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Research Article

PREPARATION AND *IN VITRO* CHARACTERIZATION OF SOLID DISPERSION CONTAINING IBUPROFEN

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ABSTRACT

The intention of the current exploration was to develop a better dissolution characteristic of ibuprofen by solid dispersion (SD) technique. During this research, solid dispersion of ibuprofen was formulated by melt dispersion technique using four water soluble polymers e.g. polyethylene glycol (PEG) 6000, 4000; hydroxy ethyl cellulose (HEC) and sodium lauryl sulphate (SLS). The developed formulations were assayed using scanning electron microscopy (SEM) analysis, *in vitro* dissolution test, and fourier-transform infrared spectroscopy (FTIR) study. The SD ibuprofen containing PEG 6000 showed faster and better drug release in comparision with marketed preparation and also active ibuprofen which was found 72% at 60 min. The FTIR studies showed the absence of well-defined drug-polymer interactions. The SEM analysis depicted that the incorporation of polymers reshapes crystalline ibuprofen into amorphous state, thus increasing its solubility and dissolution rate. So, the solid dispersion may be a good technique to boost up the dissolution rate of ibuprofen.

Keywords: *Ibuprofen, hydroxy ethyl cellulose, polyethylene glycol, solid dispersion, SEM, FTIR.*

Introduction

The slow dissolution characteristics of poorly aqueous soluble drugs is a problem to the pharmaceutical industry because the dissolution rate of weakly water-soluble drugs could be the rate limiting process within the absorption of a drug from a solid dosage form (Masum *et al*., 2012). These drugs generally exhibit many difficulties within the improvement of pharmaceutical dosage forms due to their narrow water solubility, deliberate dissolution rate and small bioavailability (Islam *et al*., 2012). Solid dispersions have allowed a promising scope of accelerating their rate of dissolution, and absorption of such drugs in water soluble polymers (Skolakova *et al*., 2012). Numerous publications have reported the applications of soluble

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polymer excipients (such as polyvinylpyrrolidone, poly (ethylene oxide), poly (vinyl alcohol), gelatin, and some other natural products, e.g., water-soluble polysaccharide) as matrices for developing SDs using a wide variety of advanced methods (Zhang *et al*., 2018). Ibuprofen [(±)-2-(4'-isobutylphenyl) propionic acid] (Fig. 1) a phenyl propionic acid derivative, is broadly recognized as the most effective and well tolerated non-steroidal anti-inflammatory (Eichie *et al*., 2009) drugs. It is practically aqueous insoluble which have pKa value of 4.8.

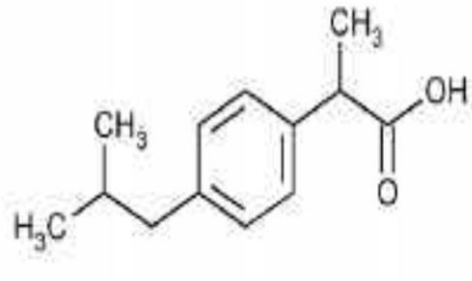

Fig. 1. Chemical structure of (2RS)-2-[4-(2-Methylpropyl) phenyl] propionic acid.

Ibuprofen is a fundamental dug listed as World Health Organization's "Essential Drugs", that means it satisfies the priority health care needs of the population (Gupta *et al*., 2011). The drug has been classified as class II drug according to the Biopharmaceutical Classification System (BCS) having low solubility and high permeability. For this reason, it shows delayed action but rapid onset of action is predominantly required for pain situations especially in dental pain, rheumatoid and osteoarthritis and breast cancers. Increasing the solubility properties and quicken the percent release of ibuprofen is very challenging because its serum concentration and therapeutic effects are correlated; immediate ibuprofen absorption is required for the quick onset of action (Tapan *et al*., 2010). In this research, comparatively fewer amount of carrier (PEG 6000, PEG 4000, SLS and HEC in 1:2 ratio as they act as highly water soluble polymer as well as surfactant) was applied to quicken the aqueous solubility and immediate percent release of ibuprofen by solid dispersion technique. Dissolution behavior have compared by release kinetics studies. Statistical analysis in response to percent release of drug has performed along with ANOVA and Tukey's multiple comparison tests (Tukey 1949).

Materials and Methods

Materials

Active ibuprofen was acknowledged as gift sample from Albion Laboratories Limited, Bangladesh. PEG 6000, PEG 4000, ethyl cellulose (HEC), sodium lauryl sulfate (SLS), potassium dihydrogen phosphate and sodium hydroxide used for the study were analytical graded.

Methods

Preparation of Solid Dispersion of Ibuprofen by Melt Dispersion Method

Samar Afifi, 2015 were prepared the solid dispersions by melting method using 1:2 drug-polymer weight ratios. By following them, the required amount of ibuprofen and polymer (PEG 6000, PEG 4000, HEC and SLS) according to the compositions presented in Table 1 were taken in

separate glass beaker and melted in hot water bath at 70ºC with continuous stirring to obtain a viscous mass. Then it was reserved at ambient temperature for five days until solid mass is created. The dried mass was pulverized utilizing mortar and pestle and sieved through mesh size 40 to obtain solid dispersions. Finally, the resultant dried solid systems were stored in a desiccator until further use.

Table 1. Compositions of different ibuprofen solid dispersion.

Serial No.	Carriers	Drug polymer ratio	Dispensing (mg)	Formulation coding
01	PEG 6000	1:2	200:400	A
02	Hydroxy ethyl cellulose (HEC)	1:2	200:400	B
03	PEG 4000	1:2	200:400	C
04	Sodium lauryl sulphate (SLS)	1:2	200:400	D

Preparation of Standard Curve for Ibuprofen

For standard curve of ibuprofen, all stock solution was prepared by taking ibuprofen in 100 ml solvent (phosphate buffer: pH 7.2) in a volumetric flask. Six different dilutions were prepared of the stock solution (0.1 mg/ml) having concentrations, 0.05 mg/ml, 0.025 mg/ml, 0.0125 mg/ml and 0.0062 mg/ml respectively. Absorbance of the sample were analysed at 221 nm by a UV-visible spectrophotometer. The average values of absorbance were plotted against respective drug concentration and a slope was developed (Fig. 2) (Akhter *et al*., 2016).

Preparation of Phosphate Buffer Solution (pH **= 7.2)**

6.804 gm of Potassium di-hydrogen phosphate and 0.1466 gm of NaOH was solvated in 1000 ml distilled water and 7.2 pH was maintained with pH meter.

Characterization of Ibuprofen Solid Dispersions

i. ***Fourier Transform Infrared Spectrophotometry (FTIR) Analysis***

The FTIR spectra for ibuprofen and solid dispersions were performed using Perkin-Elmer FTIR series (model-1615) spectrophotometer. Samples were mixed with potassium bromide (KBr) and compressed into discs. The scanning range was between 4000-450 cm^{-1} (Vijay *et al*., 2011).

ii. ***Scanning Electron Microscope (SEM) Analysis***

The morphology and surface topology of the solid power particles were interpreted under scanning electron microscopy (Akhter *et al*., 2016).

iii. ***In Vitro Dissolution Experiments of Ibuprofen From Solid Dispersions***

In vitro dissolution studies were completed utilizing UV-Spectrophotometer analysis (rpm 75, phosphate buffer containing pH 7.2 at 221 nm wavelength, one hour) for each sample (Mogal *et al*., 2012).

iv. *Release Kinetic Data Analysis*

Drug release kinetics for solid dispersion was calculated by the following five kinetic models.

(a) Zero order release kinetic model: cumulative % of drug released vs. time (*T*);

(b) First order release kinetic model: log cumulative % drug remaining vs time (*T*);

(c) Higuchi's release kinetic model: cumulative % drug released vs square root of time (*T*);

(d) Korsmeyer-Peppas model:log cumulative % drug released vs log time (*T*)

(e) Hixson-Crowell model: Cube root of initial amount - Cube root of drug remaining vs time (T) (Ryakala *et al*., 2015).

v. *Statistical Analysis by ANOVA*

One-way analysis of variance (ANOVA) was conducted for all ibuprofen solid dispersion formulations with respect to their cumulative percent of drug release at 60 min followed by Tukey's multiple comparisons test using GraphPad Prism software, where $p < 0.05$ were considered as a statistically significant (Samy *et al*., 2010).

Results and Discussion

Standard Curve of Ibuprofen in Phosphate Buffer (pH = 7.2)

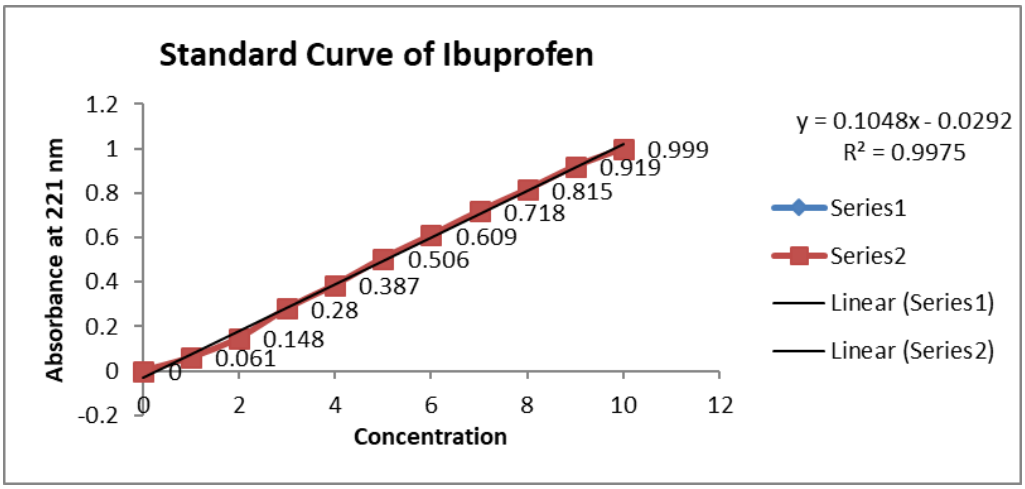

Fig. 2. Standard curve of Ibuprofen (API).

Characterization of Solid Dispersions

i. *Fourier-Transform Infrared Spectroscopy (FTIR) Analysis*

FTIR spectra of solid dispersion formulation of ibuprofen indicated characteristic peaks at different wave numbers which were also checked in the FTIR spectrum of active ibuprofen. The FTIR spectrum explains absence of several additional peaks for new functional groups, representing that no chemical interaction between drug and polymers (Figs. 3, 4 and 5).

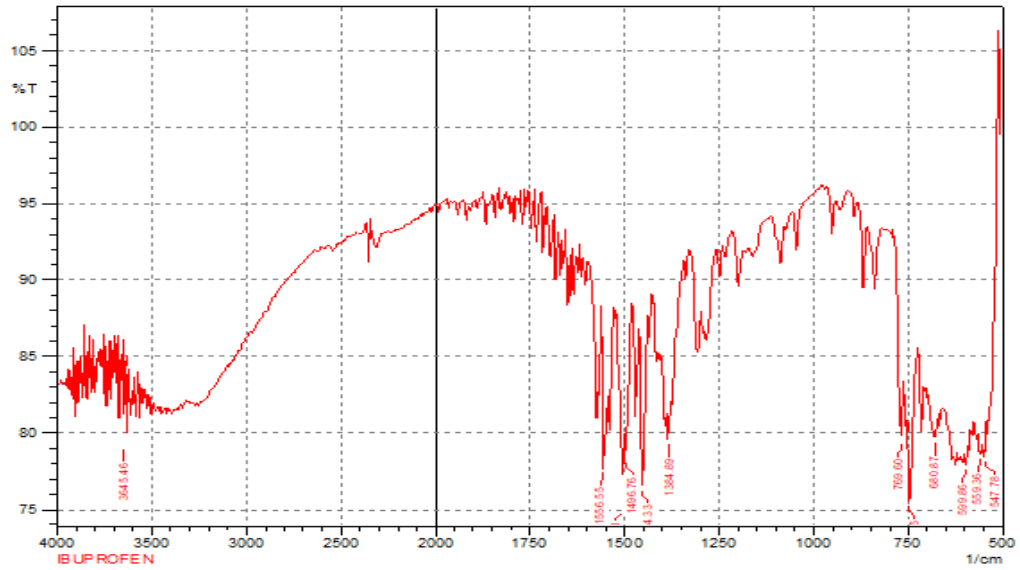

Fig. 3. FTIR spectrum of active ibuprofen.

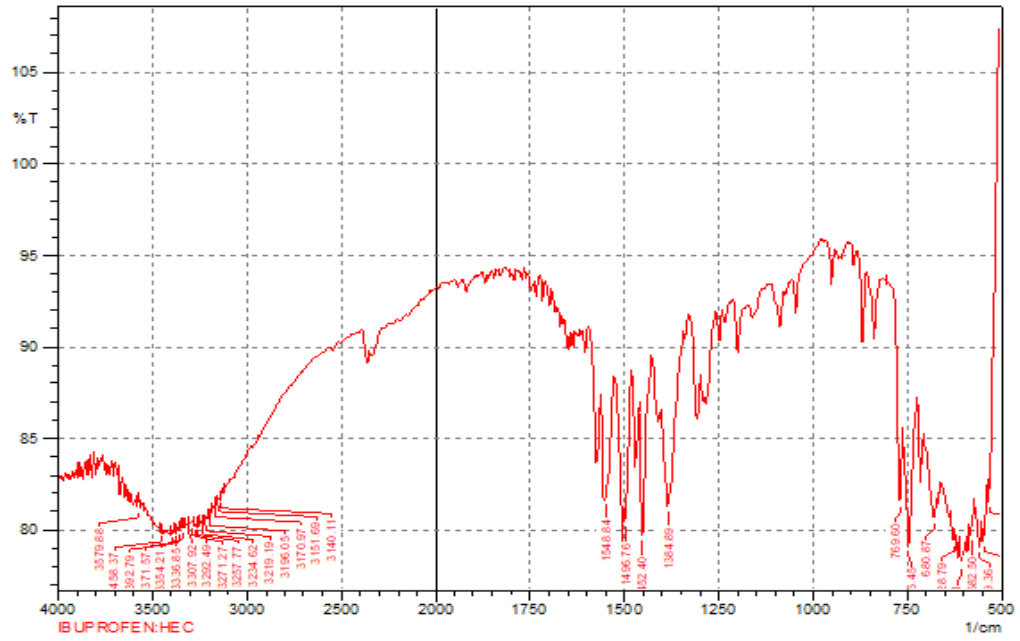

Fig. 4. FTIR spectrum of ibuprofen solid dispersion containing HEC (Formulation coding: B).

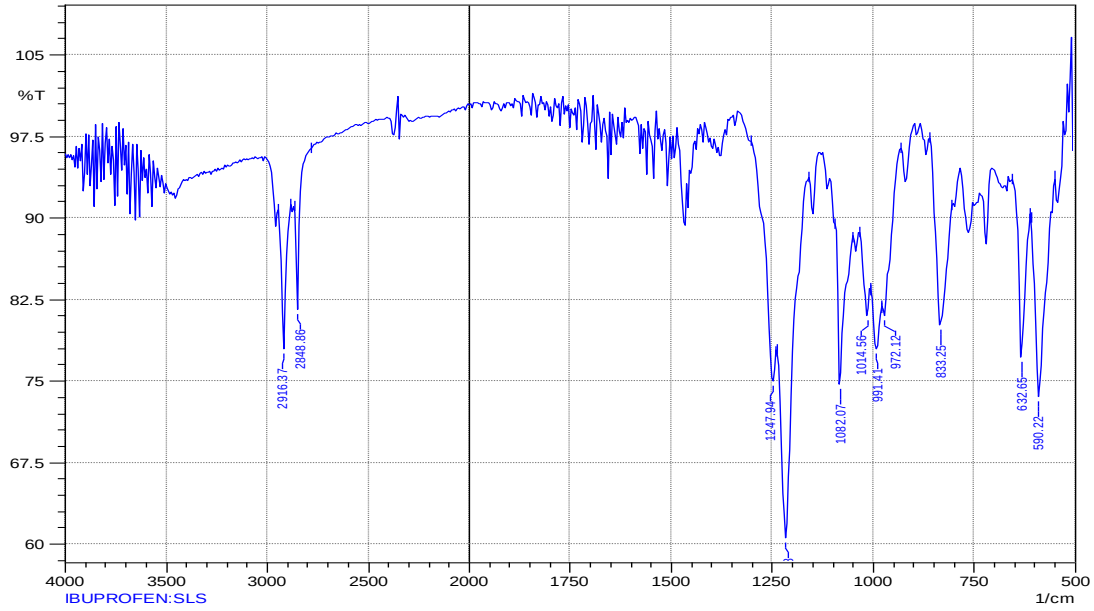

Fig. 5. FTIR spectrum of ibuprofen solid dispersion containing SLS (Formulation coding: D).

ii. ***Scanning Electron Microscope (SEM) Analysis:*** SEM examination showed the external morphological estate of the solid dispersion was in amorphous state. The surface morphology is experiential and symbolic micrographs are given in Fig. 6.

iii. In Vitro Dissolution Profile of Ibuprofen From Solid Dispersion Formulations

Dissolution characters of the active drug and drug polymer binary systems are represented in Fig. 7. As is apparent, the solid dispersions technique improved the dissolution frequency of ibuprofen. The percentages of drug dissolved at 60 min were 72%, 46%, 52%, 40%, 30% and 32% for A, B, C, D, marketed formulation Inflam and Flamex, respectively. Considering this data, release pattern from solid dispersion formulation A containing PEG 6000 showed the best result considering to active drug and all other solid dispersion formulation & also from marketed product which was 72% within an hour. However, Samar (2015) worked with solid dispersion of stiripentol and PEG 6000 and found percent release of drug 81%. And many others researchers like Akhter *et al*. (2016) also worked with solid dispersion and reported the significant release of drug due to using water soluble polymer. This increment can be attributed to the greater hydrophilic character, which can decrease the interfacial tension between a poorly water-soluble drug and dissolution medium. The intensification of the solubility of ibuprofen with carriers or polymers used might be attributed to the wetting effect of the highly water-soluble polymer in intimate contact with it. The polymers solubilized ibuprofen by breaking up water soluble clusters surrounding the non-polar molecule, raising the entropy of the process and yielding a driving pressure for the solubilization. Also, the augmentation in the dissolution frequency may be due to

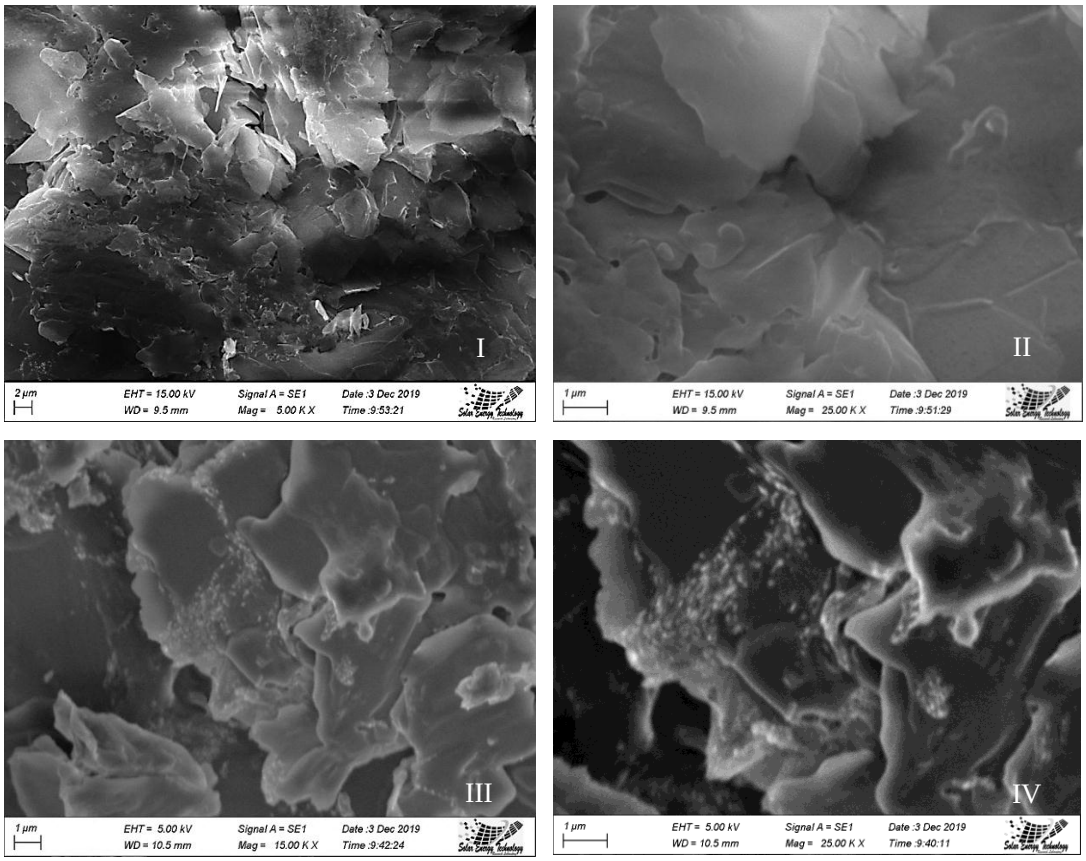

Fig. 6. (I, II, III, & IV). SEM of ibuprofen solid dispersion containing SLS (Formulation coding: D).

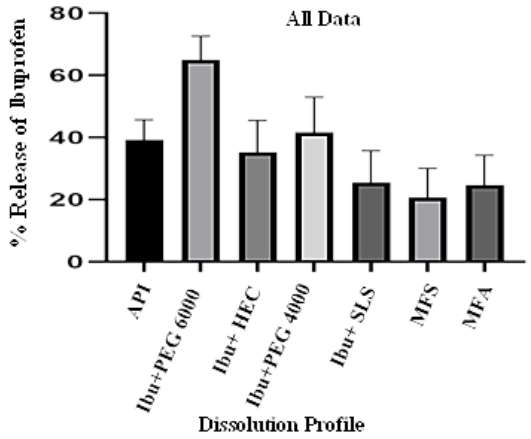

Fig. 7. Percentages of drug released from solid dispersions and market product.

the increment of the physical amorphism of the drug and this augmentation also may be due to the increment in the wettability and solubility of the drug.

iv. *Release kinetics study*

Dissolution characters of active ibuprofen, solid dispersion formulation and marketed product were calculated by zero order (Fig. 8), first order (Fig. 9), higuchi square root equation (Fig. 10), hixon-crowell (Fig. 11) cubic root law and korsmeyer log fraction of drug release (Fig. 12). Different formulation followed different release kinetic model which can be explained by statistical analysis higher correlation coefficient (R^2) values. Formulation A containing PEG 6000 followed higuchi kinetic model (R^2 =0.942, y=3.38x+ 47.4) as they showed highest R^2 value than others kinetic model.

(a) Zero order kinetics:

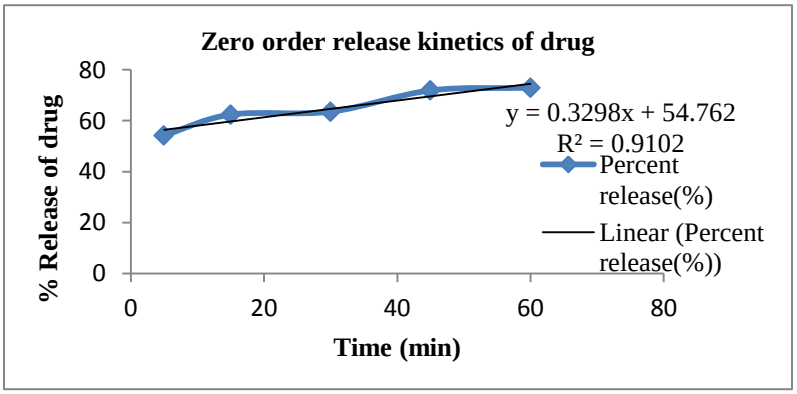

Fig. 8. Zero order plot of Ibu+PEG 6000 (A).

(b) First order kinetics:

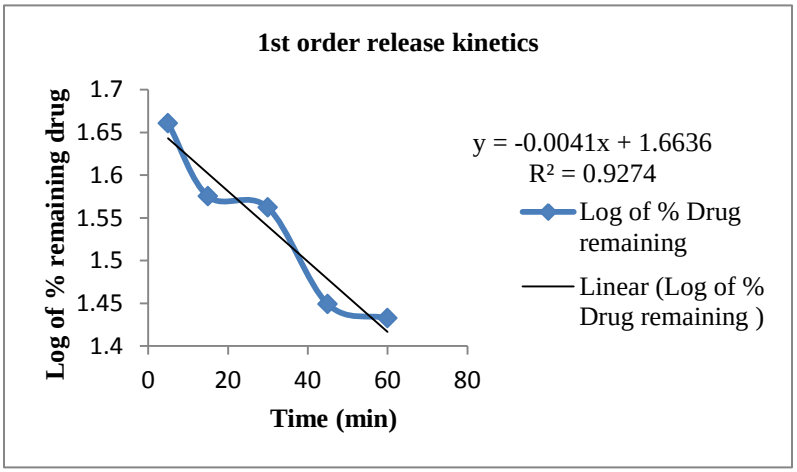

Fig. 9. First order kinetics of IBU+PEG 6000 (A).

(c) Higuchi square root law:

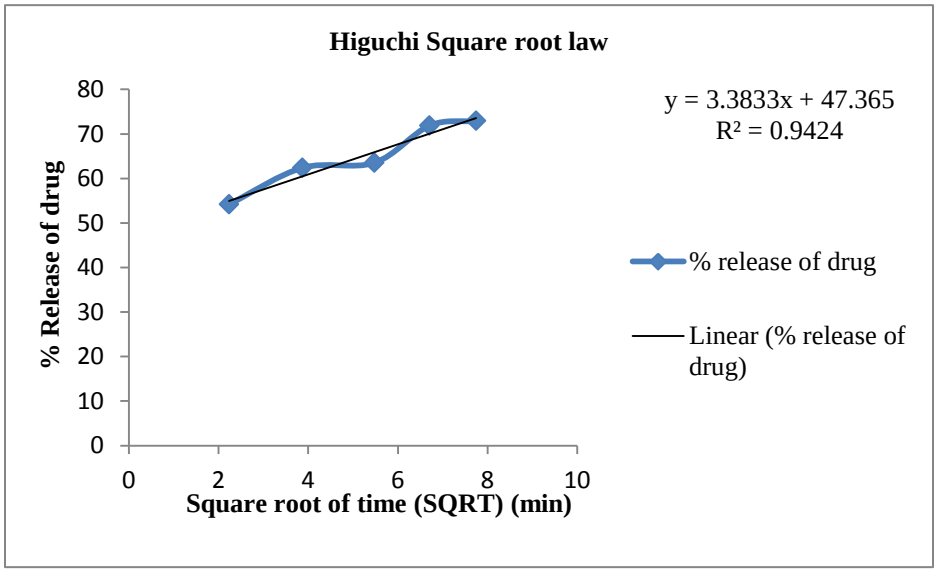

Fig. 10. Higuchi plot of IBU+PEG 6000 (A).

(d) Hixon crowell cube root law:

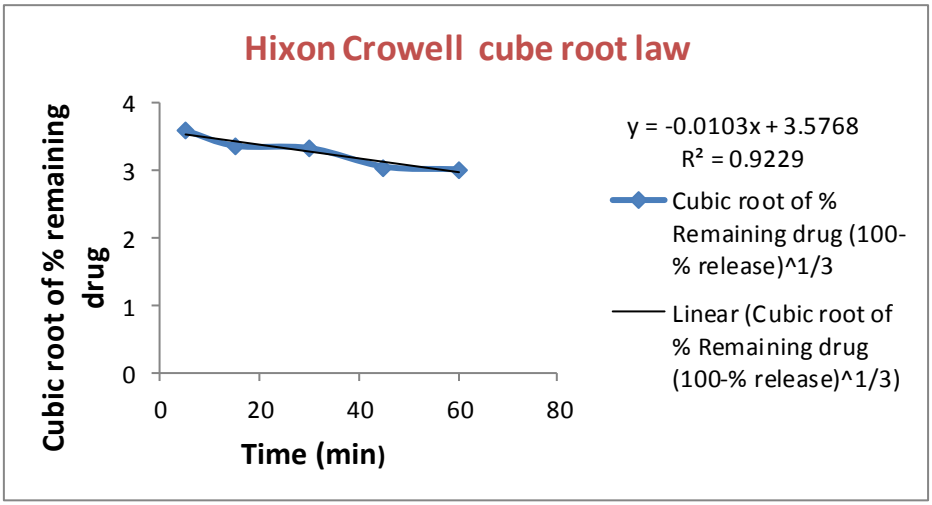

Fig. 11. Hixon plot of IBU+PEG 6000 (A).

(e) Korsmeyer log fraction of drug release:

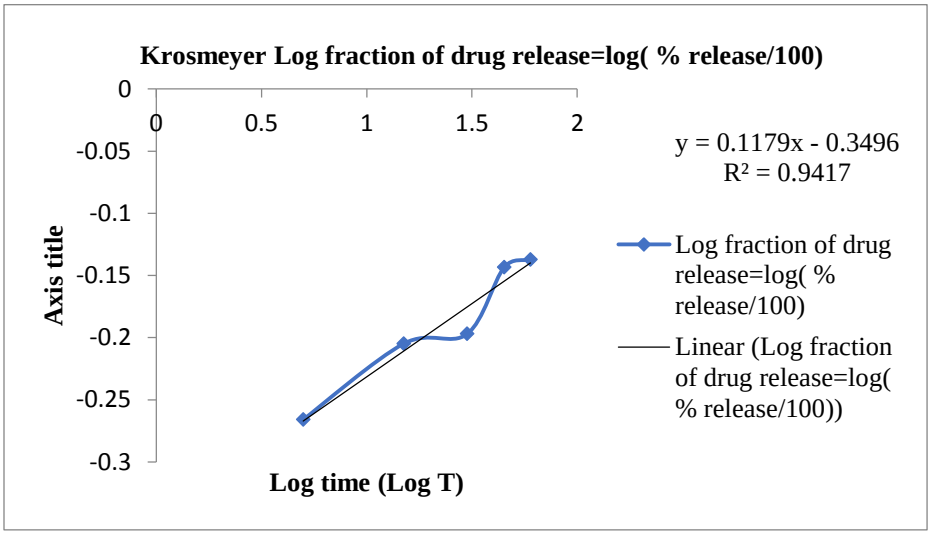

Fig. 12. Korsmeyer plot of Ibuprofen+ PEG 6000 (A).

Statistical Analysis

One-way analysis of variance (ANOVA) of ibuprofen solid dispersion was performed with respect to their % released at 60 min followed by the Tukey's multiple comparisons test (Table 2).

Conclusion

In the present study, solid dispersions of ibuprofen with different hydrophilic carriers in 1:2 w/w ratios were prepared by melt dispersion method to improve aqueous solubility and dissolution characteristics. Though different drug and polymer weight ratios can be used in solid dispersion preparation, but in our research we have tried to use lower amount of polymer to increase the percent realease of ibuprofen within one hour. Finally this research showed that when ibuprofen was dispersed in suitable immediate release polymer like PEG 6000, PEG 4000, SLS and HEC, its dissolution was enhanced in comparison to that with active drug. Among all water-soluble carriers, the PEG 6000 in 1:2 ratios (binary formulation) was found to be the best. In future *in vivo* study is also required for final selection of carrier and to produce a successful drug delivery system. The water-soluble carrier may operate in the micro environment (diffusion layer) by surrounding the drug particles, thus enhancing the solubility and dissolution of drug.

Table 2. Tukey's multiple comparisons test of active ibuprofen and ibuprofen solid dispersion.

Formulae	Mean Diff.	95.00% Confidence Interval of diff.	Significance	Adjusted *P* Value
API vs. Ibu+PEG 6000 (A)	-25.72	-44.58 to -6.863	**	0.0029
API vs. Ibu+ HEC (B)	4.055	-14.80 to 22.92	ns	0.9926
API vs. Ibu+ PEG 4000 (C)	-2.384	-21.24 to 16.48	ns	0.9996
API vs. Ibu+ SLS (D)	13.73	-5.128 to 32.59	ns	0.2747
API vs. MFS (Inflam)	18.62	-0.2379 to 37.48	ns	0.0547
API vs. MFA (flamex)	14.55	-4.309 to 33.41	ns	0.2171
IBu+PEG6000 (A) vs. Ibu+HEC (B)	29.78	10.92 to 48.64	***	0.0005
IBu+PEG6000 (A) vs. Ibu+PEG 4000 (C)	23.34	4.479 to 42.20	**	0.0082
IBu+PEG6000 vs. Ibu+ SLS (D)	39.45	20.59 to 58.31	****	<0.0001
IBu+PEG 6000 (A) vs. MFS (Inflam)	44.35	25.48 to 63.21	****	<0.0001
IBu+PEG 6000 (A) vs. MFA (flamex)	40.27	21.41 to 59.13	****	<0.0001
Ibu+ HEC (B) vs. Ibu+PEG 4000 (C)	-6.439	-25.30 to 12.42	ns	0.9279
Ibu+HEC (B) vs. Ibu+SLS (D)	9.677	-9.183 to 28.54	ns	0.6666
Ibu+HEC vs. MFS (Inflam)	14.57	-4.293 to 33.43	ns	0.2160
Ibu+HEC vs. MFA (flamex)	10.50	-8.364 to 29.36	ns	0.5807
Ibu+PEG4000 (C) vs. Ibu+SLS (D)	16.12	-2.744 to 34.98	ns	0.1327
Ibu+ PEG 4000 (C) vs. MFS (Inflam)	21.01	2.146 to 39.87	*	0.0216
Ibu+PEG 4000 (C) vs. MFA (flamex)	16.93	-1.925 to 35.79	ns	0.1005
Ibu+SLS (D) vs. Inflam (ACI)	4.890	-13.97 to 23.75	ns	0.9805
Ibu+SLS vs. flamex (Sanofi)	0.8190	-18.04 to 19.68	ns	>0.9999
Inflam (ACI) vs. Flamex (Sanofi)	-4.071	-22.93 to 14.79	ns	0.9924

***Significant at p <0.001; **Significant at p < 0.01; *Significant at p <0.05; ns= non-significant

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