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Research Article

ENHANCEMENT SOLUBILITY AND DISSOLUTION RATE OF PARACETAMOL AND IBUPROFEN BY COAMORPHOUS PARTICLES USING MICROWAVE TECHNIQUE

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ABSTRACT

Objective: The objective of the present study was to the preparation of a coamorphous (COAM) system of paracetamol (PA) (Biopharmaceutics Classification System [BCS] Class-III) and ibuprofen (IB) (BCS Class-II) for enhancement of solubility and dissolution of IB.

Methods: The COAM system was prepared by chemical electric magnetic field microwave-assisted method. Several batches with different concentrations of COAM PA and IB were prepared at constant temperature, pressure, and holding time. Solubility studies were carried out in different pH condition and the batch, which show the highest increase in solubility 98.00%. COAM samples were characterized by solubility, dissolution, Fourier transform infrared (FTIR), X-ray diffraction (XRD), and differential scanning calorimetry (DSC) studies.

Results: FTIR results showed evidence of molecular interactions between both the drugs. Maximum increase in aqueous solubility of IB was seen 500:200 mg dose ratio (COAM) batch E in phosphate buffer 7.4. The COAM system increased solubility of IB about 98.70%. The solubility and dissolution rate of IB were also enhanced. *In vitro* drug release study, 100% of the drug was released within 120 min. Thus, saturation solubility and dissolution rate of IB were found significant improved unlike PA. XRD and DSC results confirmed amorphization of IB. FTIR results evidenced hydrogen bonding interactions between both the drugs. In accelerated stability studies, powder XRD and DSC results demonstrated insignificant changes, thus confirming successful stabilization of IB by PA.

Conclusion: Hence, it concluded that the study of COAM of PA and IB successfully prepared by microwave-assisted method to enhance solubility, dissolution, stability, and bioavailability.

Keywords: Chemical electric magnetic field, Coamorphous, Ibuprofen, Optical response curve, Paracetamol, Saturation solubility.

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INTRODUCTION

Drugs solubility and dissolution are the major factors in the case of pharmaceutical formulations lead to variable oral bioavailability of poorly soluble drugs [1]. Various methods are used to increase the solubility of poorly soluble drugs [2]. The amorphous form of pharmacologically active materials has received considerable attention because it represents the most energetic solid state of a material and thus provides the biggest advantages in terms of enhance dissolution rate and bioavailability [3,4].

Coamorphous (COAM) system is the combination of two different molecules, which improves solubility, stability, and bioavailability of drug. The COAM is characterized by the combination of two or more low-molecular-weight components that form homogeneous COAM single-phase system. Various techniques are used for the preparation of COAM such as quenching, solvent evaporation, ball milling, spray drying, freeze-drying, fusion method, hot-melt extrusion, and supercritical fluid method. [5-7].

Ibuprofen (IB) (2-(4-(2-methylpropyl)phenyl)propionic acid) is a widely used nonsteroidal anti-inflammatory drug having poor solubility and high permeability (Biopharmaceutics Classification System [BCS] II) and limited bioavailability [8]. However, it has a poor processability due to its low glass transition temperature (Tg), thus difficulty in the design of solid dosage forms [9]. So as to overcome its aforesaid problems, COAM particle prepared using microwave techniques can be increased physical stability of amorphous drugs [10]. The number of products available in the market as a COAM system has long-term stability problems, difficulty in manufacturing and processing into dosage forms. Thus, attempt has been made to the development of stable COAM systems and ensuring feasibility of pharmaceutical formulation [11-13].

Keeping in view benefits reaped from appropriate COAM combinations of two drugs, we have attempted to improve processability, solubility and *in vitro* dissolution, and amorphous state stability of IB using paracetamol (PA), which is a BCS Class III drug. Clinically relevant combinations of both drugs are available in the market and have been widely recommended for analgesic, antipyretic, and anti-inflammatory conditions. Predominantly available five clinical dose combinations, namely, 500 mg:200 mg, 475 mg:125 mg, 325 mg:400 mg, 125 mg:100 mg, and 100 mg:100 mg of PA: IB were process with microwave techniques for coamorphism.

Microwave irradiation technique is green and cost effective for the production of molecular dispersion. Microwaves are electromagnetic waves containing electric and magnetic field component [14-17]. Chemical electric magnetic (CEM) field microwave required less time for reaction and prevents degradation of drug. The reaction can be held at constant temperature for the duration of time. Nowadays, it is mostly used in the preparation of solid dispersion, coating of tablets, drying of granules, and in the semisolid formulation. The microwave heating is based on the mechanism of conversion of electromagnetic radiation into heat energy, which produces rapid and homogeneous heating to reaction mixture [18]. Therefore, the present work on the preparation

of COAM system and investigate their results by solubility, Fourier transform infrared (FTIR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and *in vitro* dissolution studies.

METHODS

PA and IB drugs were procured from Sanofi India Ltd., Mumbai. All other chemicals were of analytical grade.

The COAM system of IB and PA was prepared by the process of CEM field microwave. The mixture of pure IB and PA up to 200 mg binary mixture of different concentrations was carried out. A 125 ml glass test tube was used for CEM field microwave reaction. Initially, binary mixture of drug was reacted for different time periods at different pressure, later both the drugs of different concentrations were mixed in 200 mg and fed to test tube, which occupied 25 ml of volume. It was reacted at constant parameters temperature – 90°C, pressure – 15 psig, run time – 10 min, and hold time – 20 min in CEM field microwave. The concentrations of binary mixture were 100+100 mg, 125+100 mg, 325+400 mg, 500+400 mg, and 200+500 mg of IB and PA, respectively, in 200 mg per volume. Trials were taken for optimization of temperature, pressure, and time. All the samples were stored in desiccators until further use.

Selection of dose of drugs and time period of CEM field microwave reaction

Five doses were selected, one containing more amount of IB and the other two containing less amount of IB, as shown in Table 1. Constant parameters for CEM field microwave reaction are shown in Table 2.

Characterization of COAM CEM field microwave reacted batches

The characterization of COAM batch was carried out by FTIR, XRD, and DSC.

FTIR spectrophotometry

FTIR spectrum shows the fundamental peaks corresponding to the chemical nature of the drug and excipients. FTIR studies were carried out to determine any possible interaction among drug and excipients used. IR absorption spectrum of PA and IB was determined by FTIR (Jasco-V-530 model). Spectra were recorded over the wavenumber 400–4000 cm^{-1}. Infrared spectrums of pure drug and optimized batches were recorded. From the spectrum analysis, the compatibility of ingredients in the formulations was found out by Bello *et al*. [19].

XRD studies

The XRD patterns were recorded on X-ray diffractometer (PW 1729, Philips, the Netherlands). Samples were irradiated with monochromatized Cu-Ka radiation (1.542 Å) and analyzed from 50 to 500 2θ. The voltage and current used were 30 kV and 30 mA, respectively. The XRD procedure to estimate the degree of crystallinity was based on the measurement of the total scattering and the scattering from the crystalline region of formulations and pure drug [20-23].

Table 1: Drug concentration in various formulations

Batches	Drug concentration (mg)	
	IB	PA
A	100	100
B	100	125
C	400	325
D	125	475
E	200	500

Table 2: Constant parameters for chemical electric magnetic microwave reaction

S. No.	Parameters	Values
1	Temperature	90°C
2	Pressure	15 psig
3	Run time	10 min
4	Hold time	20 min

DSC

DSC studies were carried out using (Mettler-Toledo DSC 821 instrument). Indium and zinc standards were used to calibrate the DSC temperature and enthalpy scale. The PA and IB optimized batch and pure drug were hermetically sealed in aluminum crucibles and heated at a constant rate of 10°C/min over a temperature range of 25–300°C. Inert atmosphere was maintained by purging nitrogen gas at flow rate of 50 ml/min. An empty aluminum pan was used as standard reference and results were obtained in triplicates for each sample [24,25].

Characterization of COAM CEM field microwave reacted batches

Crystallinity studies

FTIR, DSC, and PXRD have been extensively used for the study of percentage crystallinity and other thermal events at microscopic level studies of CEM field microwave reacted individual drug samples [26]. The percentages of crystalline material, present in the samples were calculated using Equation 1,

$$\% \text{ Crystallinity} = \frac{\delta \text{HmSD}}{\delta \text{HmDrug}} \times 100 \quad (1)$$

Where,

δHmCOAM is the melting enthalpy of the COAM sample (J/g), δHmDrug is the melting enthalpy of drug (J/g), and W is the weight fraction of drug in COAM system (here, W = 2/7 = 0.285 for IB and W = 5/7 = 0.714 for PA).

Saturation solubility

Solubilities of both the drugs were determined in distilled water and various pH, i.e., pH 1.2, pH 4.5, pH 6.8, and pH 7.2. Solubility of COAM samples of IB and PA was determined by adding excess amount of samples to 10 ml of water and samples were shaken using orbital shaker for 72 h at 37°C. Samples were further centrifuged at 7000 rpm for 10 min and supernatant was filtered through a 0.45 μ membrane filter, suitably diluted and analyzed using an ultraviolet (UV)–visible spectrophotometer at respective wavelength [27].

In vitro dissolution studies

In vitro dissolution kinetics of the individual pure drug samples was carried out in USP Type-II dissolution test apparatus. The dissolution medium was used 900 ml of acid buffer pH 1.2 and phosphate buffer

Table 3: Melting point of paracetamol and ibuprofen

Drug	Melting point	
	Reported	Observed
Ibuprofen	75–77.5°C	76–77°C
Paracetamol	169–171°C	169–170°C

Table 4: Saturation solubility of PA and IB in various pH

Media	PA saturation solubility (mg/L)	IB saturation solubility (mg/L)
Water	18,798.50	79.10
pH 1.2	18,724.00	49.50
pH 4.5	18,731.20	66.60
pH 6.8	1821.30	129.20
pH 7.4	1849.50	182.40

PA: Paracetamol, IB: Ibuprofen

pH 7.4 maintained temperature at 37.5±0.5°C. The paddle speed was kept constant at 100 rpm. Samples of 5 ml were withdrawn at specific time interval. The withdrawn samples were analyzed by UV spectroscopy at the 219 nm and 243 nm for phosphate buffer pH 7.4 and 260 nm and 248 nm wavelength for acid buffer pH 1.2 for IB and PA, respectively. The same amount of fresh medium was replaced at each time as amount withdrawn for respective dissolution media [28].

Stability studies

Stability studies of the potential tablet formulation were performed at accelerated condition (40°C±2°C, 75%±5% RH) and refrigerated (4°C±2°C) conditions as per ICH guidelines. The tablet formulation was placed in a stability chamber for stability study and samples were withdrawn after 3 months from the time of placing [29].

RESULTS AND DISCUSSION

IB and PA COAM systems were successfully prepared by simple, CEM field microwave method. Both solubility and bioavailability of drug are increased after the COAM.

Melting point

Melting point of IB and PA was determined by capillary method. The melting of IB and PA is given in Table 3. The observed melting points of drug were almost same as compared with reported peaks.

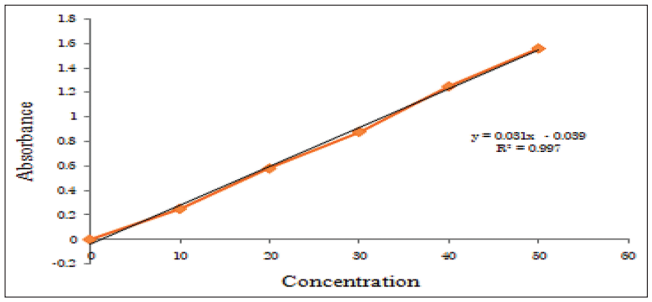

Fig. 1: Calibration curve of paracetamol in phosphate buffer pH 7.4

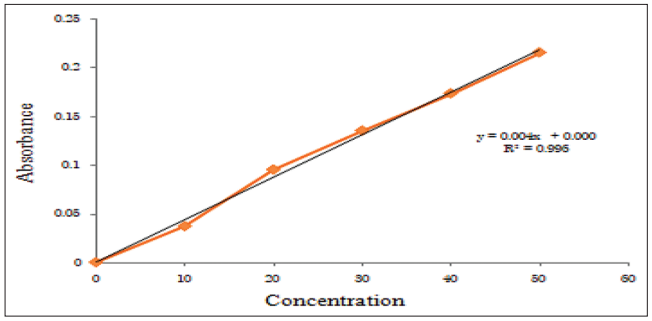

Fig. 2: Calibration curve of ibuprofen in phosphate buffer pH 7.4

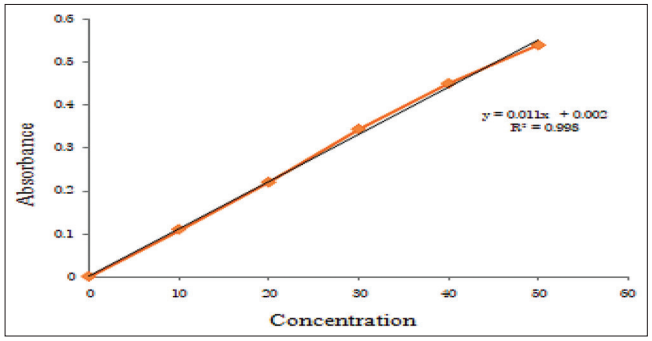

Fig. 3: Calibration curve of paracetamol in acid buffer pH 1.2

Saturation solubility

Saturation solubility studies of PA and IB drugs were determined in distilled water and various pH, i.e., pH 1.2, pH 4.5, pH 6.8, and pH 7.2. IB showed less solubility at lower pH and increase in solubility was seen at higher pH values. Saturation solubility studies indicate that PA solubility at various pH was invariably same; however, IB showed pH-dependent solubility. The reason for pH-dependent solubility is its weak acidic nature, which enhances solubility at higher pH values and reduces solubility at lower pH, as shown in Table 4.

Preparation of calibration curve

Along with the preliminary characterization of drug, standard curve in phosphate buffer and 0.1 N HCL+methanol (2:3) was carried out for comparison of release data. Calibration curve of PA and IB in phosphate buffer pH 7.4 is shown in Figs. 1 and 2. Calibration curve of PA and IB in acid buffer pH 1.2 is shown in Figs. 3 and 4.

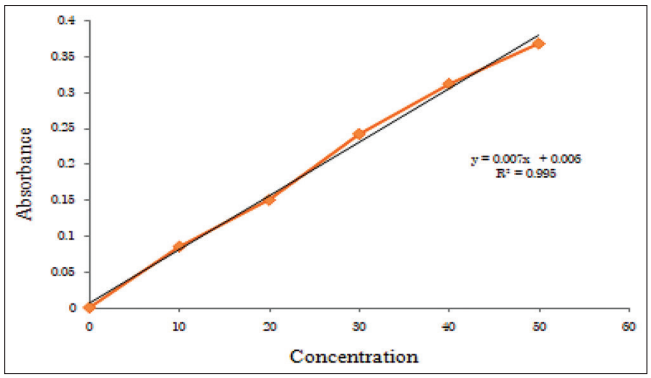

Fig. 4: Calibration curve of paracetamol in acid buffer pH 1.2

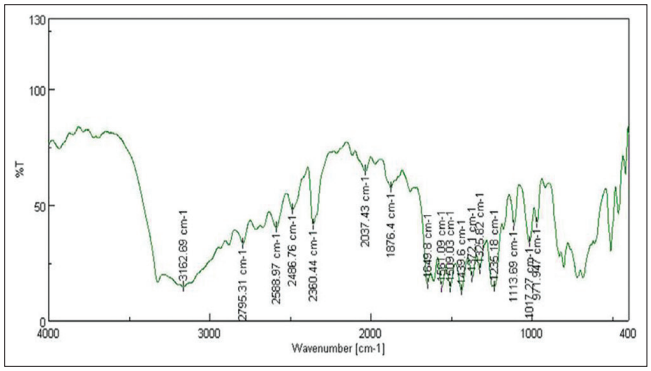

Fig. 5: Fourier transform infrared of paracetamol pure drug

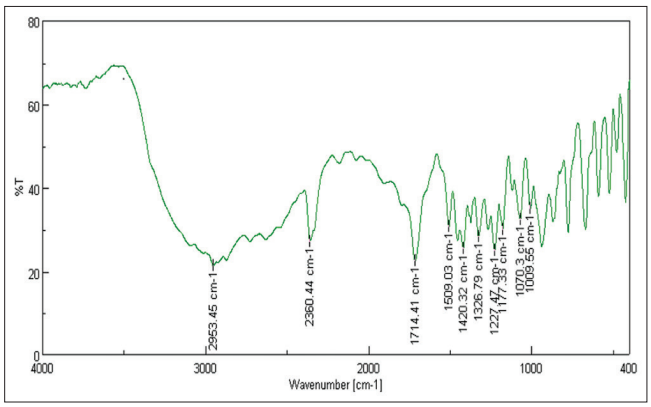

Fig. 6: Fourier transform infrared of ibuprofen pure drug

FTIR spectrophotometry

IR absorption spectrum of PA and IB was determined. Peak observed at 3162.69 cm^{-1} is attributed to N-H stretching. Peaks at 1561.09 cm^{-1} and 1509.03 cm^{-1} are attributed to the presence of amide II band and 2360.44 cm^{-1} attributed to O-H stretching. Peaks at 2795.31, 2588.97, and 1649.8 cm^{-1} attributed to C-H stretching, O-H stretching, and C=O amide stretching, respectively. FTIR of PA and IB pure drug is shown in Figs. 5 and 6, respectively.

The peak observed at 2953.45, 1714.41, and 1227.47 cm^{-1} attributed to O-H, C=O, and C-O stretching of carboxylic acid, respectively. Peak at 1009.55 cm^{-1} attributed to the presence of para-disubstituted aromatic ring in the structure. FTIR studies of PA confirmed the presence of phenolic OH group and secondary amide in its structure. FTIR studies of IB confirmed the presence of carboxylic acid and a para-disubstituted aromatic ring in its structure. It was confirmed that there are no major shifting as well as no loss of functional peaks between the spectra of PA and IB.

DSC

DSC studies of PA show a sharp endothermic peak at 174.04°C which indicates its melting point and crystalline nature. The second endothermic

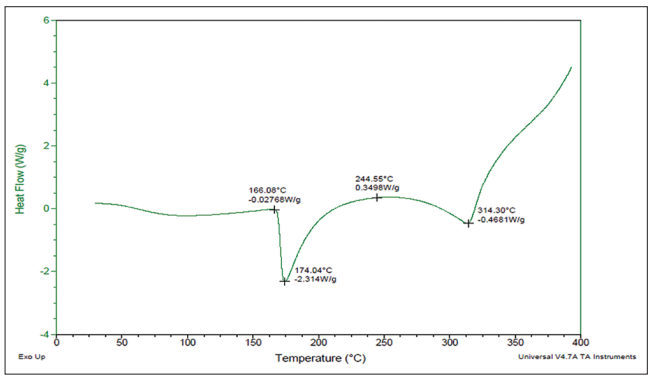

Fig. 7: Differential scanning calorimetry of paracetamol pure drug

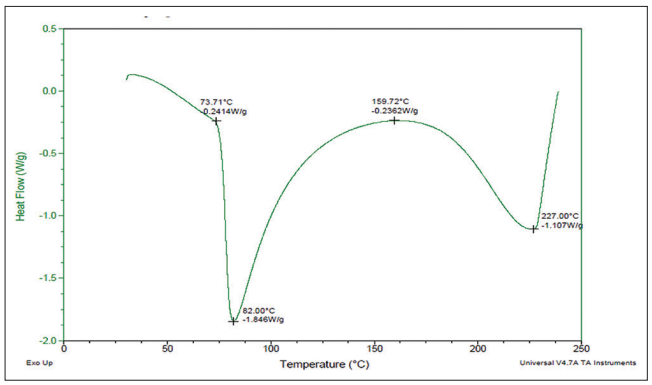

Fig. 8: Differential scanning calorimetry of ibuprofen pure drug

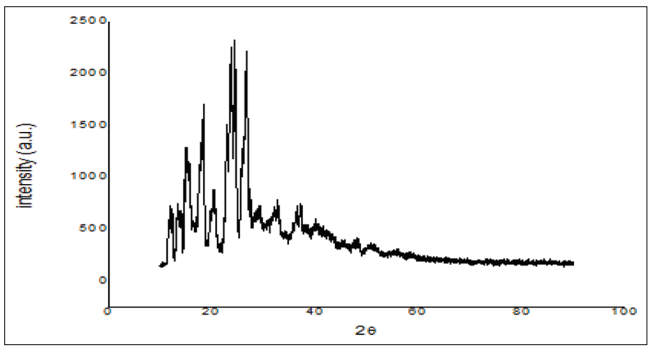

Fig. 9: X-ray diffraction of paracetamol pure drug

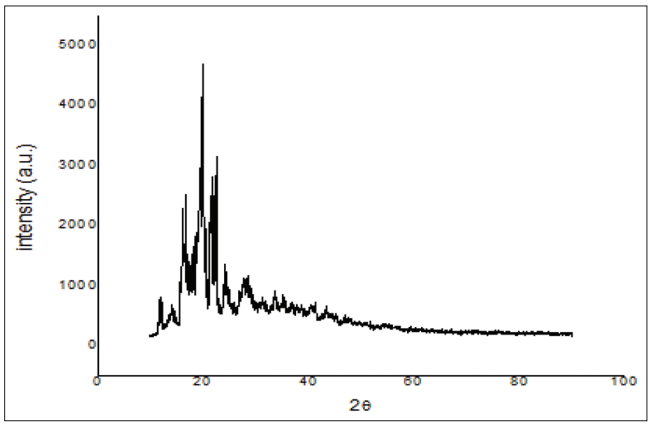

Fig. 10: X-ray diffraction of ibuprofen pure drug

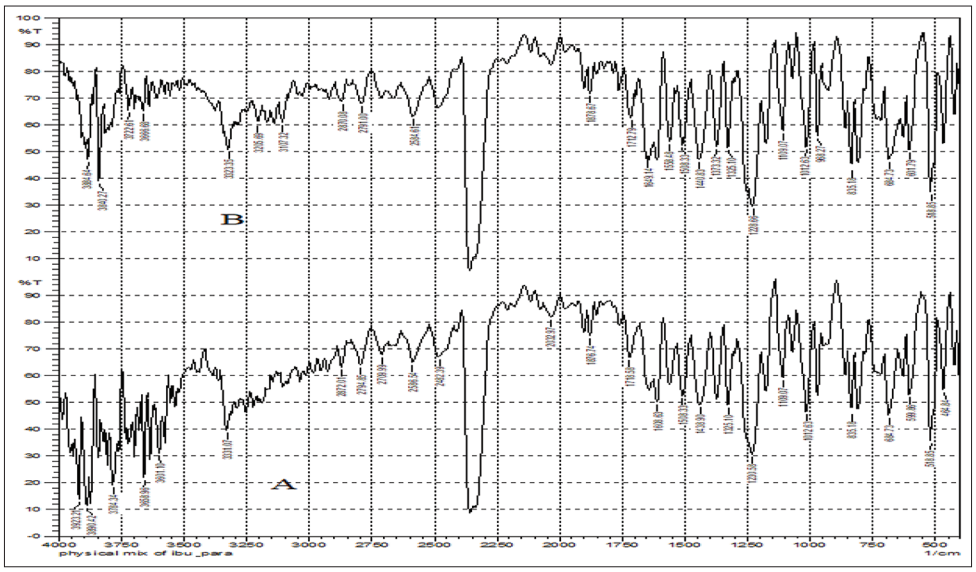

Fig. 11: Overlain Fourier transform infrared spectra of (a) pure drugs mixture, (b) optimized batch

peak was seen 314.30°C which is the boiling point of PA, as shown in Fig. 7. The DSC of IB shows a sharp endothermic peak at 82.00°C which indicates its melting point and crystalline nature. The second endothermic peak was seen at 227°C which is the boiling point of IB, as shown in Fig. 8.

PXRD

PXRD results of PA show intense peaks 2θ at 23.2, 24.1, and 26.3. The intensity of these peaks was high; thus, PA was found to be crystalline in nature, as shown in Fig. 9. High-intensity peaks were observed 2θ at 12.3, 16.7, 20.1, and 22.4; peak 16.7 showed the highest intensity of 15,046. These high-intensity peaks were observed due to crystalline nature of IB, as shown in Fig. 10. The diffraction spectrum of pure drugs showed that the drug was of crystalline nature as indicated by numerous, relative sharp, and distinct peaks at a diffraction angle of 2θ.

Table 5: Coamorphous formulation in distilled water

Batch no.	Ibuprofen (mg/ml)	Paracetamol (mg/ml)
A	80.23	1955
B	23.91	3450
C	25.71	2019
D	59.88	1101
E	70.64	8004

Table 6: Coamorphous formulation in acid buffer pH 1.2

Batch no.	Ibuprofen (mg/ml)	Paracetamol (mg/ml)
A	52.61	3785.7
B	43.62	2973.6
C	47.22	322.3
D	69.06	5021.4
E	72.89	4884.9

Table 7: Coamorphous formulation in phosphate buffer pH 4.8

Batch no.	Ibuprofen (mg/ml)	Paracetamol (mg/ml)
A	87.58	4241.5
B	80.17	4532.0
C	84.47	5775.4
D	86.35	7022.6
E	90.64	8192.0

Table 8: Coamorphous formulation in phosphate buffer pH 6.8

Batch no.	Ibuprofen (mg/ml)	Paracetamol (mg/ml)
A	86.73	7064.7
B	77.68	5364.1
C	88.58	6148.0
D	79.75	6426.3
E	89.81	7703.7

Table 9: Coamorphous formulation in phosphate buffer pH 7.4

Batch no.	Ibuprofen (mg/ml)	Paracetamol (mg/ml)
A	62.11	4019.0
B	112.24	8233.5
C	111.87	6371.6
D	33.84	44.07
E	119.45	9636.0

Table 10: Saturation solubility of optimized batch E (200–500)

Concentration	Distilled water	Acid buffer	Phosphate buffer		
		pH 1.2	pH 4.8	pH 6.8	pH 7.4
200–500	70.64 8004.3	72.89 4884.9	90.64 8192.4	89.81 7703.7	119.45 9636.0

Preparation and evaluation of COAM preparation

The COAM system of IB and PA was prepared by the process of CEM field microwave technique. The sample was prepared according to the formulation batch and each batch was calculated in 200 mg.

Saturation solubility

Solubility of all selected formulations was carried out in distilled water, acid buffer pH 1.2, and phosphate buffer 4.8, 6.8, and 7.4, as shown in Tables 5-9, respectively, whereas maximum increase in solubility of IB

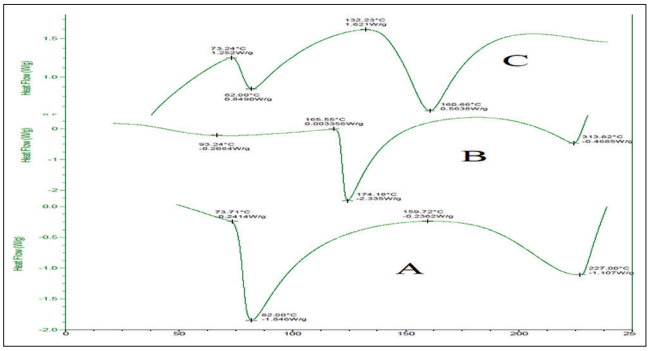

Fig. 12: Overlain differential scanning calorimetry thermogram of (a) pure ibuprofen, (b) pure paracetamol, and (c) batch E (200–500) chemical electric magnetic sample

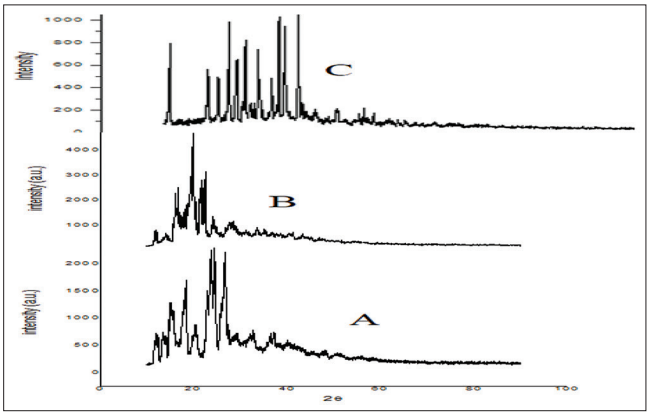

Fig. 13: Overlain X-ray diffraction of (a) pure paracetamol, (b) pure ibuprofen, and (c) chemical electric magnetic sample

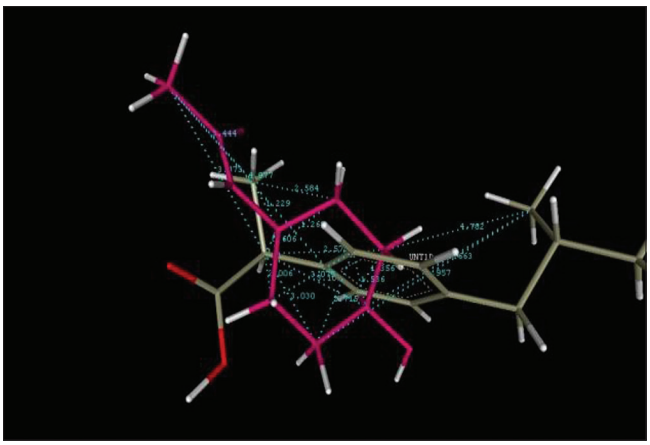

Fig. 14: Molecular docking of ibuprofen and paracetamol

was observed after 12 h. Maximum increase in aqueous solubility of IB was seen in 500 mg:200 mg dose ratio (batch E), indicating role of PA and coamorphism toward solubility enhancement of IB, even if its solubility is pH dependent. All the five clinical combinations showed increase in solubility of IB, but among them, batch E showed maximum increase in solubility of IB. Therefore, batch E (200–500) was selected as optimized batch for further characterization, results are shown in Table 10.

Table 11: Endothermic peak pure IB, pure PA, and optimized batch E

Drug	Endothermic peak 1	Endothermic peak 2
Pure PA	174.0°C	314.30°C
Pure IB	82.00°C	227.00°C
Optimized batch E	82.0°C, 116°C	-

IB: Ibuprofen, PA: Paracetamol

Table 12: Peak intensities of pure IB, pure PA, and CEM optimized batch

IB		PA		Optimized batch E	
2θ	Intensity	2θ	Intensity	2θ	Intensity
12.3	6884	11.8	2701	13.7	2286
16.7	15,046	13.6	4699	15.5	4152
19.6	7732	15.2	4531	16.7	3557
20.2	12,683	17.9	4219	18.1	3736
22.4	10,562	20.1	3048	20.1	2980

IB: Ibuprofen, PA: Paracetamol, CEM: Chemical electric magnetic

FTIR spectra

FTIR spectra of pure drugs mixture and optimized batch E were carried out. Phenolic C=O stretch of PA at 1372.1 cm^{-1} was shifted to higher wavenumber in CEM sample, i.e., at 1396.84 cm^{-1}. C=O stretch of carboxylic acid of IB at 1714.41 cm^{-1} was shifted to lower wavenumber at 1647.77 cm^{-1}. O-H stretch of carboxylic acid of IB at 2953.45 cm^{-1} was shifted to higher wavenumber at 2980.20 cm^{-1}. Such strong adhesive molecular interactions might have led to band shifts in the IR spectra. The shifting occurred due to interactions between both the drugs after CEM microwave reaction. These shifts are also observed when a crystalline drug is converted into its amorphous form. Here, molecular interaction between PA and IB was confirmed due to the shift of phenolic C=O stretch, N-H stretch (amide) of PA, and C=O stretch, O-H stretch (carboxylic acid) of IB. Overlain FTIR spectra of pure drugs mixture and optimized batch E are shown in Fig. 11.

DSC

The DSC thermogram (Fig. 12) of PA and IB showed sharp endothermic transitions at 174.0°C (Fig. 12b) and 82.0°C (Fig. 12b), respectively, corresponding to their melting points. The second endothermic peak seen in thermogram of IB at 227°C was corresponding to its boiling point, whereas, in optimized batch E, significant transformation of both crystalline PA and IB to amorphous form. Interestingly, shift in melting point of PA from 116.0°C (in PA) to 82.0°C (in optimized batch E) has been noted (Fig. 12c) and boiling point of IB at 227°C was

Table 13: *In vitro* dissolution studies of COAM sample

Time (min)	Acid buffer pH 1.2		Phosphate buffer pH 6.8 mean±*SD, n=3		Phosphate buffer pH 7.4	
	IB	PA	IB	PA	IB	PA
5	1.916±0.13	30.372±0.21	27.891±0.15	25.456±0.28	28.688±0.29	27.897±0.24
10	2.569±0.25	56.112±0.23	40.092±0.14	47.675±0.25	42.041±0.26	31.287±0.21
20	4.788±0.28	68.752±0.25	52.723±0.27	58.329±0.29	52.459±0.15	54.824±0.18
30	6.123±0.39	75.752±0.24	69.803±0.28	68.781±0.18	81.915±0.17	71.983±0.22
45	7.327±0.23	81.077±0.35	76.392±0.23	79.808±0.17	87.922±0.19	88.350±0.26
60	9.227±0.22	89.65±0.37	84.111±0.24	89.076±0.14	93.034±0.25	94.750±0.29
90	10.058±0.26	93.538±0.34	97.710±0.22	95.796±0.15	97.940±0.28	96.155±0.16
120	11.032±0.29	98.498±0.33	98.607±0.21	97.097±0.28	98.703±0.26	98.157±0.13

*SD indicates standard deviation n=3, SD: Standard deviation, IB: Ibuprofen, PA: Paracetamol

Table 14: *In vitro* dissolution studies of pure drug, coamorphous sample of optimized batch E, and marketed formulation

Time (min)	Pure drug		Coamorphous sample of optimized batch E *mean±SD, n=3		Marketed formulation	
	IB	PA	IB	PA	IB	PA
5	18.02±0.14	17.67±0.16	28.68±0.17	27.89±0.19	29.91±0.23	28.16±0.21
10	19.88±0.25	40.25±0.22	42.04±0.16	31.28±0.21	43.34±0.28	33.31±0.27
20	25.23±0.29	56.21±0.21	52.45±0.19	54.82±0.22	54.16±0.29	59.82±0.13
30	38.17±0.22	67.81±0.27	81.91±0.28	71.98±0.28	83.65±0.25	79.75±0.15
45	45.42±0.12	81.37±0.26	87.92±0.29	88.35±0.18	88.87±0.16	83.26±0.17
60	50.02±0.27	89.89±0.28	93.03±0.25	94.75±0.15	96.32±0.15	91.46±0.14
90	53.11±0.21	94.11±0.23	96.09±0.23	96.15±0.23	95.10±0.17	95.70±0.23
120	55.09±0.25	96.91±0.17	97.00±0.27	97.82±0.26	96.02±0.13	96.81±0.26

*SD indicates standard deviation n=3. SD: Standard deviation, IB: Ibuprofen, PA: Paracetamol

Table 15: Enthalpy and percentage crystallinity

Parameters	Pure drug		Coamorphous sample of optimized batch E	
	Paracetamol	Ibuprofen	Paracetamol	Ibuprofen
Enthalpy	180	128.75	79.87	12.4
% Crystallinity	100	100	44.37	9.63

Table 16: *In vitro* drug release of optimized batch E in acid buffer pH

Time (min)	Coamorphous optimized batch E (1)		Coamorphous optimized batch E (2)	
	Paracetamol	Ibuprofen	Paracetamol	Ibuprofen
5	1.21	27.97	1.18	25.31
10	2.43	50.12	2.35	48.02
20	3.79	82.49	3.65	79.98
30	6.76	87.49	6.61	85.98
45	10.11	93.92	9.98	92.65
60	12.14	98.55	11.79	97.14
90	14.08	99.11	12.94	97.31
120	14.55	99.52	13.37	97.54

Table 17: *In vitro* release of optimized batch E in phosphate buffer pH7.4

Time (min)	Coamorphous optimized batch E (1)		Coamorphous optimized batch E (2)	
	Paracetamol	Ibuprofen	Paracetamol	Ibuprofen
5	49.1	1.21	48.2	1.02
10	83.6	2.43	82.4	2.22
20	99.8	3.79	98.9	3.57
30	101.33	6.76	99.2	6.53
45	101.5	10.11	99.6	9.84
60	101.7	12.14	99.9	11.57
90	102.1	14.08	100.1	12.94
120	102.4	14.55	100.1	13.37

also not observed in DSC of optimized batch E, indicating strong solid-state interactions between PA and IB, and partial dissolution of PA in molten IB.

DSC studies of overlain (a) pure ibuprofen, (b) pure paracetamol, and (c) optimized batch E are shown in Fig. 12 and Table 11. The glass transition temperature of COAM samples was predicted theoretically using the Gordon-Taylor equation. The Tg was predicted to be 29.60°C. Thus, the CEM batches were stable at room temperature.

PXRD

COAM sample showed PA peaks 2θ at 13.7, 15.5, 18.1, 20.1, 23.4, 24.3, and 26.5 with less intensity than pure PA. The COAM sample showed only one peak of IB 2θ at 16.7 with very less intensity. The COAM sample showed peak of PA 2θ at 20.1, 23.2, 24.1, and 26.3, with very less intensity. This indicates that PA was converted into its amorphous form with very less crystallinity, as shown in Fig. 13 and Table 12. The XRPD of optimized batch E shows some peaks of PA and two very low-intensity peaks of IB, which suggests almost complete amorphization of IB and outweighs role of PA. The conversion of IB in COAM form was responsible for increase in its aqueous solubility, although it has pH-dependent solubility.

It was confirmed that CME batches existed in amorphous state due to the disappeared sharp peak of pure drugs in the diffraction pattern.

***In vitro* dissolution studies**

In vitro dissolution study showed that PA 14.0% drug release in both acid buffer pH 1.2 and phosphate butter pH 4.8, pH 6.8, and pH 7.4 did not show much changes. IB in acid buffer pH 1.2 showed slight increased released and in phosphate buffer pH 7.4 was 100% release in 20 min. Thus, dissolution rate of IB was improved in its COAM form, as shown in Tables 13 and 14.

Crystallinity study

The percentage crystallinity of PA and IB in optimized batch E found to be 44.37% and 9.63%, respectively, which indicates a significant decrease in crystallinity of IB in COAM system. Enthalpy and percentage crystallinity of pure drugs and optimized batch are shown in Table 15.

Molecular docking study

Molecular docking of IB and PA showed the presence of Van der Walls force of attraction and hydrophobic interactions between both the drugs. Hydrophobic interactions were observed between methyl group of PA and methyl group of IB. The same methyl group of PA showed hydrophobic interactions with -CH group of IB.

PA helps in deagglomeration of IB particles after CEM field microwave reaction due to the hydrophobic interactions between both of them. Thus, these hydrophobic interactions may be responsible for increased dissolution rate of IB CEM field microwave reaction with PA. Molecular docking of IB and PA is shown in Fig. 14.

Stability studies

Accelerated stability studies suggested that the optimized batch E was stable up to 2 months. Neither PXRD, DSC results nor the *in vitro* dissolution studies showed significant change, thus confirming stability of the product. Eventually, PA not only assisted in disruption of IB crystallinity but also stabilized its amorphous form at molecular level, thus indicating that the optimized batch E formulation was stable up to 2 months stress condition, as shown in Tables 16 and 17. Thus, from the stability studies, it can be proved that the prepared optimized batch E formulation was stable and not much affected by stress condition.

CONCLUSION

PA-IB COAM system was successfully prepared by CEM field microwave method. The COAM system increased the solubility of IB about 98.70%. *In vitro* drug release study, 100% of the drug was released within 120 min. FTIR studies showed shift in the peaks of PA and IB, due to hydrogen bonding between both the drugs. Diffractometric studies have revealed amorphism/reduced crystallinity of IB and its subsequent stabilization by PA. DSC studies of COAM sample show less crystallinity as compared to pure drug and the decrease in melting point was due to molecular interaction between both the drugs. From the studies of FTIR, XRD, and DSC, it indicates that IB converted into the COAM system, which was responsible for the enhancement of solubility and dissolution. Molecular docking study of IB, PA, and CEM field batch indicates that these hydrophobic interactions may be responsible for increased dissolution rate of IB after CEM reaction with PA. Amorphization and subsequent adsorption of IB on PA can speculate generation of a particulate system. Hence, work has demonstrated generation of COAM form of PA and IB in clinical dose ratio 500 mg:200 mg, which may overcome poor processability, solubility and dissolution, and bioavailability constraints of IB. The method is simple, green, cost effective, and novel for PA-IB combination, holds great potential for industrial application.

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AUTHORS' CONTRIBUTIONS

The author designed and performed the experiment, analyzed data, and prepared the manuscript. All authors played an equal role in completing this research work.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest to disclose. The authors alone are responsible for the content and writing of the paper.

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