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Original Article

FORMULATION AND EVALUATION OF IBUPROFEN CONTROLLED RELEASE MATRIX TABLETS USING ITS SOLID DISPERSION

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ABSTRACT

Objective: The aim of the present work was to prepare solid dispersion of ibuprofen with PEG 6000 to increase the aqueous solubility of the drug and to develop the solid dispersed ibuprofen into tablet formulation with the combination of a hydrophilic and hydrophobic polymer to attain controlled release of ibuprofen.

Methods: Solid dispersion of ibuprofen was prepared by melting-solvent method by varying the ratio of drug and PEG 6000. The solid dispersed ibuprofen was subjected to tablet formulation by using a hydrophilic swellable polymer-carbopol and hydrophobic non-swellable polymer-ethyl cellulose. The release of the drug from the polymer matrix was studied as the polymer ratio changes.

Results: Compatibility between drug and polymers was established from FT-IR study. The saturated solubility was found to increase in the solid dispersed formulation. The swelling index was found within the range of 90±5.43 to 137±6.41. SEM image of swollen tablet confirmed the presence of irregular and porous surface. The cumulative drug release was found to vary within the range of 68.76±3.04 to 95.33±2.34 % after 8 h of dissolution.

Conclusion: The combination of solid dispersion and application of hydrophilic and hydrophobic polymers in matrix formation can facilitate better dissolution and absorption profile with greater patient compliance.

Keywords: Ibuprofen, Solid dispersion, PEG 6000, Carbopol, Ethylcellulose

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INTRODUCTION

Orally administered drugs go through dissolution and then permeate across the epithelial membrane before appearing in the systemic circulation. Apart from solubility and permeability, the dissolution rate of the drug is one of the major factors for the bioavailability of the drug. Solubility of the drug in the gastro-intestinal medium is a major concern for most of the drugs [1]. Around 40 % of the new drug substances are having poor aqueous solubility. This leads to reduced bioavailability and possible adverse effects [2]. Thus solubility of new drug substances is the biggest challenge to formulation scientists [3, 4]. In spite of these challenges, oral route has been predominantly preferred route for drug administration due to its easy administration, high patient compliance and flexibility in dosage form design [3, 5].

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) widely used to reduce pain, tenderness, inflammation, and stiffness caused by gout and arthritis [6]. It is also used in the therapy of muscle ache, fever, menstrual pain and post-surgical pain [7]. Ibuprofen is a non-selective inhibitor of cyclooxygenase (COX) which inhibits two isoform of cyclooxygenase, COX-1, and COX-2 [8]. The inhibition of COX-1 is responsible for unwanted effects on GI tract and platelet aggregation, whereas COX-2 is responsible for the analgesic, antipyretic, and anti-inflammatory activity of NSAIDs [9, 10]. However, the function of each isoform of COX on analgesic, antipyretic, anti-inflammatory activity, and the severity of gastric damage of NSAIDs is uncertain and different compounds can cause different degrees of physiological effects and gastric damage [11, 12].

Solid dispersions can be defined as a dispersion of one or more active ingredients in an inert carrier or matrix in the solid state prepared by co-melting or solvent extraction or by the solvent-melt method [13]. Solid dispersion drug formulation represents an excellent method to enhance the solubility of poorly water-soluble drugs, as well as for the reduction of the ulcerogenic effect of non-steroidal anti-inflammatory drugs (NSAIDs). Ibuprofen is a BCS class II drug with less solubility and high permeability [14]. Use of solid dispersion technique can enhance the solubility and dissolution rate and result in increasing the drug absorption of several BCS class II drugs [15-17]. The promising outcome of solid dispersion in enhancement of solubility and dissolution rate of poorly soluble drugs can be attributed to different aspects, such as crystalline to amorphous structure, improvement of local solubility and wettability for poorly soluble drugs in solid dispersion matrix and formation of metastable form of drug with increased solubility and dissolution rate in the presence of carrier [18, 19]. In present work, an attempt has been made to develop controlled release matrix tablets of solid dispersed ibuprofen. A combination of swellable hydrophilic polymer and the non-swellable hydrophobic polymer was used to control the drug release from tablet matrix.

MATERIALS AND METHODS

Materials

Ibuprofen was received as a gift sample from Aurobindo Pharma Ltd., Hyderabad, India. Carbopol 934, Magnesium stearate and talc were commercially procured from Loba Chemie Pvt. Ltd., India. PEG 6000 was procured from Merck. Ethyl cellulose and lactose were purchased from SD Fine Chemicals. All the chemicals used were of analytical grade.

Methods

Fourier transform infrared spectroscopy

Drug-excipient interaction plays a vital role in the stability of drug from the formulation. Fourier transmitted infrared (FTIR) spectroscopy has been used to study the physical and chemical interactions between drugs and excipients. FT-IR spectra were recorded with FT-IR spectrometer (IRAffinity-1S, Shimadzu, Japan). Each sample was powdered and mixed with KBr (Uvasol, Merck, and KgaA, Germany). Pellets were prepared by using hydraulic press with a pressure of 100 Kg/cm^2 for 15 min. The pellets were then scanned from 4000 to 400 cm^{-1} with a mirror speed of 2 mm/sec.

Drug-excipient compatibility study was carried out by the FT-IR analysis of pure drug ibuprofen, and the formulation containing ibuprofen and polymers [20].

Preparation of solid dispersion of ibuprofen

Solid dispersion of ibuprofen was prepared by melting-solvent method. Accurately weighed quantity of drug was taken in a clean and dry glass mortar and triturate well to a fine powder. Add sufficient quantity of methanol to above powder and triturate to get a uniform dispersion. Required amount of PEG 6000 was taken in a glass container and melted in a water bath at 60̊ C [21 , 22]. Then the ibuprofen-methanol solution was added to the molten mass of PEG 6000 and mixed uniformly for 5 min. Then the mixture was placed on ice bath for rapid cooling until it solidified. The hardened mass was powdered in a mortar and then sieved through sieve no 60. Then it was stored in an airtight glass vial at room temperature [23, 24].

Preparation of controlled release matrix tablets of solid dispersed ibuprofen

Six different formulations of ibuprofen were prepared by varying the polymer concentrations. All the ingredients, in which the drug, carbopol, ethyl cellulose, anhydrous lactose, talc, and magnesium stearate were weighed individually and sifted manually through mesh # 40 separately. Thereafter, drug, ethyl cellulose, carbopoland lactose were mixed uniformly. Talc and magnesium stearate were finally added as lubricant and then mixed for further 5 min. The weight of the tablet was determined as 500 mg and the tablets were compressed (Rimek press) using a punch and die set to produce round shaped tablets with 3.35 mm thickness dimensions. Formulations F2 to F6 were also prepared by direct compression method but instead of pure ibuprofen, an equivalent weight of solid dispersed ibuprofen was used. Combinations of hydrophobic and hydrophilic polymers were used in a different concentration in order to achieve a controlled release of ibuprofen [25].

Table 1: Formulation of ibuprofen solid dispersed matrix tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Ibuprofen or solid dispersed ibuprofen equivalent to	100	100	100	100	100	100
PEG 6000	-	100	150	200	250	300
Carbopol	15	20	25	30	35	40
Ethyl Cellulose	35	30	25	20	15	10
Lactose	330	230	180	130	80	30
Talc	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10

Evaluation of pre-compression parameters for powder blend

All the pre-compression parameters such as bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio were measured by following standard procedure [26].

Evaluation of post-compression parameters of ibuprofen solid dispersed tablets

Tablet thickness

Five tablets from each formulation were selected randomly and used for thickness test. Thickness of the prepared solid dispersed tablets was measured in mm by using Vernier calliper (Acculab, Ambala, India) [27].

Hardness test

Randomly selected five tablets were taken for hardness test which was subjected to "Monsanto" hardness tester by fitting them between the spindle and anvil through their diameter. The pressure was gradually increased then by turning the knurled knob until the tablet breaks. The force (Kg) required to break the tablet is noted from the scale [27].

Friability test

The friability of tablets was determined by "Roche" friabilator. 10 tablets were weighted and placed in a plastic chamber of friabilator and allowed to rotate 100 revolutions at 25 rpm for 4 min. Then the tablets were removed, de-dusted and reweighed. The percentage friability was calculated as per formula [28].

$$\% \text{ Friability} = \frac{Initial\ weight - Final\ weight}{Initial\ weight} x\,100$$

Weight variation test

Average weights of randomly selected twenty tablets were determined by weighing them individually. Individual weights of the tablets were compared with the average weight. If more than two of the individual weights should deviate from the average weight by more than 7.5 % deviation and none should deviate by more than twice the percentage [27].

Determination of saturated solubility

Amodified solubilitydetermination method was used to determine the solubility of pure ibuprofen and solid dispersed ibuprofen. Solubility study for all the samples along with pure ibuprofen was carried out in distilled water. Pure ibuprofen and solid dispersed ibuprofen were taken in excess quantity in a stopper conical flask containing 10 ml of distilled water. Then the flasks were sealed and shaken on a rotary shaker for 24 h. The sample solutions were collected and then filtered through Whatmann filter paper. Then 1 ml of filtered solution was taken and suitably diluted with the respective media before measuring the absorbances in UV-Visible spectrophotometer at 220 nm. The solubility of all the samples was determined in triplicates and the mean value and standard deviation were noted [29].

Drug content uniformity

10 tablets were selected randomly and then weighed and powdered by using a glass mortar and pestle. Powder quantity equivalent to 50 mg was taken and dissolved in 100 ml of ₍P₎H 7.2 phosphate buffer. From the above drug solution, 1 ml was withdrawn and diluted with 9 ml of ₍P₎H 7.2 phosphate buffer. The solution was then filtered using a Whatman filter paper [20]. The absorbance of the filtered drug solution was measured by using a UV-VIS spectrophotometer (Thermo Spectronic UV-1, USA) at λ_{max} 220 nm and the drug content was determined by the following equation-

$$\% \text{ Drug content} = \frac{Actual\ ibuprofen\ content\ in\ weighed\ quantity\ of\ tablets}{Theoritical\ amount\ of\ ibuprofen\ present\ in\ taken\ tablets} \times 100$$

Swelling study

Swelling study was performed by placing an accurately weighed tablet in a petri dish containing 20 ml of phosphate buffer ₍P₎H 7.2. The tablets were withdrawn at the predetermined time interval and the excess amount of fluid was soaked by a tissue paper [30, 31]. Then the tablet was weighed and the percentage weight gain was calculated by following formula-

$$Swelling\ index = \left[\frac{W_t - W_0}{W_0}\right] \times 100$$

Where, W_t = Weight of tablet after time "t"

W_o = Initial weight of the tablet.

Scanning electron microscopy

The swelled tablet sample was collected and after drying it was coated with metal by using an ion sputtering device. The coated sample was then mounted on SEM instrument and the morphology of the surface was examined by SEI detector [32].

***In vitro* drug release studies**

Dissolution of the tablets was carried out on USP type II paddle type dissolution apparatus (Veego VDA-6D, Veego Instruments Co-operation, India). According to I. P. 7.2 phosphate buffer was selected as dissolution medium and the volume was maintained 900 ml. The temperature of the medium was set at 37±0.5 °C. The rotational speed of paddle was set at 50 rpm. 10 ml of sample was withdrawn at predetermined interval up to 8 h and the same volume of fresh dissolution medium was replaced for maintaining sink condition. The withdrawn samples were filtered and analyzed by UV-VIS spectrophotometer (Thermo Spectronic UV-1, USA) at λ_{max} 220 nm using $_{P}$H 7.2 phosphate buffer as a blank and the cumulative percentage of drug release was calculated [20].

Release Kinetics

In order to understand the mechanism and kinetics of drug release, the result of the *in vitro* drug release study of formulated tablets were fitted with various kinetic equations, such as zero-order (percentage release versus time), first-order (log percentage of cumulative drug remaining versus time), Higuchi's model (percentage drug release versus square root of time), Korsmeyer-Peppas model (log cumulative amount versus log time). Correlation coefficient (R^2) values were calculated for the linear curves obtained by regression analysis of the above plots [33-35].

Zero-order kinetics

The zero order rate describes the systems where the drug release rate is independent of its concentration.

A zero order release would be predicted by the following equation,

$$Q_t - Q_0 = K_0 t$$

Where,

Q_t = Amount of drug release dissolved in time 't'.

Q_o = Initial amount of drug concentration in solution.

K_0 = Zero order rate constant.

When the data was plotted as cumulative % drug release Vs time, if the plot is linear then data obeys zero order kinetics with slope equal to K_0. This model represents an ideal release profile in order to achieve the prolonged pharmacological action.

First order kinetics

The first order describes the release from the system where release rate is concentration dependent.

A first order release would be predicted by the following equation

$$Log\ Q_t = Log\ Q_0 - \frac{K_1 t}{2.303}$$

Where,

Q_t = Amount of drug released in time 't'.

Q_o = Initial amount of drug concentration in solution.

K_1t = First order rate constant

When data were plotted as log cumulative % drug remaining verses time yields a straight line indicating that the release follows first order kinetics. The constant Kcan be obtained multiplying slope values.

Higuchi's model

Higuchi described the release of drugs from the insoluble matrix as a square root of a time-dependent process based on Fickian diffusion.

The graph was plotted as % cumulative drug released Vs square root of time.

$$Q = Kt^{1/2}$$

Where,

K =constant reflecting design variable system

t = time in hours.

Korsmeyer-peppas equation

This model describes drug release from a polymeric system. To find out the mechanism of drug release, an initial 60% drug release data were fitted in the Korsmeyer-Peppas model.

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released Vs time.

$$M_t / M_\alpha = Kt^n$$

$$Log\ M_t / M_\alpha = log\ K + n\ log\ t$$

Where,

M_t/M_α = fraction of drug released at time t

t = Release time

K = Kinetic constant (incorporating structural and geometric characteristics of preparation)

n = Diffusional exponent indicative of the mechanism drug

This model is used to analyze the release of pharmaceutical polymeric dosage forms depending on 'n' value when the release mechanism is not known or more than one type of release phenomenon was involved. $n \leq 0.43$ symbolize Fickian release, $0.43<n<0.85$ symbolize non-Fickian release, and $n \geq 0.85$ indicates a case II transport.

Hixson-crowell

The Hixson-Crowell model describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$$Q_t^{1/3} - Q_t^{1/3} = K_{HC}t$$

Where,

Q_t = remaining amount of drug in the dosage form at time t,

Q_0 = initial amount of the drug in the tablet

K_{HC} = rate constant for Hixson-Crowell rate equation

RESULTS AND DISCUSSION

Fourier transform infrared spectroscopy (FT-IR)

FTIR spectrum of ibuprofen and formulation was shown in Fig.1. FTIR spectrum of ibuprofen shows the peak at 2955.47 cm^{-1} for C-H stretching of alkane which is observed in the formulation at 2956.25 cm^{-1}. Peaks for C=O stretching for carboxylic acid shows peak at1722.58 cm^{-1}which can be observed in the formulation at 1718.82 cm^{-1}. C-C stretching in the aromatic ring is observed for pure ibuprofen at 1418.10 cm^{-1}which is observed in the formulation at 1437.72 cm^{-1}. C-O stretching for carboxylic acid shows peak at 1183.03 cm^{-1}which is also present in the formulation at 1184.23 cm^{-1}. O-H bending for carboxylic acid is observed at 936.73 cm^{-1} which can be seen in the formulation at 932.47 cm^{-1}. The characteristic peaks appeared in the FTIR spectrum of ibuprofen is observed in the formulation without any significant shifting of peaks which indicates the absence of any chemical or physical interaction during and after preparation.

Post-compression parameters

Post-compression parameters such as tablet thickness, hardness, friability, and weight variation tests were carried out for prepared ibuprofen solid dispersed tablets and the results were found within the specified limits (table 2).

Saturated solubility

The saturated solubility of ibuprofen and solid dispersed ibuprofen in distilled water was shown in table 3. The result of solubility studies indicated that ibuprofen is having low aqueous solubility in room temperature. The saturation solubility of ibuprofen was found

to increase in solid dispersed ibuprofen. An increase in the concentration of PEG 6000 in the physical mixture of solid dispersed ibuprofen increased the saturation solubility of ibuprofen. This phenomenon could be due to the enhanced wetting property of ibuprofen [36, 37].

Drug content

The average drug content was calculated for each formulation. The drug content for prepared solid dispersed formulation was found to be within the range of 98.68±0.71% to 99.38±0.46 % (table 2).

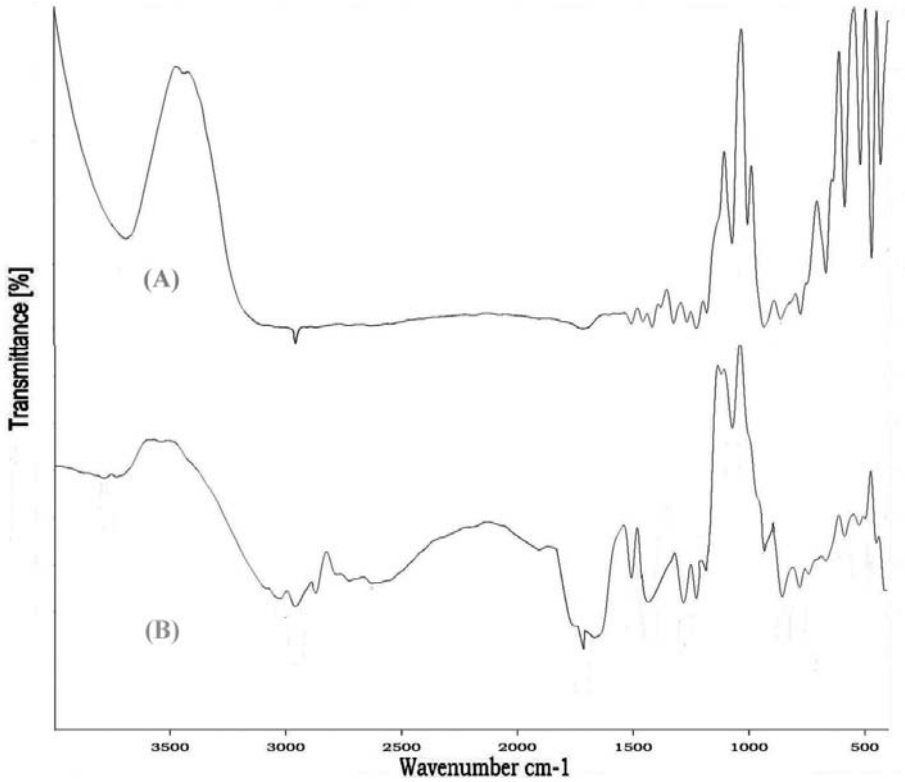

Fig. 1: FT-IR spectrum of–(A)-pure ibuprofen and (B)-formulation mixture

Table 2: Post-compression parameters of ibuprofen matrix tablets

Formulation code	Thickness* (mm)±SD	Weight variation test** (%)±SD	Hardness* (Kg/cm^3)±SD	Friability* (%)±SD *(n=10)*
F1	3.28±0.036	497±1.80	5.75±0.26	0.61±0.07
F2	3.34±0.073	499±1.63	5.64±0.87	0.52±0.04
F3	3.24±0.029	498±1.14	5.43±0.49	0.47±0.05
F4	3.37±0.062	497±1.38	5.48±0.52	0.54±0.03
F5	3.31±0.058	497±1.72	5.61±0.42	0.51±0.05
F6	3.26±0.071	499±1.47	5.32±0.28	0.42±0.06

*n = 10;** n=20; SD-Standard deviation

Table 3: Saturated solubility, percentage drug content and swelling index of prepared ibuprofen solid dispersed matrix tablets

Formulation code	Saturated solubility mg/ml	% Drug content mean±SD	Swelling index %±SD at SIF pH=7.2
F1	1.82±0.07	98.27±0.80	90±5.43
F2	3.27±0.24	97.35±0.46	99±4.28
F3	3.41±0.18	99.17±0.54	113±8.76
F4	3.53±0.27	98.93±0.67	118±7.42
F5	3.59±0.34	97.28±0.52	126±5.87
F6	3.86±0.39	98.79±0.39	137±6.41

n = 3; SD-Standard deviation

Swelling study

The swelling characteristics of solid dispersed matrix tablets of ibuprofen were studied in simulated intestinal fluid (pH 7.2). The swelling index for all the formulation was found within the limit of 90±5.43 to 137±6.41 as given in table 3. From the above data it can be predicted that with the increase in the hydrophilic polymer in the formulation, the swelling index increased gradually. There was gradual disintegration found on the swollen tablet which created pores in tablet surface that has facilitated fluid penetration.

Scanning electron microscope

The surface morphology and porosity for the swelled tablet matrix was examined by scanning electron microscope. Fig. 2 displays the SEM image of F6 formulation. It is clearly observed from the image

that the tablet surface is rough and porous in nature. The uneven swelling was achieved because of the unequal swelling of hydrophilic and hydrophobic polymers which created channels responsible for the inward flow of aqueous fluid and outward drug diffusion.

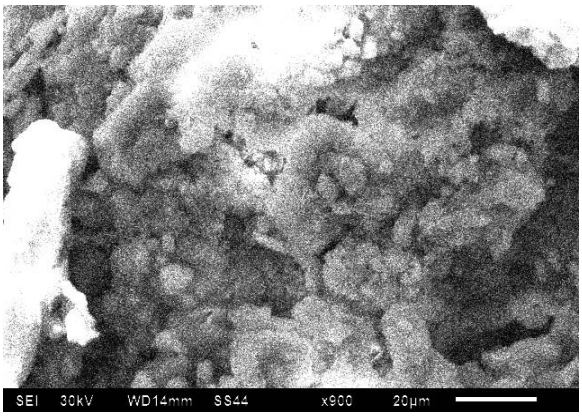

Fig. 2: SEM image of swollen tablet surface

In vitro drug release study

To understand the drug release profile from solid dispersed tablets of ibuprofen *in vitro* release study was performed in phosphate buffer at pH 7.2 up to 8 h. Then the cumulative percentage release was calculated. The cumulative percentage drug released Vs time plot is shown in fig. 3 for all formulations. The cumulative percent drug release after 8 h of dissolution was found to be within the range of 68.76±3.04 to 95.33±2.34 %. The drug release was gradually increased with a higher concentration of carbopol which is a hydrophilic polymer. A higher amount of hydrophobic polymer tends to decrease the release of the drug. Due to the high viscosity of the polymers sustained release of ibuprofen was achieved [38].

In vitro release kinetics

The release kinetics of various formulations is described in table 4. The average percentage release was fitted into different release models: Zero order, First order, Higuchi's plot, korsmeyer-peppas, and Hixson-Crowell model. The correlation coefficients for formulations F1, F2, F3, F4, F5 and F6 are calculated from respective graphs. Based on the correlation values the release mechanism for F1, F2, F5, and F6 were found to follow korsmeyer-peppas kinetics for which value was found within the range of 0.290-0.33, indicating an anomalous behaviour (non-Fickian kinetics corresponding to coupled diffusion/polymer relaxation). F3 and F4 followed Hixson-Crowell model.

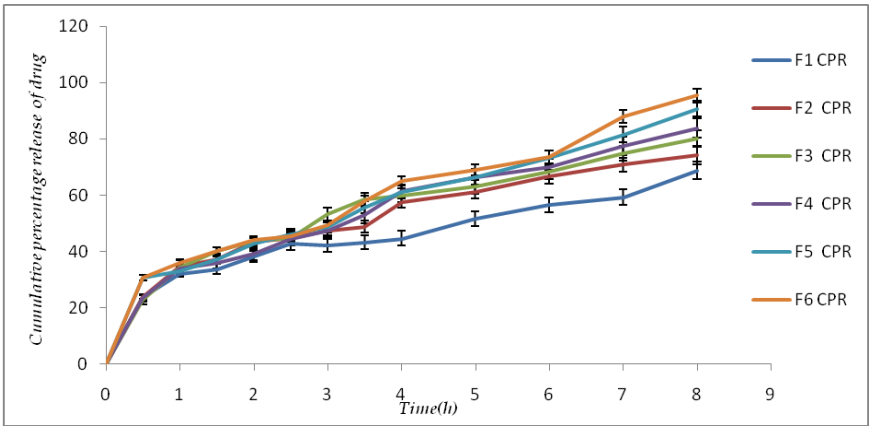

Fig. 3: Comparative C. P. R. of ibuprofen from solid dispersed matrix tablets (number of experiments, n = 3; data given in mean±SD)

Table 4: Result of curve fitting of *in vitro* release of ibuprofen from solid dispersed matrix tablets

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer-peppas		Hixson-crowell	Best fit model
				R^2	N	R^2	
F1	1.50	0.922	0.927	0.935	0.251	0.925	Korsmeyer-Peppas
F2	0.98	0.975	0.970	0.967	0.290	0.965	Korsmeyer-Peppas
F3	0.80	0.960	0.921	0.965	0.313	0.004	Hixson-Crowell
F4	0.16	0.978	0.990	0.986	0.336	0.002	Hixson-Crowell
F5	0.20	0.918	0.978	0.965	0.308	0.961	Korsmeyer-Peppas
F6	0.11	0.857	0.968	0.959	0.311	0.729	Korsmeyer-Peppas

CONCLUSION

The objective of the present research was to formulate solid dispersed tablets of ibuprofen to improve the dissolution rate and to investigate the effect of the combination of hydrophilic and hydrophobic polymers on drug release. The drug and excipient compatibility was checked by FT-IR. Solid dispersed tablets of ibuprofen were prepared by direct compression method with solid dispersed ibuprofen. Saturated solubility was examined in distilled water and it was found to increase for solid dispersed ibuprofen. The swelling study was also performed for all the formulation and swelling index was found satisfactory. After swelling, SEM image of the tablet surface confirmed the presence of numerous pores and swelled tablet surface. Then tablets were evaluated for *in vitro* drug release study which was carried out in phosphate buffer pH 7.2 up to 8 h to give release range from 68.76±3.04 % to 95.33±2.34 %. The dissolution data were subjected to different kinetics models. F1, F2, F5, F6 followed Korsmeyer-Peppas model and F3, F4 followed Hixson-Crowell. F6 was considered as best formulation based on drug release profile.

In conclusion, this system can be considered as one of the promising formulation technique for ibuprofen. The controlled release of the drug from polymer matrix can maximize the drug absorption and reduce the side effects. This technique can be used as a very useful means to increase the dissolution rate and reduction in dose.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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