintegration test apparatus, model: VTD-AV, Veego Instruments Corporation, Mumbai, India), *in vitro* dispersion time, wetting time and water absorption ratio.[9,10]

Tablet crushing strength

Texture analyzer (TA XT plus, Stable Microsystems, UK; maximum load 50 kg) was used to measure the hardness of tablets. The tablet tensile strength was measured by compressing tablet in radial direction. For measuring the hardness of the tablets, the texture analyzer probe with 25 mm diameter aluminum cylinder was set in compression mode. The other parameters maintained were 2 mm/s pretest speed, 0.03 mm/s test speed, distance target mode with target distance of 1 mm. Tablet crushing strength was calculated as per USP-36 using the formula.[11]

For cylindrical tablets:

$$\sigma_x = \frac{2F}{\pi DH}$$

For convex-faced tablets:

$$\sigma_x = \frac{10F}{\pi D^2}\left[\frac{2.84H}{D} - \frac{0.126H}{W} + \frac{3.15W}{D} + 0.01\right]^{-1}$$

Where "σ_x" is tensile strength, "F" is the breaking force, "D" is the tablet diameter, "H" is the tablet thickness and 'W' is the central cylinder thickness (tablet wall height). The data reported are the mean of six individual determinations.

High-performance liquid chromatography analysis

The quantitative analysis of drugs was performed using an HPLC (Waters 2695 series, USA, PDA Detector (Waters 2996 PDA, USA) and an integrator (Empower). For ODT of LX, PCM and LX-PCM combination, buffer solution (mobile phase A) was mixed with acetonitrile (mobile phase B) in the ratio of 40:60. Sonicated and degassed for 10 min using sonicator. The stationary phase was Inertsil C-18 column, 250 mm × 4.6 mm, 5 µm GL Science, Japan. The effluent was monitored at 247 nm (for PCM) and 265 nm (for LX) simultaneously. The column temperature was 25°C. The injection volume was 20 µL. The flow rate was 1 mL/min, and the retention time was 7 min.[12,13]

Drug content and uniformity of dosage units

Oral disintegrating tablets were crushed and dissolved in 0.1 N sodium hydroxide, sonicated for 10 min and kept for cooling, made volume with water. The solution was filtered through 0.45 micron filter and diluted before HPLC analysis.

In vitro drug dissolution study

The dissolution experiment was performed in 900 ml of simulated salivary fluid and 0.1 N Hydrochloric acid using Lab India DISSO 2000 dissolution apparatus with autosampler at 37 ± 0.5°C with a paddle rotation speed at 50 rpm. For ODTs with solid dispersion with Eudragit E100 (SDEE), additional dissolution was performed in 750 ml of 0.1 N hydrochloric acid for 30 min followed by addition of 250 ml of 0.7 M dipotassium hydrogen orthophosphate buffer to the same dissolution vessel (buffer stage, pH 6.8), based on the media proposed by Gryczke *et al*. and Patel *et al*.[14,15] Dissolution was performed with paddle speed of 50 rpm, and the temperature was maintained at 37 ± 0.5°C. The samples collected through inbuilt 10 micron filter were diluted before HPLC analysis.

Evaluation of taste masking and in vivo disintegration time

Taste-masking was assessed by ten human volunteers from whom informed consent was obtained and they had

participated in the test under the supervision of a clinician and the study protocol was approved by Institutional Ethical Committee - Ultra College of Pharmacy, Madurai (UCP/IEC/2013–2014/29). Volunteers were asked to rinse their mouth with a cup of water (200 ml) before the test and instructed to move the dose against the upper part of the mouth with the tongue without biting. They were also instructed to spit the contents when the dose got disintegrated. Volunteers were asked to rate the initial taste, after taste, mouth feel, flavor and overall acceptability of formulations as given in Table 3.[16]

Differential scanning calorimetry

The powdered sample (2–3 mg) was hermetically sealed in aluminum pans and heated at a constant rate of 5°C/min, over a temperature range of 0–300°C. Thermogram of the samples was obtained using differential scanning calorimetry (DSC, Q20, TA Instruments, USA). Thermal analysis data were recorded using Universal Software. Indium standard was used to calibrate the DSC temperature and enthalpy scale. Aluminum pan with lid was used for all samples. An empty aluminum pan was used as reference.

Powder X-ray diffraction

The powder X-ray diffraction (PXRD) patterns were obtained from an X-ray diffractometer (Rigaku MiniFlex 600) working with Cu-Kα radiation and in 2θ range of 10–90° at 40 kV and 15 mA. The scan duration time was 10°/min with step size of 0.020. The diffracted radiation from the samples passed through 1.25° divergence slit and 0.30 mm receiving slit.

RESULTS AND DISCUSSION

Drug-excipient compatibility study

IR spectra of drugs, polymer and blends are given in Figure 1. The FTIR spectrum of LX showed a characteristic peak at 3132.50/cm corresponding to −NH stretching vibration. Intense absorption peak was found at 1645.33/cm due to the stretching vibration of the C=O group in the primary amide. The stretching vibrations of the O=S=O group appeared at 1084.03/cm, 1147.68/cm and aromatic C–N group stretching at 1327.07/cm. Other peaks were observed at 2924.18/cm and 2875.96/cm and indicate aromatic C–H stretching vibrations and peaks at 1624.12/cm, 1595.18/cm, 1546.96/cm indicate aromatic C=C stretching. The prominent peaks appeared at 829.42/cm corresponding to C–H aromatic ring bending and heteroaromatics and at 786.98/cm due to the C–Cl stretching vibration that indicates groups is matched with structure of drug and confirms the purity of the drug.

The spectrum of EE is dominated by the carbonyl (C=O) stretching vibration of alkyl ester at 1734.06/cm and the ester C–O stretching vibrations at 1242.20/cm. In addition, aliphatic amine C–N and C–O–C stretching was observed at 1149.61/cm and C–H stretching vibrations can be discerned at 2955.04/cm and 2821.95/cm. The spectrum of SDEE corresponds to the superimposition of LX and EE with no significant shift in the major peaks. This confirms the presence of LX in the complex.

Zhang *et al*. reported that the peak around 3067/cm was enhanced significantly for high soluble form of LX (Form II). Similar observation was found in FTIR spectrum of LX and SDEE indicating the presence of high soluble form II polymorph in drug and drug complex. Also, the results confirm the absence of polymorphic changes due to formulation procedure of LX solid dispersion.[17]

The FTIR spectrum of PCM showed a characteristic peak at 3325.39/cm corresponding to −NH stretching vibration.

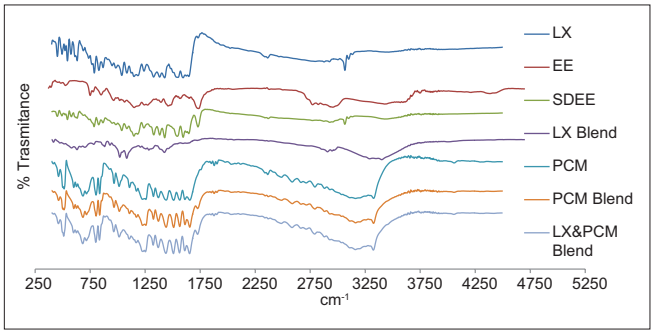

Figure 1: Infrared spectroscopy spectra of lornoxicam (LX), Eudragit E100, solid dispersion of LX with Eudragit E100; LX blend-LX oral disintegrating tablet (ODT) blend; paracetamol (PCM) ODT; PCM blend-PCM ODT blend and LX and PCM blend-combination ODT Blend

Table 3: Taste evaluation reference table

Parameters	Score of taste evaluation				
	1	2	3	4	5
Bitterness*	Extremely bitter	Highly bitter	Acceptable	Very slightly bitter	Not at all bitter
Sweetness*	Not at all sweet	Very slightly sweet	Acceptable	Highly sweet	Extremely sweet
Mouth feel	Very gritty	Gritty	Acceptable	Creamy	Very creamy
Flavour	Very unpleasant	Unpleasant	Acceptable	Pleasant	Very pleasant
Overall acceptability	Worst	Poor	Acceptable	Good	Very good

*Parameter accessed for initial taste and after bitterness

The characteristic absorption peak at 3161.43/cm was due to the presence of O–H stretching vibration. Absorption peaks observed at 1,654.98/cm, 1255.7/cm were due to the stretching vibrations of the C=O group and C–O group respectively. The stretching vibration of the aromatic C=C group appeared at 1610.61/cm, 1564.32/cm, 1508.38/cm and 1440.87/cm. The stretching vibrations of C−N group were observed at 1325.14/cm. Other peaks were observed at 2793.02/cm, 2665.71/cm and 2586.63/cm indicate aromatic C–H stretching vibrations and peaks at 966.37/cm and 684.75/cm indicate aromatic C–H bending vibration.

The prominent peak appeared at 1369.50/cm was due to O–H bending vibration. All these stretching and bending vibrations indicate groups present in the structure of PCM and confirm the purity of the drug.

The FTIR spectrum of all ODT blend designates that all the prominent peaks of the pure drugs were present in the spectrum that shows the absence of interaction between both the drugs and excipients.

Blend characterization

The taste-masked drugs were mixed with direct compressible excipients. The final lubricated blends were characterized for bulk density, tapped density, compressibility index, Hausner ratio and angle of repose. The results are given in Table 4. All the parameters analyzed showed satisfactory flow properties and compression characteristics.

Characteristics of oral disintegrating tablet

The results of the characterization of ODTs given in Table 5 show that the percentage weight variations for all batches were found to be within the maximum standard deviation of ±1.5 mg and within the USP limit. The thickness of the batches was ranged from 2.13 to 2.23 mm for LX ODT and 3.89–4.26 mm for PCM ODT and combination ODT. The hardness of all batches was in between 2 and 3 kg/cm^2 and also the results of tablet crushing strength indicate that ODTs possessed good mechanical strength with sufficient hardness. The % friability of all batches was below 0.5% that shows

Table 4: Blend characterization of ODTs

Parameters	Formulation description					
	LX				PCM	LX and PCM
	F1	F2	F3	F4		
Bulk density (g/mL)	0.539	0.589	0.60	0.586	0.498	0.509
Tapped density (g/mL)	0.761	0.692	0.673	0.680	0.679	0.694
Compressibility index (%)	29.2	14.88	10.84	17.64	26.67	26.67
Hausner ratio	1.41	1.17	1.12	1.16	1.36	1.36
Angle of repose	28°07’	29°74’	29°39’	28°26’	20°32’	20°62’

F1: ODT with drug only, F2: ODT with beta-cyclodextrin inclusion complex (1:1 g ratio), F3: ODT with beta-cyclodextrin inclusion complex (1:1 molar ratio), F4: ODT with solid dispersion of Eudragit E100. ODT: Oral disintegrating tablet, LX: Lornoxicam ODT, PCM: Paracetamol ODT, LX and PCM: Combination ODT

Table 5: Characterization of ODTs

Parameters*	Formulation description					
	LX				PCM	LX and PCM
	F1	F2	F3	F4		
Weight (mg)	100.1±1.0	101.5±1.5	100.4±1.2	101.1±0.9	500.9±1.36	500.9±1.44
Thickness (mm)	2.14±0.01	2.22±0.01	2.21±0.01	2.16±0.01	3.95±0.06	4.21±0.05
Hardness (kg/cm^2)	2.40±0.21	2.20±0.48	2.35±0.34	2.30±0.26	2.80±0.35	2.70±0.26
Tablet crushing strength (N/mm^2)	1.16±0.06	1.04±0.04	1.11±0.05	0.99±0.14	0.31±0.04	0.28±0.02
Friability (%)	0.42	0.28	0.36	0.32	0.20	0.25
Disintegration time (sec)	7.4±0.11	7.3±0.05	7.4±0.21	7.4±0.15	7.3±0.25	7.4±0.26
Wetting time (sec)	16.8±0.21	18.5±0.18	18.4±0.15	27.4±0.86	20.5±0.43	20.6±0.35
Water absorption ratio (%)	231.5±2.02	195.4±0.93	165.5±1.59	109.0±1.36	93.2±2.11	82.2±0.26
In-vitro dispersion time (sec)	7.7±0.43	9.3±0.07	10.1±0.10	8.5±0.30	10.4±0.18	11.2±0.75

*Values represent the mean±SD and *n*=10 for weight, thickness, tablet wall height, hardness and *n*=6 for others. F1: ODT with drug only, F2: ODT with beta-cyclodextrin inclusion complex (1:1 g ratio), F3: ODT with beta-cyclodextrin inclusion complex (1:1 molar ratio), F4: ODT with solid dispersion of Eudragit E100. ODT: Oral disintegrating tablet, LX: Lornoxicam ODT, PCM: Paracetamol ODT, LX and PCM: Combination ODT, SD: Standard deviation

that ODTs are mechanically stable and could handle the rigors of transportation and handling. The FDA recommends a disintegration time of 30 s or less for ODTs based on the USP disintegration test.[18] Disintegration time of all the batches was between 7 and 8 s and *in-vitro* dispersion time was 9–12 s satisfying the recommendations for ODT.

The results also reveal that water absorption ratio of LX ODT increases with decrease in wetting time. Wetting time is closely related to the inner structure of tablets and hydrophilicity of the excipients, which might be the reason for higher wetting time of F_4 with hydrophobic EE (26–29 s) compared to F_2 and F_3 with BCD inclusion complex (18–19 s). No significant differences were observed in wetting time and water absorption ratio of PCM ODT and combination ODT.[19,20]

Drug content and uniformity of dosage units

Drug content of all the batches was ranged from 98.0% to 102.3%. The uniformity of dosage unit of all six formulations showed L1 value <15 indicating the accuracy and uniform distribution of drug present in the ODT formulations.

In vitro drug dissolution study

In vitro drug release studies of all four formulations were performed in simulated salivary fluid and 0.1N Hydrochloric acid for 30 min to simulate the dissolution at mouth followed by gastric environment. Dissolution profile of LX ODT is shown in Figure 2. The results indicate that drug solubility and dissolution was enhanced by the inclusion complex with BCD. ODT with inclusion complex 1:1 molar ratio (F_3) showed better release profile than 1:1 g ratio (F_2). LX is having pH dependent solubility and highly soluble in alkaline media that is reflected by the limited dissolution in 0.1 N Hydrochloric acid. Though Eudragit E100 is soluble at acidic pH, solubility of LX is very less in acidic condition. Hence, the dissolution rate and extent of LX from ODT with SDEE (F_4) was on lower side in 0.1 N hydrochloric acid.

Dissolution profile of PCM ODT and combination ODT is shown in Figure 3. Release of PCM from PCM ODT and Combination ODT in simulated salivary fluid was slower at initial time points. The lesser rate of release at initial time points could be attributed to co-grinding of PCM with Eudragit EPO. Release of PCM from PCM ODT and Combination ODT in acid media showed rapid and complete release.

According to FIP/AAPS Guidelines for Dissolution for solid solutions and dispersions in oral dosage form, dissolution tests under nonsink conditions can be a predictive tool during formulation development as well as for batch-to-batch quality control.[21] To account for the faster emptying, the dissolution method was modified with a change in dissolution medium at an earlier stage that is, 30 min to a medium of pH 6.8. *In vitro* dissolution profile of LX from F4 and combination ODT showed complete release on changing pH of media from pH 1.2 (0.1 N HCl) to pH 6.8 indicated that the EE was dissolved and released all the drug content within 30 min and on changing to higher pH, in favorable dissolution condition drug dissolved completely.

Vincent *et al*. and Meyer *et al*., reported that finer the particle size, faster the gastric emptying. Solid dispersions lead to finest particle size in gastric environment.[22,23] Consequently, LX solid dispersion may empty fast.

Evaluation of taste masking and *in vivo* disintegration time

The results of taste evaluation are given in Table 6. PCM ODT and Combination ODT showed comparable *in vivo* disintegration time of 15–22 s. Among the LX ODT batches, two best formulations based on good dissolution profiles [Figures 3 and 4] were selected for taste evaluation in human volunteers. *In vivo* disintegration time of both the batches (13–17 s) was comparable with *in vitro* disintegration time (8–10 s). ODT with SDEE (F4) showed excellent bitterness masking whereas ODT with induced circular dichroism ICD (F3) showed high after bitterness that are correlated well with the *in vitro* dissolution profile of both the batches in simulated salivary fluid. Hence, formulation F4 was considered as the best formulation.

Further, to characterize the solid dispersion and to ascertain the absence of physical changes due to formulation process, DSC and PXRD studies were carried out on drug, EE, SDEE and blends of final formula.

Differential scanning calorimetry

Figure 4 shows the DSC curve of drugs, polymer and final lubricated blends of ODT. DSC curve of LX exhibited a small endothermic peak at 249.86°C with simultaneous sharp exothermic peak at 256.85°C, which is due to melting of LX with decomposition. A peak at 92.13°C indicates the loss of moisture in the sample. EE is amorphous in nature and exhibits a glass transition at 52.56°C which indicated the amorphous nature and stability of the polymer in the operation temperature.[24] DSC curve of SDEE exhibited broad endothermic peak at 219.72°C and exothermic peak at 236.85°C. The exothermic peak of solid dispersion showed noticeable broadening at lower temperature indicating the interaction with the polymer. A peak at 96.32°C indicates the loss of moisture in the sample. DSC of LX blend shows a small exotherm at 231°C is due to the presence of LX solid dispersion.

DSC curve of PCM exhibited a characteristic sharp endothermic peak at 180°C, which is due to melting of

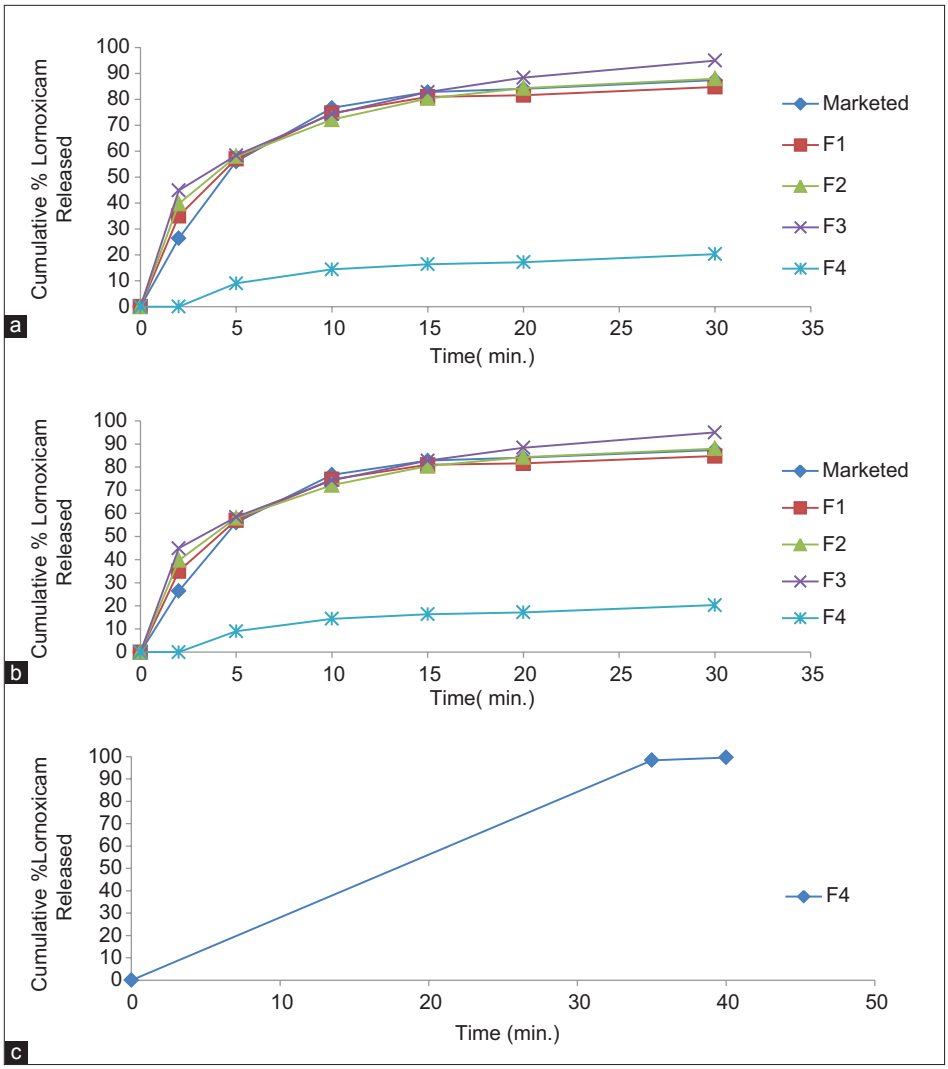

Figure 2: *In vitro* drug release profile of lornoxicam (LX) oral disintegrating tablet (ODT) in Simulated Salivary Fluid (a) 0.1 N HCl (b) and modified dissolution medium-acid stage followed by buffer stage (c) marketed-commercially available LX IR tablets; F1-ODT with drug only; F2-ODT with BCD inclusion complex (1:1 g ratio); F3-ODT with BCD inclusion complex (1:1 molar ratio); F4-ODT with solid dispersion of Eudragit E100

Table 6: Results of taste masking, as evaluated by a panel composed of ten human volunteers

Formulation	*In-vivo* disintegration time (s)	Average points by the human volunteers			
		Initial observation			
		Bitterness	Sweetness	Mouth feel	Flavour
LX (F3)	15.5±2.27	4.0	4.1	4.4	4.3
LX (F4)	15.5±1.96	4.8	4.6	4.2	4.8
PCM	18.6±3.92	4.5	4.5	4.4	4.9
LX and PCM	18.6±2.88	4.7	4.6	4.6	5.0
Formulation		**After 5 min**			
		Bitterness	**Sweetness**	**Overall acceptability**	
LX (F3)		2.4	2.8	2.2	
LX (F4)		4.5	4.4	4.7	
PCM		4.5	4.5	4.7	
LX and PCM		4.6	4.6	4.7	

LX (F3): Lornoxicam ODT with beta-cyclodextrin inclusion complex (1:1 molar ratio), LX (F4): Lornoxicam ODT with solid dispersion of Eudragit E100. ODT: Oral disintegrating tablet, LX: Lornoxicam ODT, PCM: Paracetamol ODT, LX and PCM: Combination ODT

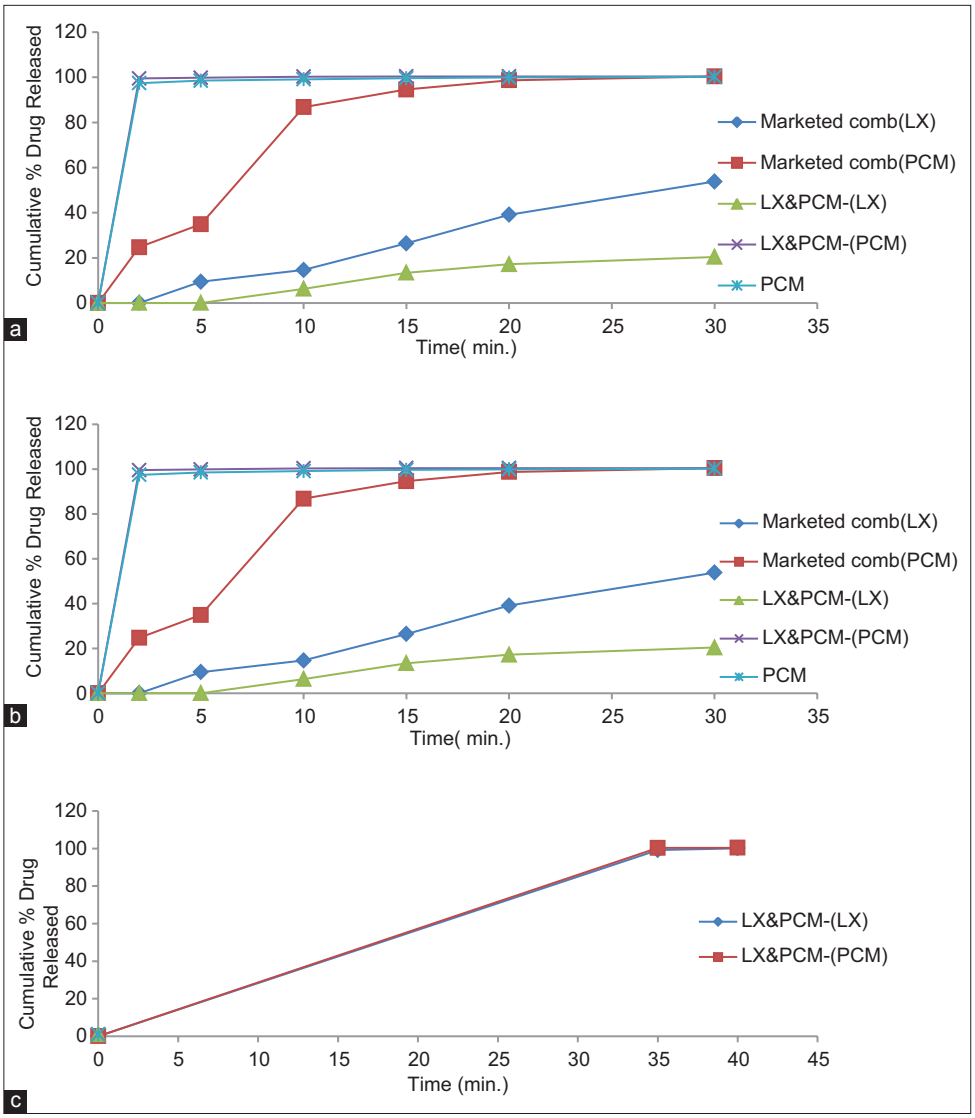

Figure 3: *In vitro* drug release profile of paracetamol (PCM) oral disintegrating tablet (ODT) and combination ODT in simulated salivary fluid (a), 0.1 N HCl (b) and modified dissolution medium-acid stage followed by buffer stage (c) marketed combo-commercially available combination IR tablets; lornoxicam (LX) ODT; PCM ODT; LX and PCM–combination ODT

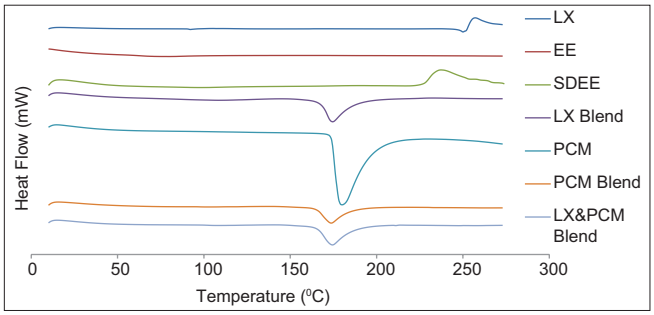

Figure 4: Differential scanning calorimetry profiles of lornoxicam (LX), Eudragit E100, solid dispersion of LX with Eudragit E100; LX blend-LX oral disintegrating tablet (ODT) blend; paracetamol (PCM) ODT; PCM blend-PCM ODT blend and LX and PCM blend-combination ODT blend

PCM. According to Zimmermann and Baranovic, PCM in polymorph form I melt above 170°C.[25] In DSC curve of pure PCM and ODT blend endothermic peak appears above 170°C, proves the existence of polymorph form I.

DSC of combination ODT blend showed characteristic endotherm at 174.38°C that is due to the presence of major proportion of PCM. A small endotherm and exotherm at 211°C and at 249°C respectively were due to the presence of LX in solid dispersion.

X-ray powder diffraction

X-ray powder diffraction pattern of drugs, polymer and blends are shown in Figure 5. PXRD of LX reveals many distinct reflections in its diffractogram, pointing to its highly crystalline nature. Various diffraction peaks of the drug crystals can be traced in the spectrum of the pure drug at 2θ values of 13.0, 13.4, 13.9, 18.8, 21.5, 22.9, 24.6, 25.4,

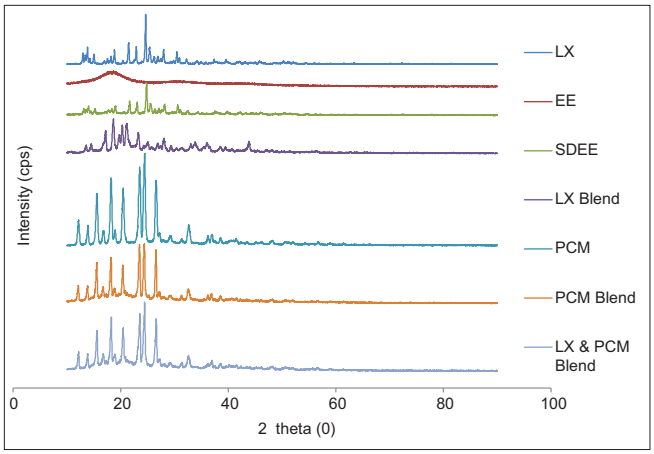

Figure 5: X-ray diffraction pattern of lornoxicam (LX), Eudragit E100, solid dispersion of LX with Eudragit E100; LX blend-LX oral disintegrating tablet (ODT) blend; paracetamol (PCM) ODT; PCM blend-PCM ODT blend and LX and PCM blend-combination ODT blend

27.5 and 30.5. The significant X-ray diffraction patterns demonstrated the existence of form II polymorph in LX.

Eudragit E showed halo patterns that are typical of amorphous substances.[26] Diffraction pattern of SDEE showed reduced peak intensity and peak height indicate the loss of crystallinity. The broadened peaks and increased peak width indicate the reduction in particle size.

The diffraction patterns of the PCM ODT blend showed identical crystalline peaks to those of pure PCM but at a lower intensity and reduced peak height. The XRD patterns of PCM ODT blend showed increased amorphous trends compared with the pure PCM due to the drug-EPO co-grind mixture and other excipients.[27]

LX peaks were not found in PXRD of combination ODT blend. This might be due to the less drug content (0.8% per tablet) which is also present as a solid dispersion with EE. All the PCM peaks observed with reduced intensity. PCM present in monoclinic (Form I) polymorph and the PXRD results of individual and combination ODT blend proves that process and procedure did not change the PCM polymorph.

CONCLUSION

The present study has revealed the use of a novel and simple method taste masking technique for PCM of co-grinding with a saliva-insoluble acrylic polymer compared to hot extrusion technique[27] reported earlier. Also, the combination analgesic PCM with LX ODT has also been studied for the first time in the current study. To conclude, the developed LX ODTs with solid dispersion of drug in Eudragit E 100 (F_4) have acceptable taste when compared to ODT with inclusion complex with BCD (F2 and F3) whereas the bitterness of PCM in ODT could be masked by simple co-grinding process of drug with Eudragit EPO. The formulated ODTs have sufficient mechanical strength and rapid disintegration time which on administration will result in rapid pain relief and could be used as an alternate to the commercially available immediate release tablets resulting in improved patient adherence.

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