

# Milk-Based Oral Formulations of Ibuprofen: An Investigation on the Role of Milk in Improving Dissolution Rate of Drug

## Abstract

**Introduction:** More than 40% of the newly developed drugs pose a problem of aqueous insolubility which is a major challenge for pharmaceutical scientists since in this form; drug doesn't show required bioavailability and hence sufficient therapeutics effect. **Objective:** The improvement of dissolution rate of ibuprofen (IBF) (poorly water-soluble drug) by formulating its solid dispersions using milk as generally recommended as safe carrier was the goal and purpose of this study. **Method:** For this, milk containing 1.5% fat (named yellow milk due to yellow-colored pack) and milk containing 4.5% fat (named green milk due to green-colored pack) were used. Initially, both types of milk were rota evaporated to obtain free flowing powdered form. Then, the physical mixtures were prepared in different ratios by simple mixing and solid dispersions were formulated in different ratios by solvent evaporation method using hot air oven. Various techniques were used to evaluate and characterize the physical mixtures and solid dispersions, which included melting point determination, solubility studies, differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy, X-ray diffraction (XRD), in vitro dissolution studies, and scanning electron microscopy (SEM). **Results:** DSC and XRD studies showed reduction in peak intensity of drug indicating the conversion of crystalline drug into amorphous form. SEM studies indicated that the agglomerates formed were smaller and denser with a smooth surface. In vitro dissolution studies showed that the quantity of drug solubilized and the rate of dissolution increase after formulation into the solid dispersions. **Conclusion:** The milk powder was found to enhance the solubility of IBF due to the presence of casein which entrapped the hydrophobic drug by forming micelles.

**Keywords:** Dissolution rate, ibuprofen, milk, solid dispersion, solubility

## Introduction

Ibuprofen (IBF) is a 2-arylpropionic acid derivative, i.e., (*RS*-2-[4-isobutylphenyl] propionic acid). It was first introduced in 1969 in the UK and afterward marketed worldwide as a prescription medication only and now probably ranks after aspirin and paracetamol in nonprescription over-the-counter drugs. Thus, the drug has a better tolerability as compared to other nonsteroidal anti-inflammatory drugs.<sup>[1]</sup> IBF is a nonselective reversible inhibitor of the cyclooxygenase (COX) isozymes COX-1 and COX-2, which are responsible for the conversion of arachidonic acid into prostaglandins including thromboxane and prostacyclin. Since prostaglandins play a key role in pyrexia, inflammation, and pain sensation, both analgesic and antipyretic potentials of IBF are attributed to the inhibition of prostaglandins. Thus,

IBF is one of the most active compounds used as an antipyretic and analgesic in acute as well as chronic pain in osteoarthritis, dysmenorrhea, rheumatoid arthritis, migraine, postoperative pain, and dental pain and also has vasoconstriction action due to constriction of coronary arteries and some blood vessels because of inhibition of vasodilating prostacyclin produced by COX-2.<sup>[2]</sup> Owing to its poor aqueous solubility (<1 mg/ml), the rate of dissolution of IBF from the solid dosage forms currently available is limited which leads to poor bioavailability that ultimately results in various unwanted effects. The major side effects include gastritis, dyspepsia, epigastric pain, heartburn, and peptic ulcer-gastrointestinal hemorrhage, which are dependent on the dose.<sup>[3]</sup> By improving the solubility and dissolution rate of the drug, bioavailability and therapeutic importance of drug can be enhanced. Moreover, IBF has been declared as core medicine by the World Health

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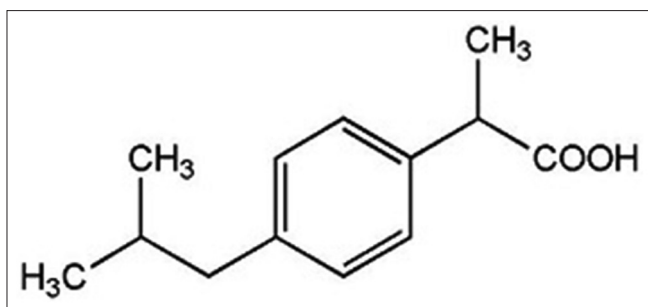


Figure 1: Structure of ibuprofen

Organization's in the "essential drug list," indicating its medical need for a basic health-care system [Figure 1].<sup>[1]</sup>

Solubility is one of the major challenges for pharmaceutical industries to acquire desired drug concentration in systemic circulations for effective pharmacological results since more than 40% newly developed chemical entities are practically insoluble in water.<sup>[4]</sup> The process of solubilization takes place in three steps: first, the separation of the molecule of solvent which provides the space for solute molecules, second, breaking of ionic bonds in the solute, and finally, interaction between solute and solvent molecules to form a solution.<sup>[5]</sup>

There are several traditional and novel approaches to increase the solubility and thus bioavailability of the drug such as modification of the crystal habit, particle size reduction, cryogenic techniques, drug dispersion in carriers, complexation, supercritical fluid process, change in pH, use of buffer, co-solvency, polymeric alterations, and use of surfactant and hydrotrope.<sup>[6,7]</sup> Out of these methods, one of the popular approaches is to prepare solid dispersions (SDs) to enhance the oral bioavailability of poorly water-soluble drugs. This pharmaceutical technique of SD presented by Sekiguchi and Obi (early 1960s) investigated sulfonamide drug's eutectic melts for their dissolution performance using water-soluble carrier. This investigation found an improvement in the dissolution, absorption, as well as therapeutic efficacy of drug from the dosage form.<sup>[8]</sup>

Milk is highly nutritious drink with rich content of nutritious elements and a large number of peptides which are biologically active. Milk-made formulations are beneficial for ionized as well as unionized hydrophobic drug delivery by providing a simple, novel, and patient-friendly approach. Furthermore, the incorporation of milk in the formulation results in solubilization of drugs with improved pharmacokinetic properties along with taste masking and gastroprotective properties making it a promising carrier for drugs.<sup>[9]</sup>

The preparation of SD with milk is one of the best approaches for modulating aqueous solubility as well as gastric irritation of drug without any noticeable side effect because of its surface-active action and presence of amino acids.<sup>[10]</sup> Based on all these considerations, the purpose

of this project was to investigate the benefit of milk as dispersion carrier to enhance solubility and dissolution rate of IBF and consequently its bioavailability.

## Materials and Methods

### Materials

IBF was received from the IOLS Chemical and Pharmaceutical Limited, Ludhiana, Punjab, India. Milk (yellow and green) were purchased from Verka milk plant, Hoshiarpur (Punjab), India. All the reagents and chemicals utilized in this study were of analytical grade.

### Methods

#### Melting point

Capillary method was used to determine melting point. This method involves filling of drug into capillary tube sealed at one end at a height of 3 mm from the closed end. The melting point was determined digitally using drug-filled capillary and digital melting point apparatus.<sup>[11]</sup>

#### Determination of absorbance maxima ( $\lambda_{max}$ ) of drug

IBF 100 mg was weighed and dissolved into few milliliters of pH 7.2 phosphate buffer and finally made up the volume in 100 ml volumetric flask. From this stock solution, further concentrations were made. The samples were scanned using double-beam ultraviolet (UV)-visible spectrophotometer between 200 nm and 400 nm. The  $\lambda_{max}$  was selected as the analytical wavelength of IBF in particular media.<sup>[12]</sup>

#### Preparation of milk powder

One liter (1000 ml) of yellow milk (YM) and green milk (GM) each was dried in rotary evaporator at 35°C and 100 rpm under vacuum. The powdered milk obtained was then dried in an oven (100 ml of YM yielded approximately 12 g while that of GM yielded 22 g/100 ml); passed through sieve no. #80 and stored separately in desiccator for further use.<sup>[13]</sup>

#### Solubility studies

Solubility studies of pure IBF and SDs were carried out in different media, i.e., distilled water and phosphate buffer pH 7.2. Pure drug (PD) and each SD equivalent to 100 mg of IBF were taken in 15-ml screw-cap test tubes containing 10 ml of media. The solutions were shaken well and kept aside for 24 h with continuous stirring at a temperature of 25°C ± 0.5°C for enhancing the maximum solubilization of the drug in each solvent at room temperature by achieving equilibrium. After 24 h, the sample solutions were filtered through Whatman filter no. 1. One milliliter of filtrate was taken and diluted to a suitable concentration with respective media.<sup>[14]</sup> The absorbance of the prepared dilutions was measured at 222.8 nm using UV-visible spectrophotometer.

#### Preparation of physical mixtures

The physical mixtures (PMs) were formulated by triturating IBF with YM powder (YMP) and GM

powder (GMP) in different ratios 1:1, 1:2, and 1:3 in mortar and pestle for 10 min, after that the samples were passed through sieve no. 80 and finally kept in desiccator till further use.<sup>[15]</sup>

#### Drug-excipient interactions

The YMP, GMP, and mixtures of drug with YMP and GMP (1:1 ratio) were sealed in separately closed glass vials and exposed to conditions of 25°C and 70% RH for a period of 1 month. The initial color and appearance of samples were periodically observed on days 1, 3, 5, 7, 14, 21, and 30.<sup>[16]</sup>

#### Preparation of solid dispersions

##### Preparation of solid dispersion by solvent evaporation technique using hot air oven

An accurately weighed quantity of drug (200 mg) was transferred into mortar and a few milliliters of ethanol was added to get a clear solution. Furthermore, 200 mg of YMP was added to above-prepared solution and triturated for 20 min and kept in the oven for 5 min at 30°C. Likewise, SDs in a ratio of 1:2 and 1:3 were also prepared. The dried mixture was passed through sieve #80 and preserved in a desiccator for further use. The same procedure was repeated with GMP.<sup>[17,18]</sup>

#### Characterization and evaluation methods

##### In vitro dissolution studies

The *in vitro* dissolution study was done in USP II dissolution rate test apparatus (paddle type) using phosphate buffer (900 ml) pH 7.2 at 37°C ± 0.5°C and 50 rpm. Amount of SDs and PMs each equivalent to 100 mg were weighed and kept in the dissolution vessel. Samples were taken at predetermined time interval at 0, 5, 10, 15, 20, 25, 30, 40, 50, and 60 min, and the withdrawn samples were suitably diluted with the same buffer, and at scanned wavelength of 222.8 nm, the absorbance of the samples was determined.<sup>[19]</sup> The study was performed in triplicate. Based on the observations, the best formulation from each batch was selected and subjected to further characterization techniques.

##### Fourier transform infrared spectroscopy

SDs and PMs were analyzed for drug carrier interactions based on the Fourier transform infrared (FTIR) spectra obtained using PerkinElmer FTIR spectrometer. The spectra in absorbance mode were obtained (spectral region: 500–4000 cm<sup>-1</sup>; resolution: 4 cm<sup>-1</sup>).<sup>[20]</sup>

##### X-ray diffraction studies

X-ray diffraction (XRD) studies were brought about in the SD systems to determine the physical state of the drug using X'Pert PRO instrument. A Cu K $\alpha$  source fitted with a nickel filter generates the radiation (wavelengths: 0.154 nm at 40 mA and 45 kV). Samples were scanned for 2  $\theta$  values

over a range from 5° to 45° and at a scan rate of 10°C/min.<sup>[21]</sup>

##### Differential scanning calorimetry

The thermal behavior of IBF, milk powders (YMP and GMP), prepared SDs and PMs were analyzed using diamond differential scanning calorimetry (DSC) (Perkin, USA).

Accurately weighed samples were hermetically sealed in an aluminum crucible. The system was purged with nitrogen gas at a flow rate of 60 ml/min. Heating was done from 30°C to 200°C at a rate of 10°C/min to obtain the required thermograms.<sup>[22]</sup>

##### Scanning electron microscopy

The scanning electron microscopy (SEM) analysis of SDs was brought about using scanning electron microscope (JSM 6390, JEOL, Peabody, MA, USA) with 10-kV accelerating voltage. The samples were mounted on a double-faced adhesive tape and sputtered with thin gold palladium layer using sputter coater unit, and the surface topography was analyzed with a SEM.<sup>[23]</sup>

## Results and Discussions

### Melting point

The melting point of IBF was found to be in a range of 76°C–80°C which was in compliance with the reported value.<sup>[24]</sup>

### Determination of absorbance maxima ( $\lambda_{max}$ ) of drug

The scanned wavelength ( $\lambda_{max}$ ) of IBF was observed to be 222.8 which was in accordance with the reported value.<sup>[12]</sup>

### Solubility studies

Solubility of PD was determined at 25°C ± 0.5°C, in distilled water and phosphate buffer having pH 7.2 as shown in Figures 2 and 3, respectively. The solubility profile indicated a gradual decline in solubility when the drug was formulated into SD with GMP as compared to YMP. Moreover, drug was having maximum aqueous solubility in drug: YM (D: YM) 1:3 ratio, i.e., 174.038  $\mu$ g/ml while

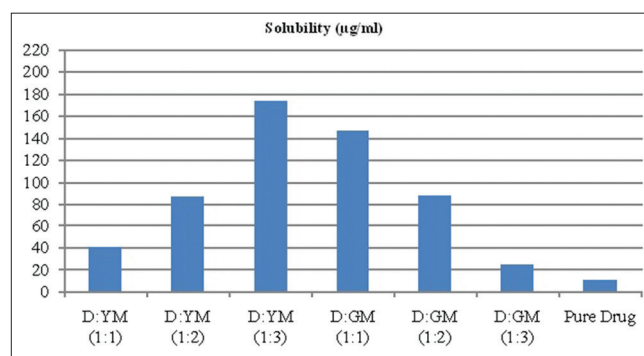


Figure 2: Solubility of pure drug, drug: Yellow milk, and drug: Green milk in distilled water

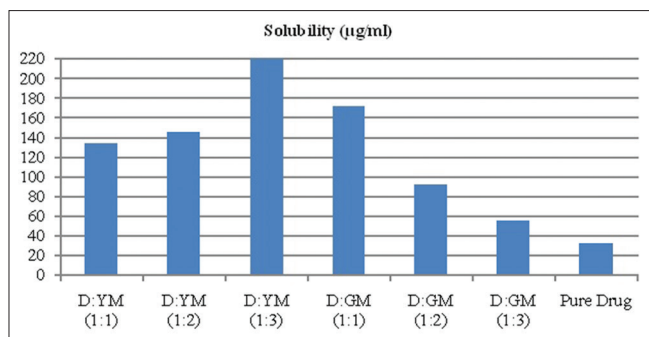


Figure 3: Solubility of pure drug, drug: Yellow milk, and drug: Green milk in pH 7.2 phosphate buffer

**Table 1: Solubility study data of pure drug and various formulations**

Formulation	Solubility in water (µg/ml)	Solubility in phosphate buffer pH 7.2 (µg/ml)
Pure drug	10.906	32.425
D:YM (1:1)	40.558	133.327
D:YM (1:2)	86.827	145.385
D:YM (1:3)	174.038	223.846
D:GM (1:1)	146.731	171.635
D:GM (1:2)	88.077	91.654
D:GM (1:3)	24.519	54.923

D: Drug, YM: Yellow milk, GM: Green milk

in case of drug: GM (D: GM) maximum solubility was observed in 1:1 ratio. Similar kinds of results were obtained with phosphate buffer pH 7.2 [Table 1]. The improved aqueous solubility of drug observed with SD (especially D: YM in ratio 1:3) was because of particle size reduction and appearance of an amorphous state. The YMP was having relatively more content of protein per unit fat content of GMP. The aqueous solubility enhancement can be attributed to the presence of amino acids and surface-active agent content that entrapped the hydrophobic drug in the hydrophilic casein micelles.<sup>[13]</sup>

#### Drug-excipient interactions

The drug-excipient study results did not show any significant change in color, odor, or the physical state of the mixtures as well as the individual components. The observations indicated that there were no detectable physical changes after 1-month study.

#### In vitro drug release studies

PM of IBF with YM was evaluated for *in vitro* drug release in different ratios such as 1:1, 1:2, and 1:3. The maximum percentage of drug release from the PMs prepared using YMP was found to be 46.353, 47.592, and 57.424, respectively, after 10 min, while in case of PMs with GMP, the percentage of drug release was observed to be 43.257, 40.247, and 38.745 as shown in Figure 4. Hence, the PM prepared with YMP in 1:3 ratio was showing maximum drug release of 57.42% in 10 min.

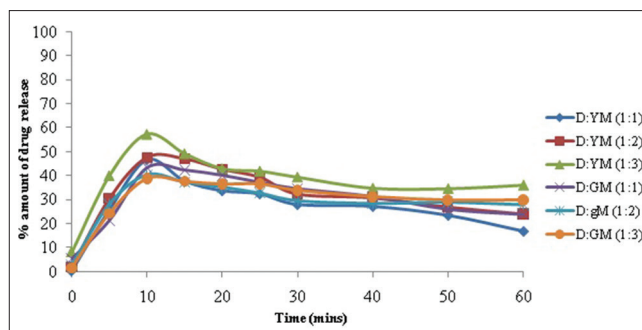


Figure 4: Dissolution profile of physical mixtures of drug with yellow milk powder and green milk powder

The SDs prepared with YMP using hot air oven showed a maximum percentage of drug release of 80.19, 85.509, and 98.539 in 20 min for 1:1, 1:2, and 1:3 ratios, respectively. The SDs prepared with GMP in the same ratios produced a maximum percentage of drug release of 37.056, 45.953, and 43.857 in 10 min, respectively.

The results clearly indicated that the YMP, owing to the presence of relatively more amount of casein, entrapped the hydrophobic drug by forming micelles. The porous structure of micelles enabled the release of entrapped drug molecules from the inclusion complex in the dissolution media at a much faster rate. Moreover, the SD mixtures displayed higher dissolution rate as compared to PM because of metastable states of the components with higher energy. Further, the dissolution of the drug increases in the presence of carrier by preventing the aggregation of fine drug particles. The wetting property also affected dissolution rate significantly.<sup>[11,25]</sup> After reaching to maximum, the dissolution rate started coming down which can be attributed to probable saturation of drug carrier.

A comparison of dissolution profiles of SDs prepared with YMP versus PD and SDs prepared with GMP versus PD is shown in Figures 5 and 6, respectively.

#### Fourier transform infrared study

The best formulation from each batch (based on percentage of drug release), namely PM with GMP and YMP (ratio 1:1 and 1:3, respectively) and SD with GMP and YMP (ratio 1:2 and 1:3, respectively) along with PD and GMP was subjected to FTIR studies. The obtained spectrum of IBF showed no significant changes on making PMs as well as SDs. SD and PM displayed all the characteristics of absorption bands of drug, GMP, and YMP indicating the absence of any well-defined interactions between them. The characteristic bands of drugs and polymers are given in Table 2 and Figure 7.<sup>[22]</sup>

It was observed that incorporation of drug into GM or YM did not affect the position of functional groups in the absorption spectra of SD and PM. The absence of some characteristic peaks of functional groups in drug in case of SD may be due to incorporation of IBF into micellar structures.

### Differential scanning calorimetry

To confirm the purity of drug and conversion of crystalline drug into amorphous state, DSC of IBF and selected formulations was performed the melting endotherms of which are shown in Figure 8. DSC of PD showed sharp melting endothermic peak ( $T_m$ ) at 79.63°C. YMP showed

endothermic peak at 175.99°C, whereas GMP showed endothermic peak at 191.50°C. After the formulation of SDs, peak of drug reduced which confirmed the formation of amorphous form of drug from crystalline form. The SDs prepared by YMP itself using rotary evaporator reduced the peak of drug to great extent which indicated that YMP was more effective carrier for this conversion.<sup>[26]</sup>

### X-ray diffraction studies

The XRD pattern of PD, SDs, and PMs is shown in Figure 9. The intense peaks of crystallinity have been shown by XRD pattern of PD and MP (green as well as yellow) exhibited distinct patterns with diffraction peak. The XRD pattern of

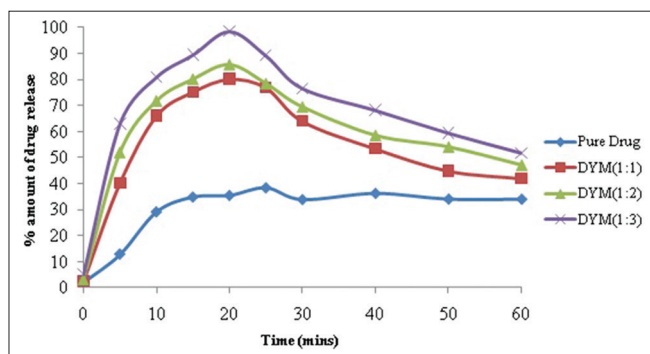


Figure 5: Dissolution profile of pure drug and solid dispersions prepared with yellow milk powder

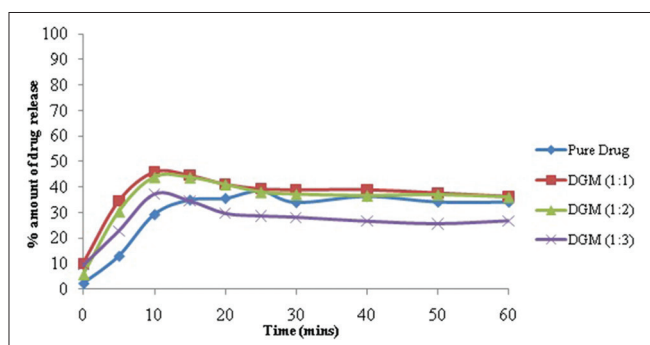


Figure 6: Dissolution profile of pure drug and solid dispersions prepared with Green milk powder

Table 2: Fourier transform infrared data of pure drug, milk powder, physical mixtures, and solid dispersions

Formulation	Functional groups	Peak (cm <sup>-1</sup> )
Drug	C=O (Carbonyl)	1721
	C=C (Ethylene)	1507
	C-H (Methane)	2865
	OH (Hydroxyl)	2626
Milk powder	C=C	1547
	C-O-C	1157
	C=O	1746
	C-H	3223
PMs	C=C	1510
	C-O-C	1228
	C=O	1712
	C-H	2858
SDs	C=C	1508
	C-O-C	1230
	C=O	1718
	C-H	2922

SDs: Solid dispersions, PMs: Physical mixtures

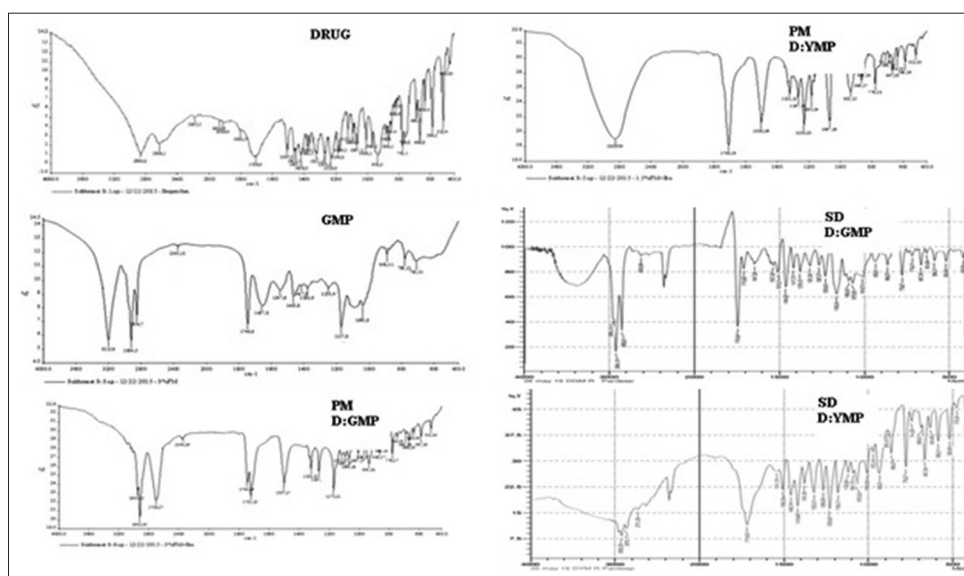


Figure 7: Fourier transform infrared spectrum of drug, green milk powder, physical mixture with green milk (physical mixture; drug: Green milk powder) and yellow milk (physical mixture; drug: Yellow milk powder), and solid dispersions with green milk (solid dispersion; drug: Green milk powder) and yellow milk (solid dispersion; drug: Yellow milk powder)

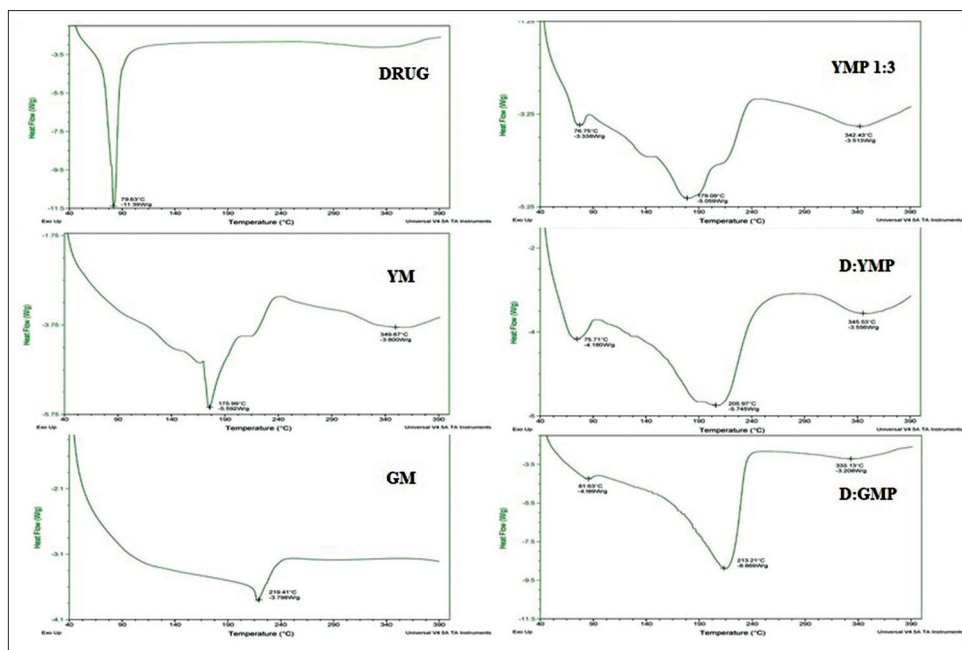


Figure 8: Differential scanning calorimetry thermographs of pure drug, yellow milk, green milk, physical mixture (drug: Yellow milk powder ratio 1:3), and solid dispersions with yellow and green milk (drug: yellow milk powder and drug: Green milk powder) in ratio 1:3 and 1:2, respectively

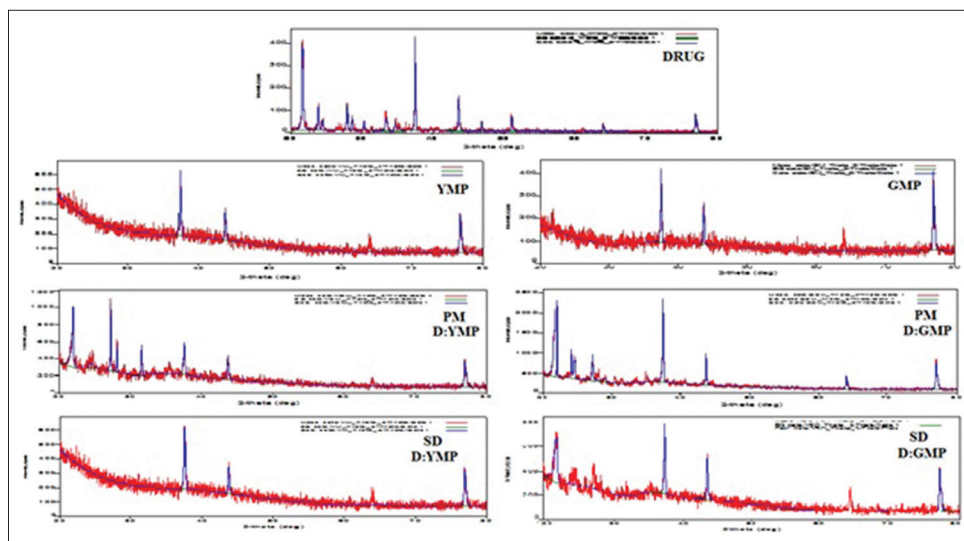


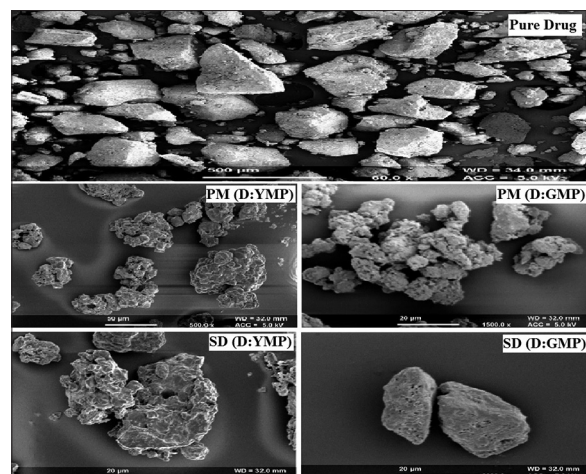
Figure 9: X-ray diffraction of pure drug, yellow milk powder, green milk powder, physical mixtures of drug with green and yellow milk powder (drug: Yellow milk powder ratio 1:3; drug: Green milk powder ratio 1:1), and solid dispersions with yellow milk powder (drug: Yellow milk powder ratio 1:3) and green milk powder (drug: Green milk powder ratio 1:2)

IBF shows sharp characteristic peaks at  $11.5^\circ$ ,  $26.8^\circ$ , and  $32^\circ$ , while milk shows characteristic peaks at  $78^\circ$  and  $36.7^\circ$ .

PM of drug with GMP reduced the crystallinity of drug to a large extent as compared to the YMP, while the SD of drug with YMP was able to reduce the crystallinity of drug to large extent as compared to GMP. Moreover, SDs prepared with rotary evaporation show great decline in crystallinity of drug with YM prepared by rotary evaporator. In SD, reduction of drug crystallinity was observed due to decreased intensity of characteristic drug peaks and some peaks got suppressed, thus indicating and its conversion to amorphous state.<sup>[27]</sup>

### Scanning electron microscopy

The SEM analysis further confirmed the results of DSC and XRD studies about the conversion of crystalline form of drug into amorphous form. The SEM images of pure IBF crystals were reported as tubular shaped with narrow crystal size distribution. The results obtained with SD disclosed that the agglomerates were produced by small particles, which get compacted into defined forms. These photomicrographs showed that there was formation of spherical agglomerates which enabled them to flow very easily. The agglomerates of all the



**Figure 10:** Scanning electron microscopy images of pure drug, physical mixtures with yellow and green milk (drug: Yellow milk powder; drug: Green milk powder), and solid dispersions with green and yellow milk (drug: Green milk powder; drug: Yellow milk powder)

dispersions were smaller and denser with irregular surfaces [Figure 10].<sup>[28,29]</sup>

## Conclusion

In the present work, dissolution rate of poorly water-soluble drug (IBF) was enhanced using milk as a natural carrier to improve the oral bioavailability. SDs and PMs were prepared and further characterized using FTIR spectroscopy, DSC, XRD, *in vitro* drug release studies, and SEM. The *in vitro* drug release for PD was found to be 38.243% only in 25 min, whereas for PMs with YM and GM, it was 57.42% (1:3 ratio) and 43.25% (1:1 ratio), respectively. SD prepared with YM in ratio 1:3 showed best results with a maximum drug release up to approximately 99% (1:3 ratio), and with that of GM, it was around 46% only (1:1 ratio). YM owing to better protein: fat ratio than GMP produced more convincing results. The successful improvement in the dissolution rate of IBF using milk as a generally recommended as safe carrier opens a wide scope of study of the delivery system with respect to improved patient compliance. Furthermore, the use of lactose-free milk for these formulations is still to be explored for patients with lactose intolerance. Thus, these advanced milk formulations have opened a new hope of using milk as a natural dispersing agent and a broad-spectrum drug carrier for a variety of drugs. Further studies are in progress to evaluate the anti-inflammatory potential of the prepared formulations *in vivo*.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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