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Solubility Enhancement of a BCS Class II Drug Using Granulated Fumed Silica as an Adsorbent

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Authors' contributions

The project was developed by authors SDT and RHD. Both authors read and approved the final manuscript.

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ABSTRACT

Aim: The aim of this study was to improve solubility and dissolution characteristics of Ibuprofen using granulated fumed silica (Aeroperl®300) as a carrier.
Methods: Ibuprofen-silica complex was prepared by solvent evaporation technique using ethanol as the solvent. Formulation I and II consisted of polymers hydroxypropyl methylcellulose (HPMC E5) and Polyvinyl Pyrrolidone (PVP K-30) respectively. Each formulation was prepared using 1:1:1 and 1:1:2 ratio of drug, polymer and silica. Dried powder obtained was characterized using Differential Scanning Calorimetry (DSC), Powder X-Ray Diffraction (PXRD), Fourier transform infrared spectroscopy (FTIR) and Polarized Light Microscopy (PLM). In-vitro dissolution studies were carried out using three different media including Phosphate buffer (pH 6.8), 0.1N Hydrochloric Acid (pH 1.2) and de-ionized water.
Results: Drug loading up to 30% w/w was successfully achieved with 1:1:1 ratio formulations. Physical characterization data confirmed change of crystalline Ibuprofen into amorphous form after processing. Maximum solubility increment of 33-37% was achieved in Phosphate buffer with formulations II A and II B within the first 5 minutes of dissolution as compared to the control (pure drug).
Conclusion: Enhancement in drug solubility and subsequent dissolution rate can be attributed to adsorption of amorphous drug molecules onto porous silica that readily desorb on contact with

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dissolution media. High porosity and huge surface area of silica makes it a potential candidate for improving delivery of poorly soluble drugs.

Keywords: Poor solubility; bioavailability; drug entrapment; dissolution rate enhancement; porous silica.

1. INTRODUCTION

New chemical entities are increasing rapidly by the day and many of them belong to BCS Class II (Poor solubility and good permeability) and class IV (Poor solubility and permeability) [1]. Poor aqueous solubility of an active pharmaceutical ingredient (API) is a major hurdle for successful development of an oral dosage form [2]. Dissolution is a rate limiting step in such cases and affects the bioavailability due to incomplete absorption of the drug [3]. This generates a constant need to develop novel methods for improving drug solubility and subsequent bioavailability [4].

Ibuprofen, a BCS class II drug was used for our research purpose. For a poorly soluble drug such as Ibuprofen [5], the most critical requirement is to form a solution in the gastrointestinal (GI) fluid for optimum absorption [6]. In such cases, enhancement in the dissolution rate is necessary to achieve suitable blood levels [7]. Method of preparation alters the physicochemical properties of the drug causing a direct effect on the drug's performance and its interaction with the carrier or excipient in the formulation [8]. Hence, for a formulation scientist solubility, permeability, dissolution rate and first-pass metabolism are of critical value to successfully develop a dosage form to achieve desired physiological effect [9]. There are several methods employed to increase dissolution rate including particle size reduction, complexation, solid dispersion, spray drying etc. [10]. A solid dispersion method known as solvent evaporation was used for our research. It is a common technique used to convert a crystalline drug into its amorphous form [11]. In this process, the long range ordered crystal structure is disrupted to form a disordered amorphous solid that has higher free energy leading to greater molecular mobility and hence, greater solubility than the former [12]. Amorphous solid forms of the API are hence desirable to attain greater dissolution rates and a lot of work has been done to stabilize them to prevent possible recrystallization over a period of time [13] [14]. Effect of two different hydrophilic polymers hydroxypropyl methylcellulose (HPMC E5) and Polyvinyl Pyrrolidone (PVP K-30) were investigated on the release of the drug in the dissolution mediums. Ethanol was used as a solvent [15].

Granulated fumed silica (AEROPERL® 300 Pharma)[16] was selected as a carrier for our research. It is basically granulated colloidal silicon dioxide with particle size ranging from 30–40 µm [17]. It has a pore volume of 1.6 ml/g, with a specific surface area as high as 300 m^2/g [18]. Porous amorphous silica has been widely used as an excipient due to its multiple properties such as high absorbability, good flowability, lubrication etc. [19] [20]. Due to these properties mesoporous silica has been widely investigated as potential drug carrier [21]. Silica–drug interactions occur due to terminal silanol groups formed on the surface of mesoporous silica materials followed by subsequent conversion into amorphous form [22] [23]. The inert nature, porous structure and high surface area makes silica a suitable candidate for high drug loading and delivery [24] [25].

Aim of the study was to increase the solubility and subsequent dissolution of Ibuprofen by adsorbing the latter on porous silica. Two polymers were incorporated in the formulations to investigate their influence on the drug solubility and release kinetics. Fourier transform infrared spectroscopy (FTIR), Differential Scanning Calorimetry (DSC) and Powder X-Ray Diffraction (PXRD) confirmed the transition of the drug into amorphous form. Polarized light microscopy (PLM) demonstrated successful loading of the drug on porous carrier. Dissolution studies performed showed an increase in the solubility and dissolution characteristics of the drug as compared to the control (pure Ibuprofen). The developed formulations proved the potential use of silica for successful oral drug delivery of poorly soluble drugs.

2. MATERIALS AND METHODS

2.1 Materials

Ibuprofen, Ethanol 200 proof and Phosphoric acid were purchased from Sigma-Aldrich Corporation (St. Louis, MO. USA). PVP K-30 and Acetonitrile was supplied by Spectrum Chemicals

(New Brunswick, NJ. USA) and HPMC E5 from Dow chemicals (Midland, MI. USA). Aeroperl® 300 (Silica) was gifted by Evonik Industries (Chester, PA. USA) and de-ionized water was obtained from Barnstead Nanopure- Thermo Scientific (Waltham, MA. USA).

2.2 Methods

2.2.1 Preparation of silica loaded ibuprofen

Ibuprofen was selected as a model BCS class II drug for our study. Solvent evaporation method was used to adsorb drug particles onto the porous silica. Drug solution was prepared by adding accurately weighed Ibuprofen to ethanol in a beaker. This mixture was stirred constantly with a magnetic stirrer to form a clear solution. Hydrophilic polymers HPMC E5 and PVP K-30 were added to separate drug solutions at room temperature to make formulations I and II respectively. These polymers were added to aid dispersibility of the drug into dissolution medium by reducing the interfacial tension between drug particles and liquid media. This facilitates faster release of the drug from the pores of silica. Drug: Polymer: Silica were added in two ratios of 1:1:1 and 1:1:2 which were labeled as A and B respectively for each polymer. Silica (Aeroperl®300) was heated in hot air oven until constant weight of the powder was obtained. Drug polymer mix was then added drop wise to this powder under gentle continuous mixing using a mortar and pestle. Ethanol added was then evaporated at 60℃ in a vacuum dryer. Complete evaporation of ethanol was confirmed via weight loss on drying. Dried powder thus obtained was stored in plastic container at room temperature.

2.2.2 Drug entrapment and loading

Silica (Aeroperl® 300) in each of the formulations I and II with polymers HPMC E5 and PVP K-30 respectively, were loaded with 200mg of Ibuprofen. These mixtures were then suspended in 5ml of ethanol and subjected to centrifugation at 12,000 rpm at room temperature (25 ℃) for one hour. The supernatant was then separated and analyzed for free drug content using HPLC. The entrapment efficacy (EE) was calculated by the equation:

Entrapment Efficiency (%) = (Total amount of drug – Amount of free drug in supernatant/ Total amount of drug) X 100 (1)

Drug loading was calculated by subtracting the amount of free drug from the total drug loaded on to the silica. All experiments were run in triplicates.

2.2.3 Powder characterization techniques

2.2.3.1 Fourier transform infrared spectroscopy

Spectra were obtained using Nicolet iS50 FT-IR Spectrometer (Thermo Scientific, Bridgewater, NJ). Pure drug, Silica (Aeroperl® 300), physical mixture and the formulations were analyzed to investigate changes in the absorption spectra of the drug on processing. All spectra were obtained in triplicates.

2.2.3.2 Differential scanning calorimetry

DSC of pure drug, physical mixture and all formulations was carried out using Q100- TA DSC 7 (Mettler Toledo, Switzerland) instrument with nitrogen used as purge gas at the rate of 50 ml/min. Samples were analyzed using a heat cool heat cycle from 25℃ to 300℃ with the heating rate of 10℃/min. An empty sealed aluminum pan (TA instruments, New castle, DE) was used as reference and sample size ranged from 6mg-8mg. All results were reported as an average of three tests.

2.2.3.3 Powder X-ray diffraction

SmartLab X-Ray diffractometer (Rigaku Americas Corporation, TX) was used for analysis. Samples were scanned from 5° to 40° with the step size of 0.02° per 0.5 seconds. Diffractograms for pure drug, physical mixture and formulations were investigated. Amorphous/crystalline phase identification was conducted using PANalytical X'pert data viewer (PANalytical INC., Westborough, MA). All tests were performed in triplicates.

2.2.3.4 Polarized light microscopy

Light microscope (Micro-optics Precision Instruments, Fresh Meadows, NY) was used to observe images of drug-carrier physical mixture, neat silica and prepared formulations to validate incorporation of drug into the pores of silica (Aeroperl® 300). Samples were placed on a glass

slide with cover slips and analyzed at 100X magnification.

2.2.3.5 In vitro dissolution

A USP type II apparatus (rotating paddle) was used for dissolution studies (Dissolution system 2100, Distek Inc., New Brunswick, NJ). Dried drug product and pure Ibuprofen (control) were hand-filled in size 0 capsules. Dissolution was performed on formulations I, II and pure Ibuprofen (control) capsules using 900ml of PB (pH 6.8), 0.1N HCL (pH 1.2) and deionized water as media. Tests were conducted at 37℃ with the rotation speed of 100rpm. Samples were collected at 5, 10, 20, 30, 45, 60 and 90 mins. These were filtered through 0.45µ filter and analyzed using HPLC. In vitro dissolution data was fit using five different kinetic models for predicting the release profile exhibited by control and formulations. These models include [26]:

Zero-order release model:

$$W = K_1 t \quad (2)$$

First-order release model:

$$\ln (100- W) = \ln 100- K_2 t \quad (3)$$

Hixson- Crowell release model:

$$(100 – W)^{1/3} = 100^{1/3} – K_3 t \quad (4)$$

Higuchi release model:

$$W = K_4 t^{1/2} \quad (5)$$

Krosmeyer-Peppas release model:

$$\frac{M^t}{M_\infty} = K_5 t^n \quad (6)$$

Where, W is the percent drug release at time 't'. K_1, K_2, K_3, K_4 and K_5 are rate constants and 'n' is the diffusion or release exponent.

2.2.3.6 HPLC analysis method

Agilent 1100 series HPLC instrument (Masspeclink Technologies LLC, Exton, PA) was used for analysis. Each sample concentration was calculated based on the standard curve. Sample analysis was carried out using a C-18 Column (4×250mm, 5µm) at 25℃. Mobile phase consisted of acetonitrile: water in the ratio of 60:40 (pH 3) with the flow rate of 1ml/min. Samples were measured at 220nm with the sample size of 30µl and retention time of about 4 minutes.

3. RESULTS AND DISCUSSION

3.1 Quantitative Determination of Silica Loaded Ibuprofen

Table 1 shows average percentages of drug entrapment and drug loading for all formulations. Drug entrapment of 86% and 89% was achieved with the formulations I A and II A. A maximum entrapment of 91% was achieved with both I B and II B formulations containing higher concentration of silica. This demonstrates that higher surface area of silica facilitates greater adsorption of drug onto the porous structure increasing the drug loading capacity. Drug loading ranged from 28-30% for formulations I A and II A and about 22% for I B and II B. The difference in the theoretical and practical drug load is attributed to the loss of the drug during processing. The results are reported as a mean of three experiments for each formulation. Drug entrapment and loading was determined by using a standard calibration curve of HPLC at 220 nm [27, 28].

3.2 Characterization of Drug Product

3.2.1 Fourier transform infrared spectroscopy

Fig. 1 shows FTIR spectra of pure drug, Silica, physical mixture of drug-silica and the

Table 1. Drug entrapment efficiency and percent drug loading onto silica

Formulation	Component ratio's	Entrapment efficiency (%)	Theoretical drug loading (%)	Practical drug loading (%)
I A	Ibuprofen: HPMC E5: Silica 1:1:1	89.94 ± 2.28	33.33	30.01 ± 2.87
I B	Ibuprofen: HPMC E5: Silica 1:1:2	91.05 ± 3.66	25	22.71 ± 1.51
II A	Ibuprofen: PVP K30: Silica 1:1:1	86.34 ± 2.84	33.33	28.45 ± 3.30
II B	Ibuprofen: PVP K30: Silica 1:1:2	91.30 ± 4.17	25	22.82 ± 1.96

formulation I A, I B, II A and II B. Pure silica shows an Si–O stretching band at 1104 cm−1 and Si-O bending at 809 cm^{-1} [29]. Drug absorption spectra clearly shows a major band at 1705 cm^{-1} corresponding to the carboxylic group of ibuprofen molecules and a band between 2850-2950 cm^{-1} corresponding to C-H stretching [30]. On processing, all the formulations exhibit reduction in the characteristic C=O band around 1711 cm^{-1} with a slight shift towards right in I A, I B, II A and II B. This shift indicates hydrogen bonding between carbonyl group of the polymers and hydroxyl group of Ibuprofen [31]. Greater reduction in the drug peak was seen among formulations I B and II B having higher amount of silica. This is attributed to the higher concentration of silica in these formulations which provides higher surface area and pore volume that helps incorporation of more ibuprofen molecules in addition to those already adsorbed onto the carrier. FTIR data suggests formation of hydrogen bond between carboxylic group of drug molecules and the silanol groups present on the surface of the pores of carrier [24], leading to amorphous behavior of processed samples.

3.2.2 Differential scanning calorimetry

DSC curves of ibuprofen, physical mixture and formulations were investigated by heating at 10° C/min from 25 to 300℃. Fig. 2a shows a sharp endotherm for pure Ibuprofen around 75° C corresponding to its melting point. A characteristic melting peak of the drug was observed for both the physical mixtures 1:1 and 1:2 of drug and silica (Fig. 2.c and 2.d). The intensity of the peak decreased considerably as compared to pure Ibuprofen because of the reduced crystallinity of the drug in presence of silica. This is attributed to the porous nature of silica that adsorbs drug molecules into the voids causing loss of orderly crystal structure. No melting peak was observed for silica (Fig. 2.b) due to its amorphous nature. Formulations I A, II A, I B and II B were lacking endothermic peak indicating conversion of the drug from crystalline to amorphous form (Fig. 2.c and 2.d). Solvent evaporation technique encapsulates the drug molecules into the pores preventing them from rearranging themselves in a crystal lattice. Absence of melting peak indicates uniform distribution and complete incorporation of the drug into porous carrier system.

3.2.3 Powder X-ray diffraction

X-ray diffraction is one of the most commonly used techniques to study the physical state of the drug and formulations [32]. P-XRD spectrograms are shown in Fig. 3 for physical mixtures, pure drug and all the formulations. Pure drug exhibited strong diffraction pattern (Fig. 3.b) with characteristic peaks, 2θ at 6.11, 16.68, 19.05,

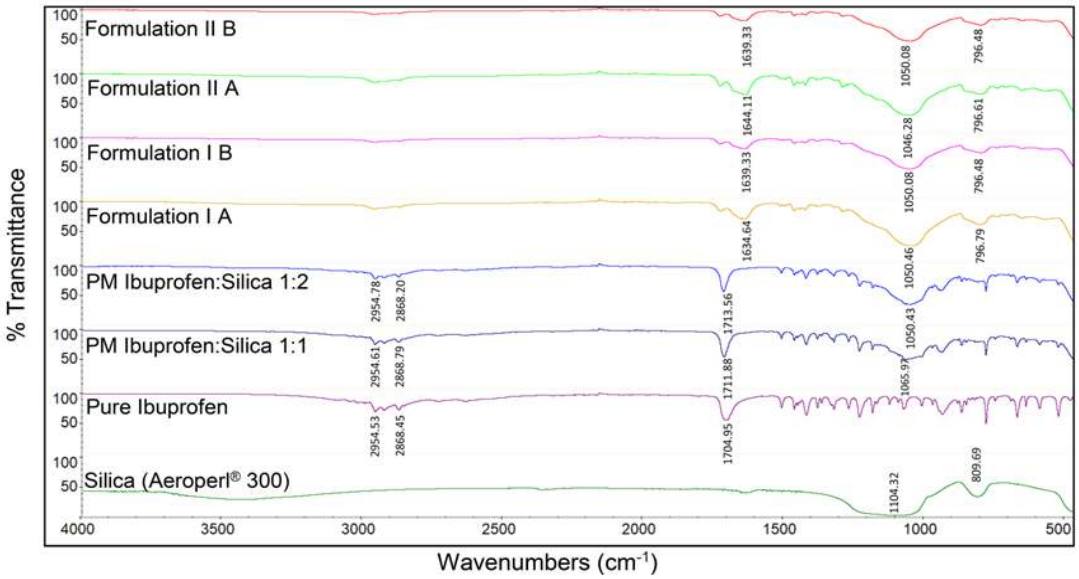
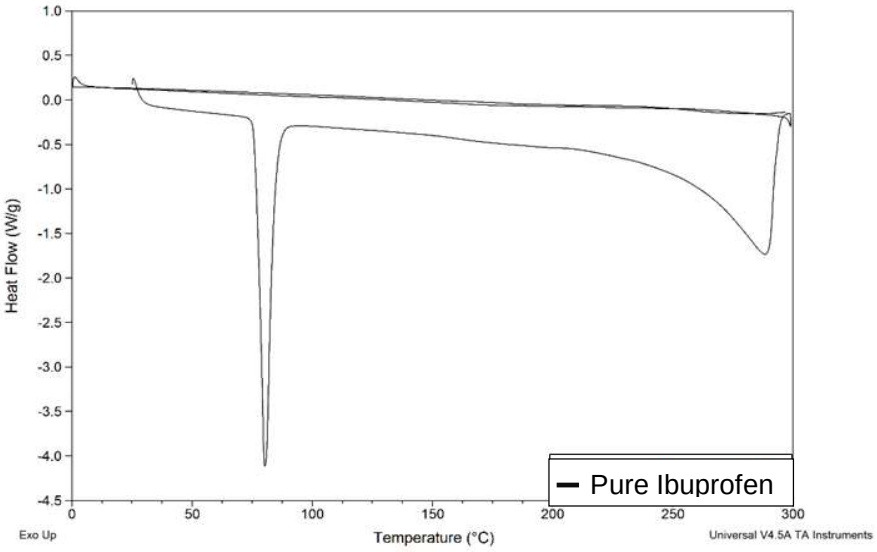


Fig. 1. FTIR spectra of pure drug, neat silica and formulations

20.16 and 22.33 indicating presence of crystalline structure. Both physical mixtures showed same diffraction pattern indicating crystallinity of the free drug in the sample (Fig. 3.b). All solid dispersions were lacking characteristic diffraction peaks exhibited by ibuprofen confirming change into the amorphous form post processing (Fig. 3.c). Drug molecules dissolved in solvent travel inside the tiny pores of silica and get entrapped during evaporation process. Due to the size constraint, it is difficult for the drug molecules to form an orderly arrangement necessary to produce a crystalline state. These results can be compared to neat silica exhibiting amorphous nature as seen in Fig. 3.a. Conversion of the drug into amorphous state was achieved with the combination of huge surface area, interaction of the drug with the silicate groups on the pore surfaces and rapid evaporation of the solvent [33].



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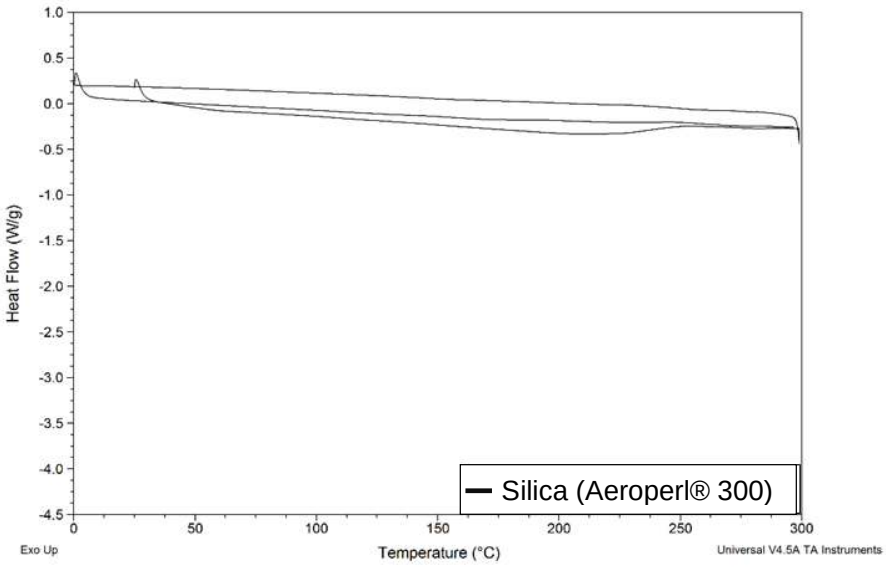

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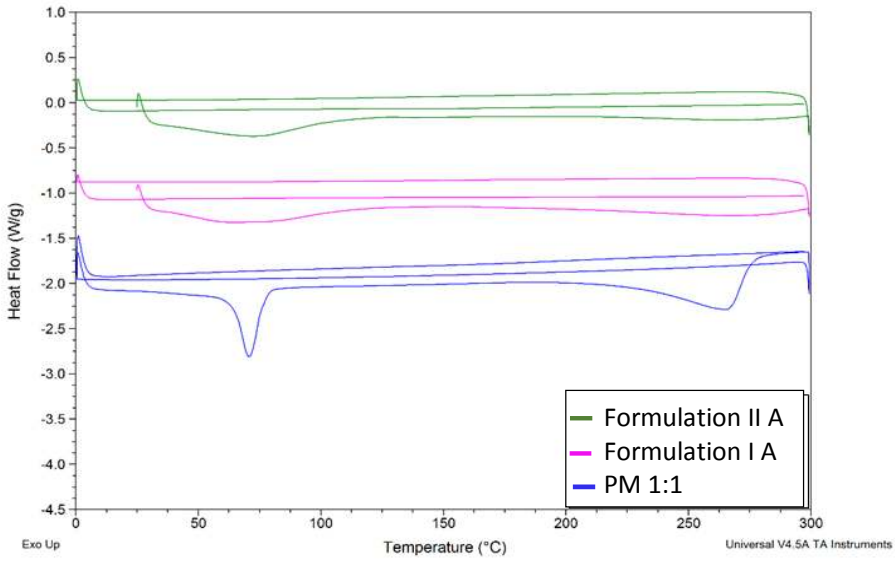

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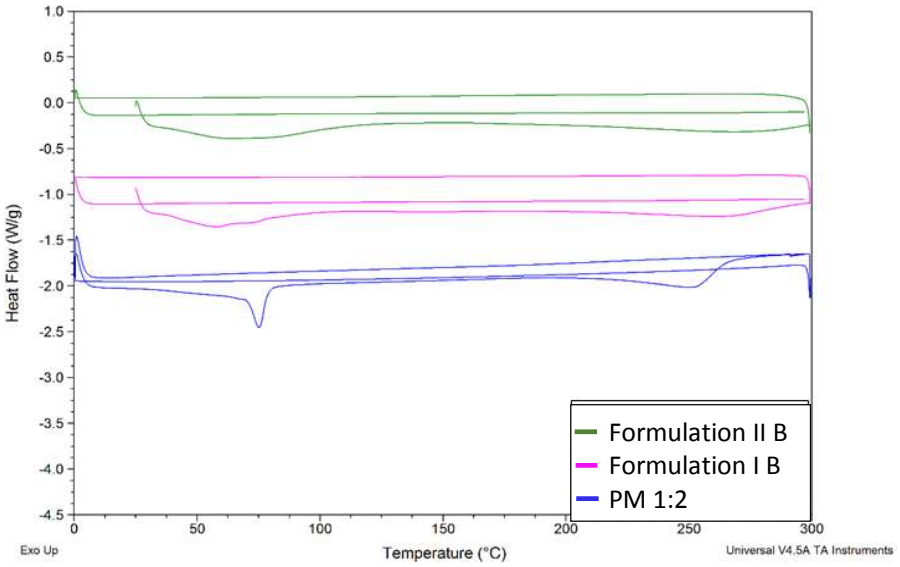


(d)

Fig. 2. DSC thermograms of: a) Pure drug, b) Neat silica, c) Formulations I A, II A and physical mixture 1:1 (drug: silica), d) Formulations I B, II B and physical mixture 1:2 (drug: silica)

3.2.4 Polarized light microscopy

PLM images of pure silica, physical mixture and formulations are shown in Fig. 4. Silica alone exhibits loose hollow spherical porous structures with large surface area (Fig. 4.b). Some silica particles seem to be broken because of their fragile nature [18]. Pure Ibuprofen image (Fig. 4.a) shows a needle like regularly shaped crystals of numerous sizes in aggregated state. Fig. 4.c and 4.d shows physical mixture of 1:1 and 1:2 drug: silica ratios indicating unchanged crystalline drug particles and spherical silica with no interaction among the two. Formulations I A, I B, II A and II B show solid images of drug-carrier mixture as seen in Fig. 4.e, 4.f, 4.g and 4.h.

These images indicate uniform adsorption of ibuprofen molecules onto the pores of silica with no sign of crystallinity observed among any of the formulations. Solvent evaporation method helps deposition of the drug molecules into the voids of porous silica by formation of hydrogen bonds between the drug and the silanol groups present on the carrier's enormous surface [34]. Solid images of formulations as compared to hollow porous structure of silica indicate complete pore filling and subsequent conversion into amorphous form post solvent evaporation.

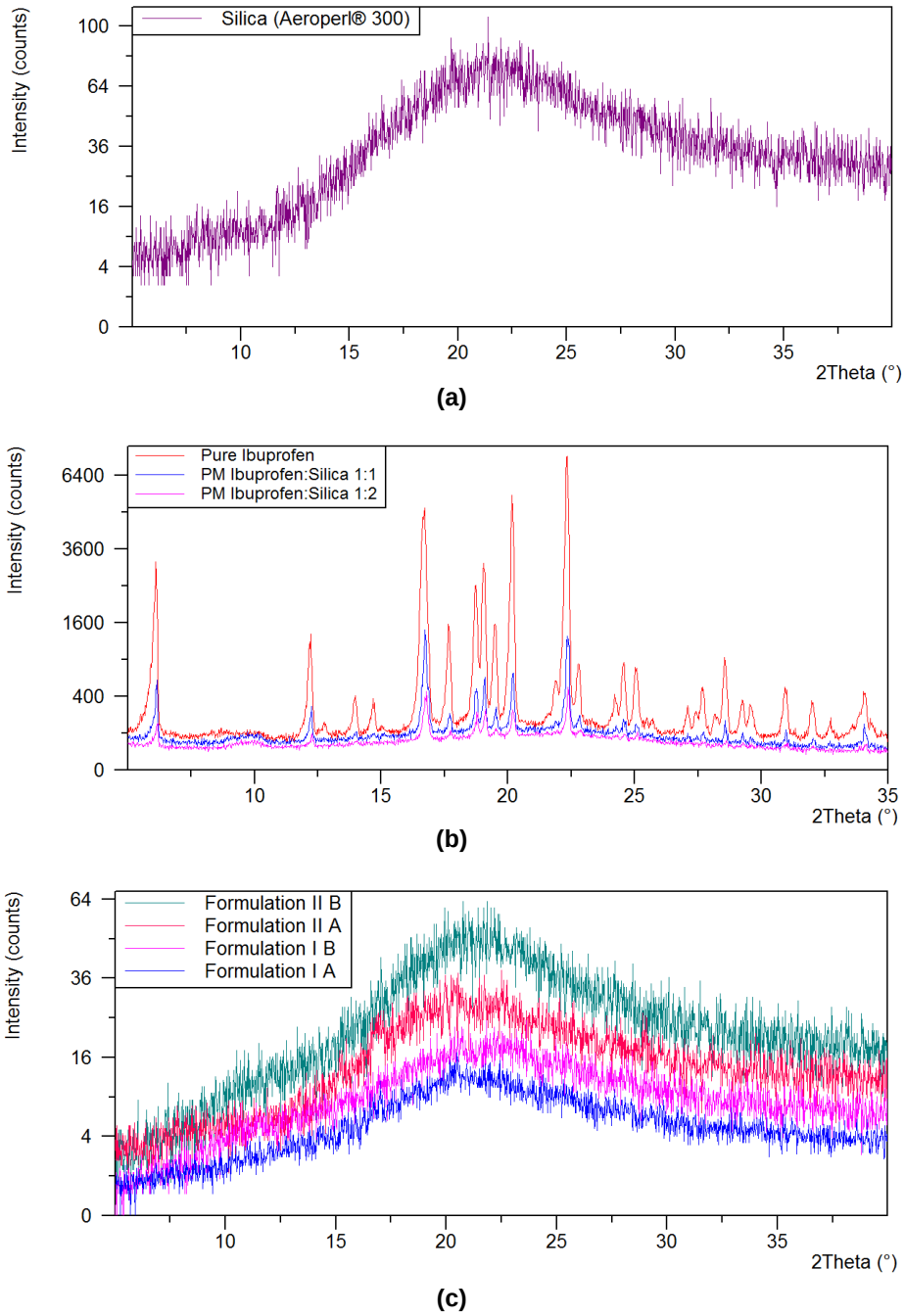


Fig. 3. PXRD diffractograms showing: a) Silica, b) Pure drug and physical mixtures, c) Formulations I A, IB, II A and II B

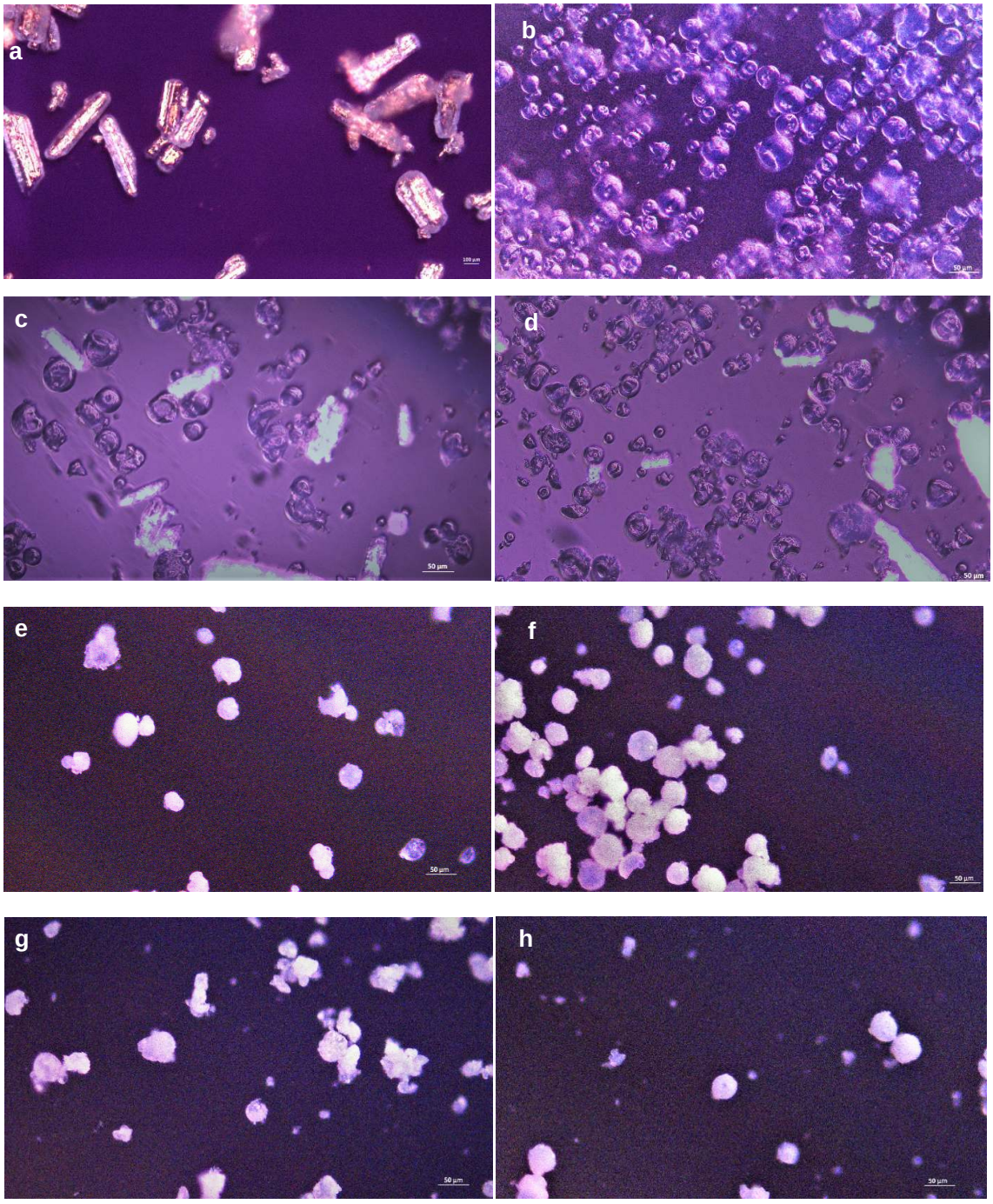
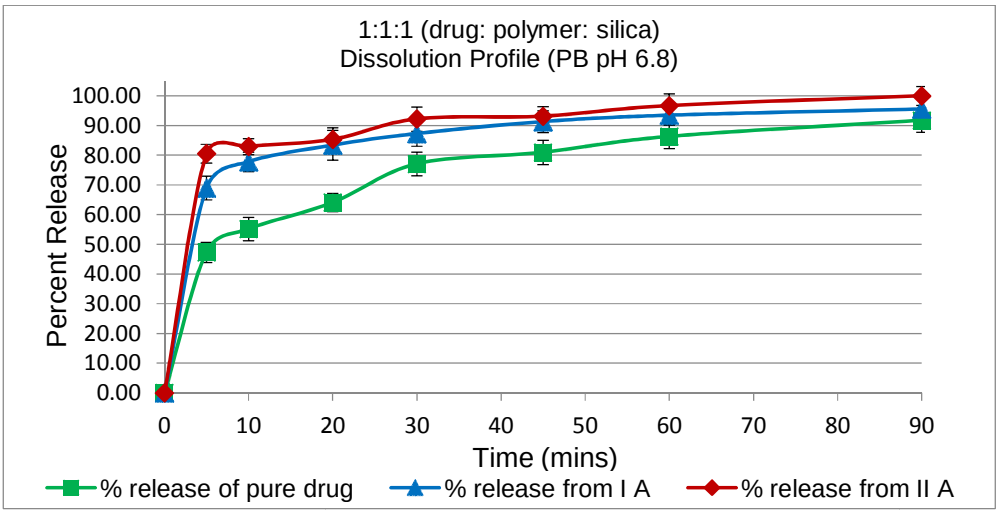


Fig. 4. PLM images: a) Pure drug, b) Silica, c) Physical mixture 1:1 (drug: silica), d) Physical mixture 1:2 (drug: silica), e) Formulation I A, f) Formulation I B, g) Formulation II A and h) Formulations II B

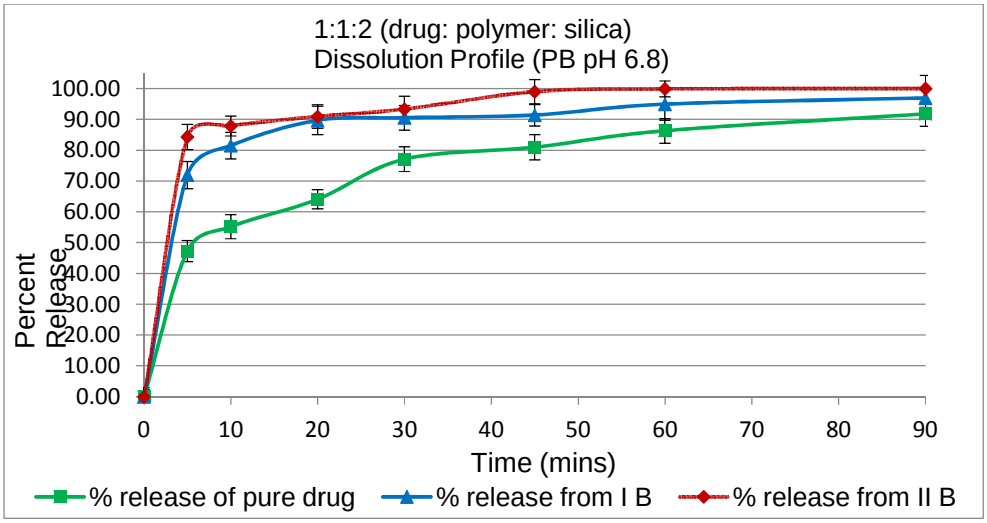
3.2.5 *In-vitro* drug release

Dissolution profile of the pure drug and drug: carrier system in all three media are shown in Figs. 5, 6 and 7. The aqueous solubility of Ibuprofen is 21 µg/mL which is considered as very slightly soluble [31]. All solid dispersions exhibited an increase in drug solubility as

compared to the control (pure drug). Effect of the two polymers added and effect of increase in carrier concentration was investigated for changes, if any in the release profile of the drug. Fig. 5.a and b show dissolution profile of IA, IIA and I B, II B respectively in PBS media. It was observed that formulation II A and II B gave a release rate of 80% and 84% respectively as compared to the 47% release of control within the first 5 minutes of dissolution. Whereas, formulations with HPMC E5, I B and II B showed a release of 69% and 72% respectively. 100% release was observed at 90mins with formulation II A and within 45 mins for II B. In all cases, drug dissolution rate improved largely as compared to the drug alone and increased with increase in the amount of porous silica. The rapid release was attributed to the entrapment of drug into the huge surface area of porous silica that provides quicker access to the dissolution liquid media into the pores containing amorphous drug molecules. Further, polymer added to the system increases wettability by decreasing the surface tension between liquid and the drug. This along with conversion of the drug into amorphous form helps lower thermodynamic barrier to dissolution increasing the solubility [35]. Analysis of the release mechanism using different models indicated that Korsmeyer-Peppas model fits best to the dissolution data. Values of 'n' were ≥ 0.89 (calculated as the slope of the straight line) suggesting anomalous and non- fickian diffusion



(a)



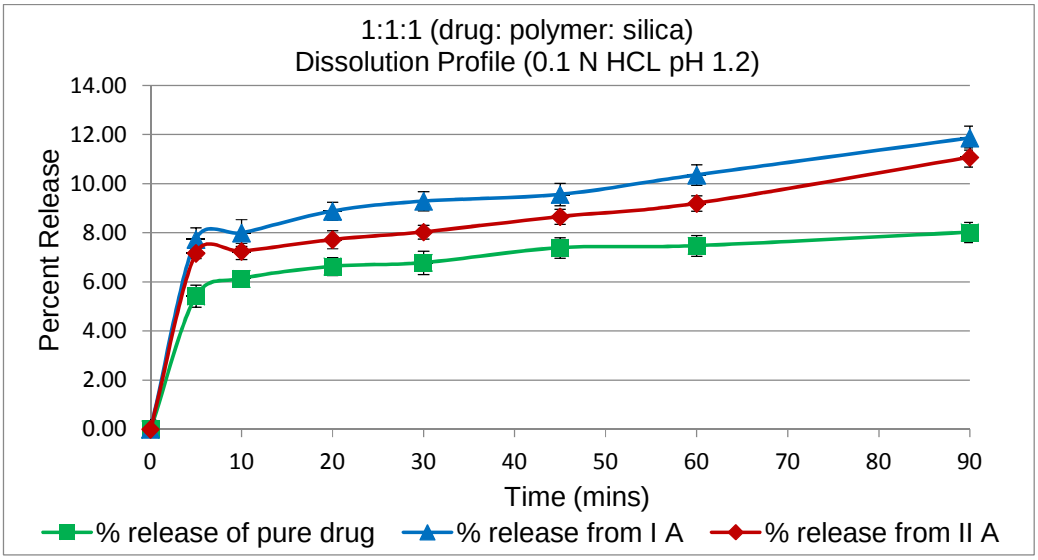
(b)

Fig. 5. In-vitro release of pure drug and formulations in PBS pH 6.8

or nearly zero-order release profile with coefficient of determination (R^2) values close to 1 [36]. Cumulative percent drug release vs. time plot gave straight line confirming zero order release in all three dissolution media.

Fig. 6.a and b display the dissolution profile of the formulations in 0.1N HCL (pH 1.2). 2- 4% increase in solubility was observed within the first 5 minutes with formulations I A, I B and II A, whereas 5% increase was observed with II B as compared to the drug alone. Incomplete dissolution was observed after 90 minutes for the drug alone as well as the formulations. Unlike PBS media, formulations I A and I B containing HPMC E5 showed slightly higher release among the two polymers. This is attributed to the pH independent solubility of HPMC [37].

Dissolution profile with de-ionized water media are showed in Fig. 7.a and b. Solubility for formulations I A, I B, II A and II B increased 3-4 times as compared to the pure drug. A maximum of 28% release was observed with I B and II B



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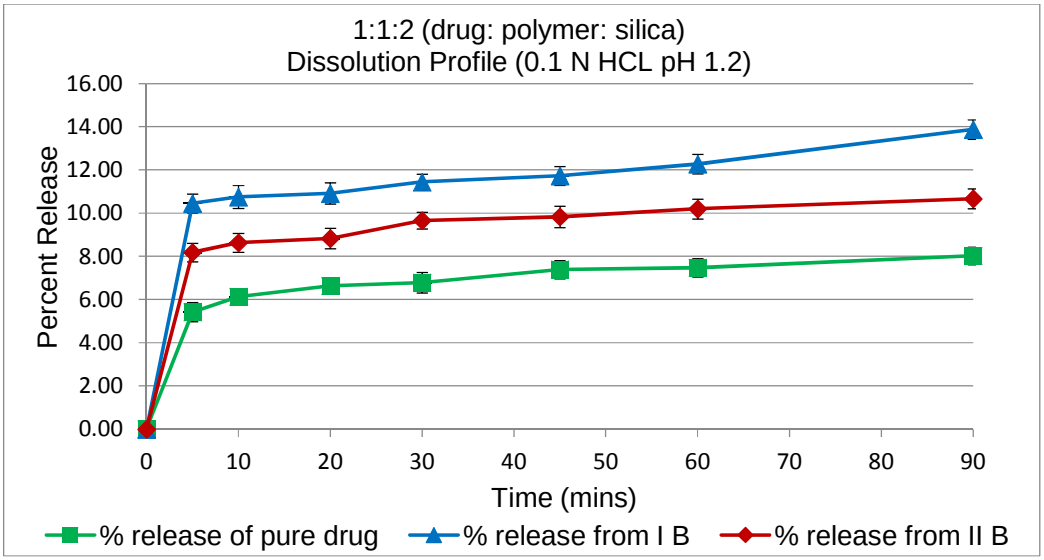
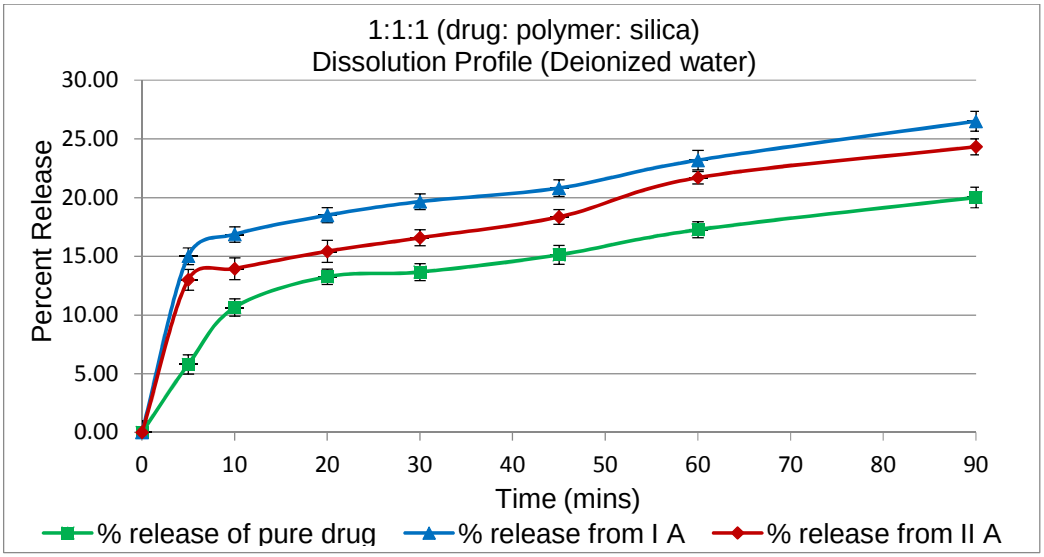


(b)

Fig. 6. In-vitro release of pure drug and formulations in 0.1 N HCL pH 1.2



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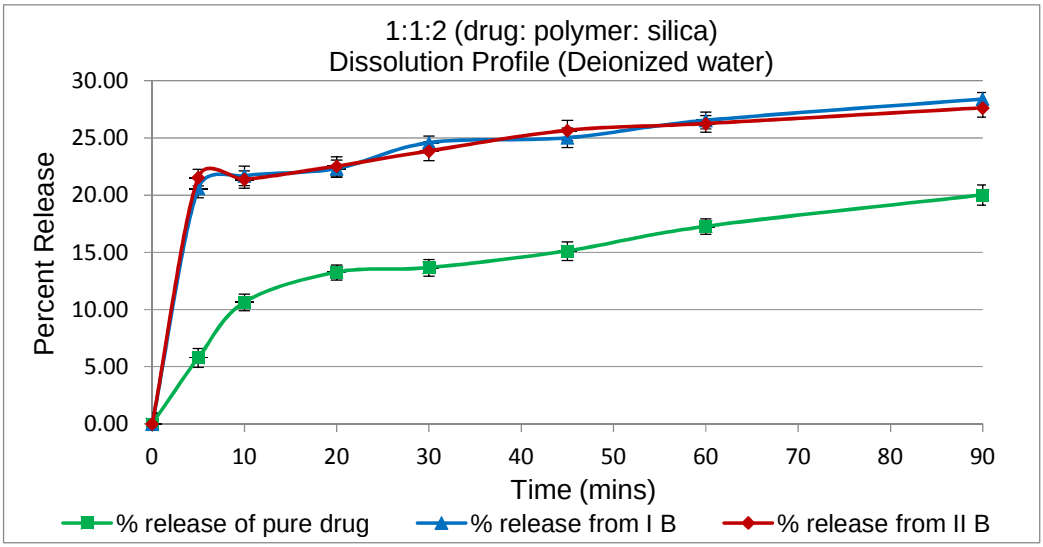

(b)

Fig. 7. In-vitro release of pure drug and formulations in Deionized water

after 90 minutes. Release from formulation I A was slightly higher than II A (formulations with 1:1:1 ratio of drug: polymer: silica). However, no difference was observed among I B and II B with higher concentration of carrier (1:1:2 ratio). This is attributed to the high available surface area of silica that provides quicker access to the liquid into the pores containing drug molecules. In all the dissolution media solubility increased with increase in the concentration of the carrier demonstrating the potential use of silica for enhancing solubility of poorly soluble drugs.

4. CONCLUSION

Current study demonstrated enhancement in the dissolution rate of poorly water soluble, BCS class II drug using porous amorphous silica. Physical characterization tests including FTIR, DSC and PXRD showed successful conversion of crystalline Ibuprofen into amorphous form after processing through solvent evaporation technique. PLM data displays successful loading of the drug into the nanopores of the adsorbent. Two polymers were investigated for their effect on solubility of the drug in carrier. In-Vitro data

shows maximum improvement of 37% in dissolution with PBS media for samples containing PVP K-30. However, samples with HPMC E5 performed better in 0.1N HCL and de-ionized water suggesting that formulations need to be optimized according to the targeted delivery of the drug. Improvement in drug solubility and subsequent dissolution was attributed to the huge surface area and pore volume of silica that helps entrap amorphous drug molecules thus preventing recrystallization. Polymer incorporation further aids wettability of the drug improving overall solubility of the formulation. Investigation showed higher solubility with higher amount of silica proving their potential use as adsorbents for improving the release profile of poorly soluble drugs. Additional research needs to be carried out for better understanding of these systems and their combination with various polymers and surfactants to obtain optimum outcomes.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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