Enhancing Dissolution of Ibuprofen via Solid Dispersion Using Hydrophilic Carrier and Fast Dissolving Sugars

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Abstract:

In this study, solid dispersion using hydrophilic carriers (polyethylene glycols) and fast dissolving sugars (sorbitol and lactose) has been employed to enhance dissolution and hence the bioavailability of ibuprofen.

Solid dispersions of different weight ratios (drug: carrier: fast dissolving sugars) have been prepared using fusion method.

Microscopic images showed disappearance of specific features of ibuprofen, carriers and sugars in the solid dispersions.

Release study of ibuprofen from prepared systems was performed in phosphate buffer pH 6.8; faster drug release was obtained from solid dispersions with high polyethylene glycol ratio and/ or from solid dispersions to which fast dissolving sugars has been added during their preparations.

The study also explored hydrogen bond interactions between polyethylene glycols and ibuprofen in the solid dispersions. FTIR spectroscopy confirmed intermolecular interaction at (2:1) drug to carrier mole ratio. This interaction was considered the most important factor in enhancing the dissolution of ibuprofen via solid dispersions.

Keywords: Solid dispersion, ibuprofen, polyethylene glycols, fusion method.

الخُلاصة:

في هذه الدراسة تم أستخدام طريقة التشتيت الصلب بأستخدام حوامل محبة للماء (البولي أثيلين كلاكول) مع سكريات سريعة الذوبان (السوربيتول واللاكتوز) لزيادة سرعة التحلل والتوافر الحيوي للأبوبروفين.

تم تحضير المتشتتات الصلب بنسب وزنية مختلفة من (العقار:الحامل:سكريات سريعة الذوبان) بطريقة الانصهار . اظهرت الصور المايكروسكوبية أختفاء الصفات المميزة لبلورات الدواء, الحامل والسكريات في المتشتتات الصلبة.

دراسة تحرر الابوبروفين من الانظمة المحضرة تم في محيط ذات دالة حامضية 6.8 وقد لوحظ تحرر سريع للعقار من المتشتتات الصلبة التي تحوي نسبة عالية من البولي أثيلين كلاكول أوالتي أضيفت اليها سكريات سريعة الذوبان أثناء تحضيرها.

الدراسة بحثت أيضا أحتمالية تكوين الاواصر الهيدروجينية بين البولي أثيلين كلاكول والأبوبروفين في المتشتت الصلب. وقد أكدت الدراسة و بأستخدام مطياف الف تي ار على تكوين الاواصر بين جزيئات العقار والحامل عند النسبة المولية (2:1) الدواء:الحامل والذي يعتبر من أهم العوامل الذي يسهم في زيادة تحلل الابوبروفين بطريقة التشتت الصلب.

Introduction:

Solid dispersion is a dispersion of one or more active ingredients in an inert carrier or matrix at solid state by melting, solvent, or melting solvent method" [1]. It is one of the new strategies that are used for improving the dissolution rate and hence the bioavailability of Class II - poorly-water soluble drugs (Biopharmaceutical Classification System) (BCS). Dissolution enhancement is contributed to one or a combination of factors; particle size reduction, drug conversion from crystalline into amorphous form and/ or changing the crystal habit of the drug. The wettability of drug particles can be improved using a hydrophilic carrier in solid dispersion, which further enhances dissolution [2]. Examples of carriers that are used in the preparation of solid dispersions are water-soluble crystalline carriers like urea; natural and synthetic polymers like hydro-xypropyl methylcellulose, polyvinyl-pyrrolidone, and polyethylene glycols. In solid dispersions, drugs are presented as

supersaturated solutions; after system dissolution it may precipitate from the solution. Recently, carriers with surface activity have been used to prevent crystallization of drug during dissolution via micellar solubilization [2, 3].

Several properties should be considered before selecting carriers for solid dispersions. In general the carrier should have high-water solubility, inert, non toxic, compatible with the drug, and convert into a stable solid, which is able to enclose the drug in either a crystalline, amorphous, or molecular state [4].

The two main methods for preparing solid dispersions are melting (fusion) and solvent methods. In fusion method, the drug is dispersed into a molten carrier and then subjected to solidification either slowly at room temperature or by quench cooling through immersing the molten mixture in ice bath or liquid nitrogen. The later method of solidification shortens the crystallisation time and may result in solid dispersion containing small drug crystals which in turn give high dissolution rates [5]. In some cases it can also prevent recrystallisation completely. On the other hand in solvent method, a mixture of drug and carrier is prepared in an organic solvent followed by evaporation. Carrier employed in melting method are characterised by low melting points, and good miscibility and stability with the drug molecules, for example polyethylene glycols [6,7] and poloxamers[8,9]. Whereas, carrier used in solvent methods, should be miscible with most organic solvents, for example polyvinyl pyrrolidone (PVP) [10,11]. However, some carriers can be employed in both methods.

Solid dispersions can be classified according to the physical state of both of the drug and carrier. Solid dispersion in which both the drug and carrier are in a fine crystalline state is known as eutectic system. Whereas, solid dispersion in which the drug dispersed molecularly is known solid solution. Other types of solid dispersions are glass suspensions and glass solutions, in which drug could also be precipitated in crystalline or amorphous form respectively in amorphous carriers [5]. In all solid dispersions, the dispersion of drug within the carrier greatly increases the surface area of the drug which in turn improves its dissolution rate [2, 12].

Ibuprofen is a non-steroidal anti-inflammatory BCS Class II drug. It is widely used to treat mild to moderate pain and fever and available in 200, 400 and 600 mg doses. The solubility of ibuprofen is low at acidic pHs but increases remarkably at pH values above the pKa of the drug, which is in the range 4.5-4.6 [13]. Ibuprofen has a melting point in the range 75- 78°C.

Various formulation approaches have been developed to improve the solubility and dissolution rate of ibuprofen. These approaches include; complex formulation with β-cyclodextrin[14], methyl β-cyclodextrin [15,16] and with nicotinamide[17]; nanosuspension [18], nanoparticles formation [19] and inclusion of ibuprofen in mesoporous template silica [20]. Solid dispersions of ibuprofen in hydrophilic carriers [21,22,23] or in combination of carriers and surfactant [24,25] have been extensively studied as a means of impro-ving its dissolution characteristic.

The aim of this study is to prepare solid dispersions of ibuprofen in polyethylene glycol 6000 and in a combination of polyethylene glycol 6000 and fast dissolving sugar; exploring the impact of sugar inclusion on the dissolution enhancement of the drug from solid dispersions.

Materials and Methods:

Ibuprofen (SDI/ Iraq), polyethylene glycol 4000 (PEG 4000) (SCR/ China), polyethylene glycol 6000 (PEG 6000) (BDH Chemical, LTD/ Pool, England), sorbitol (BDH Chemical, LTD/ Pool England), lactose (SDI/ Iraq), KBr (Shimatzo/ Japan), KH_2PO_4 (SD, Fine-

Chem. limited) and KOH (BDH Chemical, LTD / Pool, England).

Preparation of solid dispersion and physical mixture:

Solid dispersions of Ibuprofen: PEG 6000 at various weight ratios (1:9, 1:1. 2:1) were prepared by melting method. The specific amount of the drug was added to the molten carrier in a water bath (memmert/Germany) at 60°C, with continuous stirring until a homogenous dispersion was formed. The dispersion was then left to solidify at room temperature. The resultant solid product was pulverized in a mortar and sieved; the fraction was used for dissolution testing. Control physical mixtures were prepared by light mixing of the compounds at various weight ratios.

To explore the impact of inclusion of fast dissolving sugar on the release of the drug from solid dispersion; ternary solid dispersions (ibuprofen: PEG 6000: fast dissolving sugar) were prepared by adding lactose or sorbitol during the preparation of the solid dispersions. Control preparations were prepared by physically mixing of sugar with the solid dispersions. The release of drug from ternary solid dispersions was compared with that from control preparations of the same weight ratios.

Impact of carrier's molecular weight on the molecular dispersion of the drug was explored using PEG 4000 and 6000. Dispersion of drug molecularly was based on the hypothesis proved in previous study which states that molecular dispersion of ibuprofen in drug: poloxamers solid dispersions at 2:1 mole ratio. It has been suggested that ibuprofen molecular dispersion was resultant from hydrogen bond interaction of the drug with the terminal hydrogen bonds of the poloxamers [9]. Therefore, the same hypothesis could be applied here; the possibility of molecular dispersion via hydrogen bonding of the drug with terminal hydroxyl group of PEGs. It has been reported that PEG1500 has a potential for hydrogen bonding with ibuprofen [26], accordingly solid dispersions of 2:1 mole ratios, ibuprofen: PEG6000 and ibuprofen: PEG4000 were prepared to investigate this hypothesis.

Determination of melting points of raw materials:

The melting points of ibuprofen, PEG 6000, PEG 4000 lactose and sorbitol were determined by the capillary method (USP) [27]. The capillary tube was dipped in the powder and placed inside the electric melting point apparatus, the temperature was increased gradually, and the temperature at which the powder converted to liquid was recorded as melting point.

Fourier Transform Infrared (FTIR) Spectroscopy:

Fourier Transform Infrared (FTIR) Spectrophotometer (Shimadzu 8400-S/Japan) was used to record the spectra of the drug, carrier and solid dispersions to examine if there is any shift in the peaks of the drug and the carrier resultant from hydrogen bond interaction. Samples (typically 1mg) were ground and mixed with KBr using mortar and pestle to form 10 mg uniform mixtures. The mixture then compressed using Shimadzu MHP-1 Mini hand press to form KBr disc which were scanned from 4000-500 cm^{-1}.

Optical microscopy:

Optical microscope (BOECO/ Germany) was used to visualise ibuprofen, PEG 6000, sorbitol and lactose crystals in pure state, physical mix and solid dispersions. Finely powdered samples were mounted on slide and covered by cover slide, and then examined under various magnifications powers; 10X and 40X.

Dissolution testing:

Dissolution testing was performed according to the USP Paddle method/ Apparatus II (Copley/United Kingdom) under sink conditions, using phosphate buffer pH 6.8. Samples containing ibuprofen equivalent to less than 10% of saturated solubility of ibuprofen in pH 6.8 phosphate buffer were used to keep the drug under sink condition. Five millilitres

samples were withdrawn after specific time intervals filtered before analysis and an equal volume of fresh phosphate buffer, maintained at 37°C, were added to the dissolution medium to maintain sink condition. Ibuprofen release was assayed by UV spectrophotometry at 222nm and quantified using a calibration curve in the same media. All experiments were performed in triplicates [27].

UV spectroscopy:

The wavelength at which ibuprofen shows the highest absorbance in phosphate buffer pH 6.8 (British Pharmacopeia) was determined using a UV-spectrophotometer (Shimadzu/Japan). The wave length of highest intensity (λmax) was 222 nm. A series of ibuprofen solutions in the buffer pH 6.8 were used to prepare calibration curve of the drug in the prepared buffer. Their absorbance's at 222nm were determined and plotted versus concen-tration.

Results and Discussion:

Melting point results showed that all the materials used are pure. Solid dispersions of ibuprofen in PEGs at various weight ratios were successfully prepared using melting method. Independent assay for drug in the solid dispersions showed homogenous dispersion of the drug in the carrier.

The results of FTIR spectroscopy of pure drug (Figure-1) show a characteristic absorption band at 1720 cm^{-1} assigned as the carbonyl stretching vibration of dimerised ibuprofen resultant from hydrogen bonding between two ibuprofen molecules. In solid dispersions of 2:1 mole ratio ibuprofen: PEGs the position of carbonyl groups of the drug was shifted to 1732 cm^{-1} (Figure-2). This shift is resultant from the disruption of hydrogen bonds of dimerised ibuprofen molecules within its crystal lattice and subsequent incorporation of the drug molecules in hydrogen bonds with hydroxyl groups of PEGs. Similar results have been reported for ibuprofen-poloxamers solid dispersions at 2:1 ratio [9].
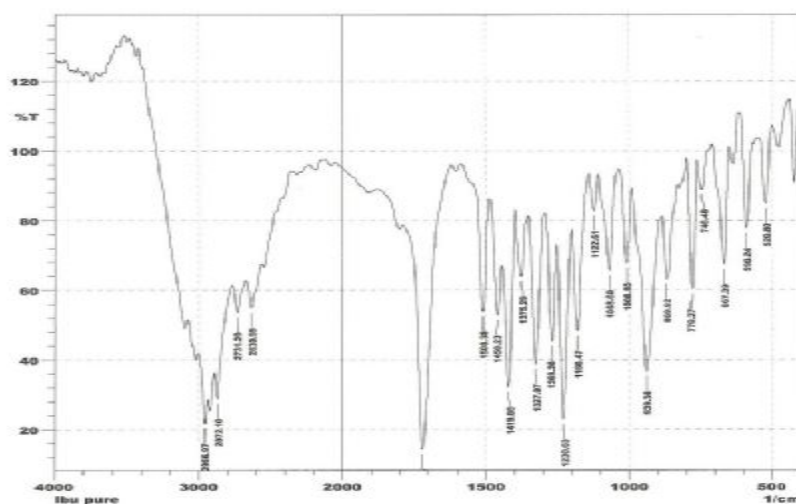

Figure-1: FTIR spectrum of ibuprofen shows the carbonyl stretching vibration of ibuprofen powder at 1720 cm^{-1}
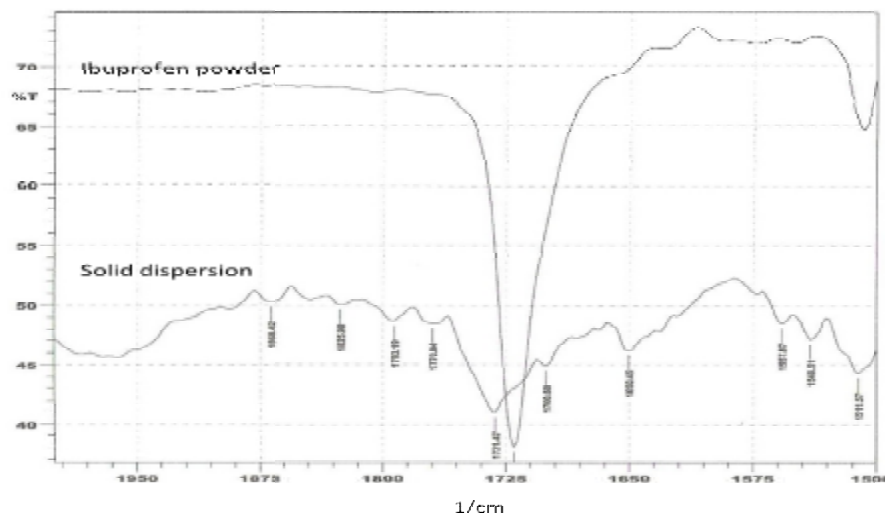
Figure-2: FTIR spectra of ibuprofen and solid dispersion of 2:1 mole ratio (ibuprofen:PEG 6000), showing the shift in carbonyl stretching vibration of ibuprofen in solid dispersion at 2:1 mole ratio to 1732cm^{-1}.

Ibuprofen, PEG 6000, lactose and sorbitol were examined under optical microscope, the results clearly showed the crystalline nature of these materials (Figure-3a, b, c and d). In the solid dispersion of weight ratio 2:1:1 (ibuprofen: PEG6000: lactose) the specific features of the crystals of starting materials are disappeared, whereas, they are still seen in the physical mixture of the same weight ratio as shown in Figure-4a and b respectively. This indicates effective solid dispersion formation by melting and solidification processes [28].

Release of ibuprofen from solid dispersions of various ibuprofen: PEG6000 weight ratios was shown in Figure-5. All solid dispersions improved dissolution rate of the drug compared with that of pure drug. The improved dissolution from solid dispersions was not simply due to enhanced wettability of the drug in the presence of PEG6000, but also due to decrease particle size and crystallinity of the drug particle. However, at low drug: PEG6000 weight ratio i.e., 1:9 the initial dissolution rate of the drug was enhanced to greater extent than those at higher weight ratios (i.e., 1:1 and 1:2). This fast dissolution could be attributed to hydrogen bond interactions between the drug and the carrier that can be broken relatively easily during dissolution compared with those bonds between dimerised ibuprofen present in pure ibuprofen powder and in solid dispersions of high ibuprofen: PEG6000 weight ratios [9].

The impact of inclusion of fast dissolving sugars on the release of drug from solid dispersions was extensively studied using sorbitol and lactose at different weight ratios. The results in Figure-6 show that as the ratio of sorbitol increased in the system, faster drug release was obtained. This is resultant from fast dissolution of the sugar and subsequently generation of more voids in the system. Such situation allows more dissolution medium to penetrate inside the system, accelerating dissolution of the drug [29]. However, type of the sugars used a disaccharide (lactose) versus an acyclic sugar alcohol (sorbitol), did not show a significant difference on the release of drug from solid dispersions (Figure-7). This could be attributed to the hydrophilic nature of the sugars that gives similar dissolution behaviour in both cases [29].
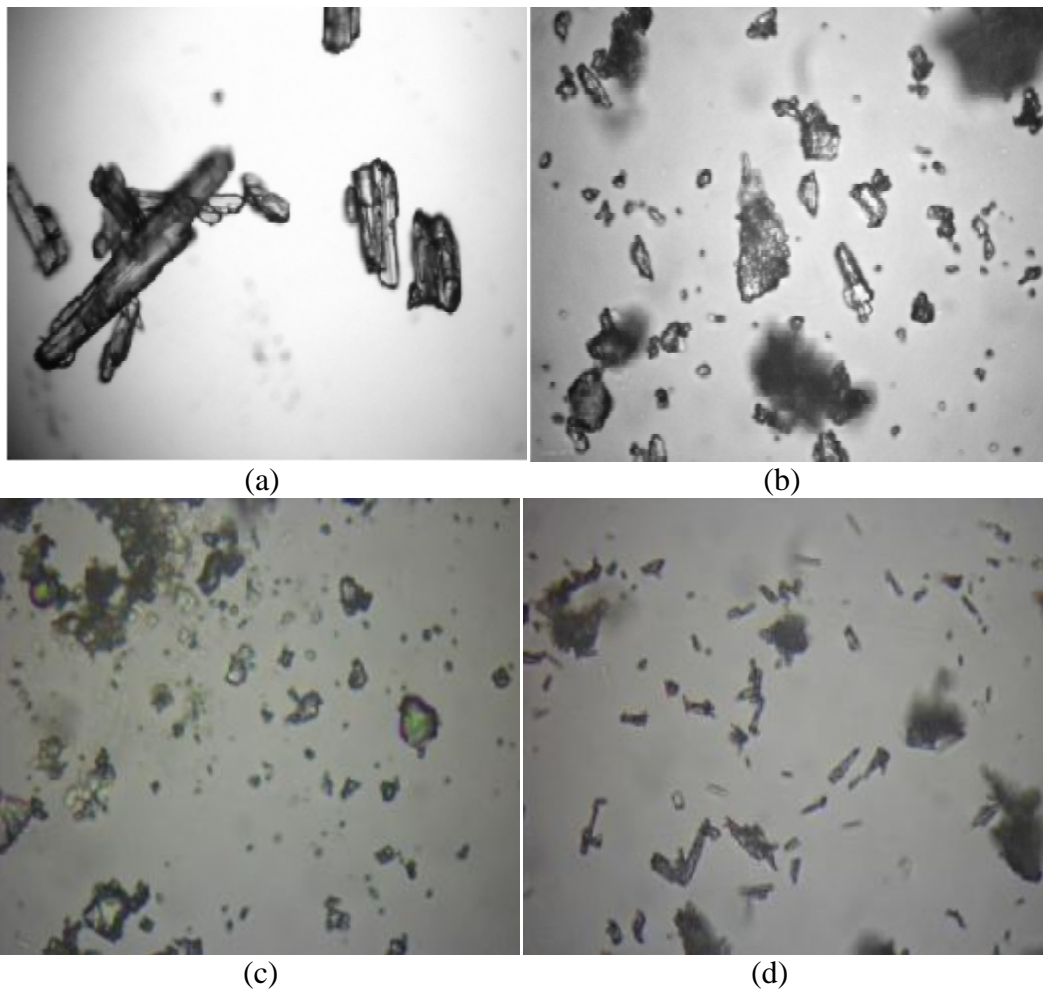
Figure-3: Optical microscope images of ibuprofen (a), PEG 6000 (b), lactose (c) and sorbitol (d) under 40X magnification.
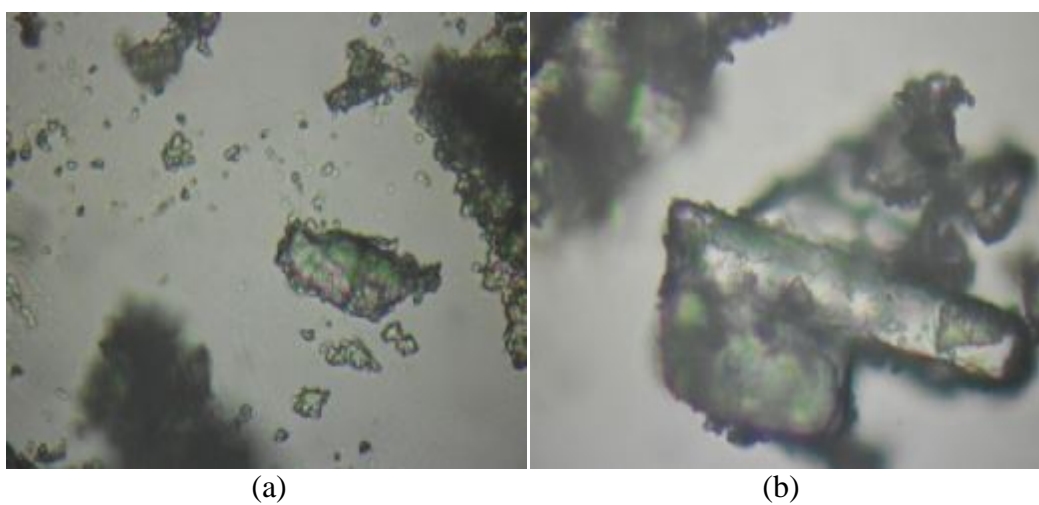

Figure-4: Optical microscope images of (a) solid dispersion (b) physical mixture of weight ratio (2:1:1) ibuprofen: PEG 6000: lactose under 40X magnification.
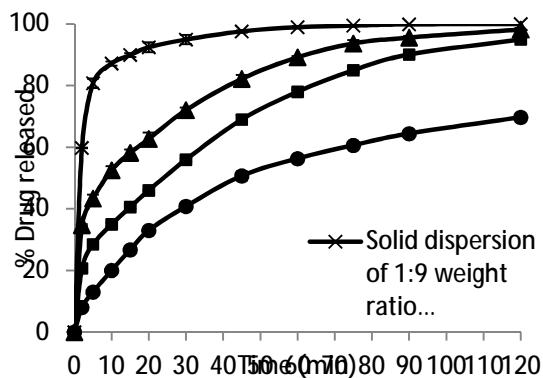
Figure-5: Dissolution profiles of ibuprofen powder and ibuprofen: PEG 6000 solid dispersions of various ibuprofen loads in pH 6.8 phosphate buffer. Values are mean ±SD, n = 3.
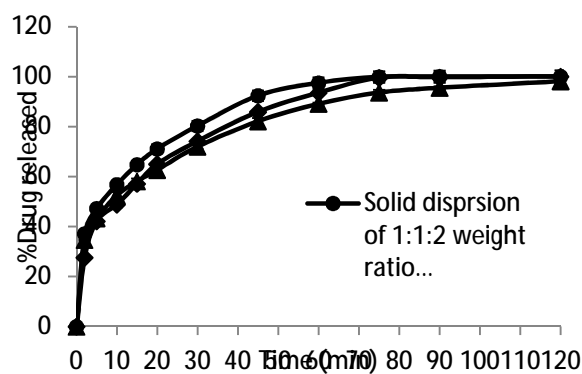

Figure-6: Impact of increasing sorbitol ratio on the release of ibuprofen from solid dispersions. Values are mean ±SD, n = 3.
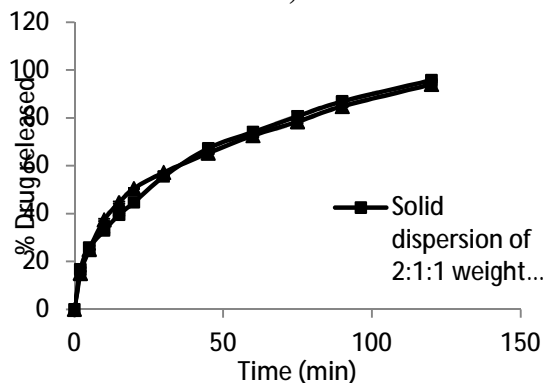

Figure-7: Release profiles of ibuprofen from solid dispersions prepared with inclusion two different types of sugars (sorbitol versus lactose). Values are mean ±SD, n = 3.

The method of sugar incorporation into solid dispersions has a significant effect on the release; incorporation of lactose during the preparation of solid dispersion of (2:1:1) weight ratio (ibuprofen: PEG 6000: lactose) showed faster release of the drug than that from a (2:1+1) system in which one weight ratio of lactose was added physically after the preparation of solid dispersion of (2:1) weight ratio (ibuprofen: PEG 6000).

The enhancement in the release of the drug by incorporation of sugar into solid dispersion was resultant from two

mechanisms. The first mechanism is related to changing in the structure of the solid dispersion in the early stage of dissolution (i.e., creation of in situ porous system). Actually fast dissolving sugars could create channels within the solid dispersion that facilitate penetration of dissolution medium into the system and releasing the drug easily [29]. The second mechanism is physically separating of the drug particles at the solid state, i.e., in the solid dispersion, preventing their aggregation into larger particles that could precipitate in the dissolution medium [30].

Release of drug from solid dispersion of (2:1:1) weight ratio (ibuprofen: PEG6000: lactose) was also compared with that of physical mixture of the same ratio (Figure-8).

Interestingly, similar fast initial release rate was obtained with physical mixture. However, the release from physical mixture becomes slower than that from solid dispersion after 1 hr. This slowing in the release could be attributed to the difference in the ibuprofen crystals size in the physical mixture compared with that in solid dispersion (see Figure-4a and b). In physical mixture larger crystal size was observed under microscope whereas in solid dispersions no longer such large crystal has been seen [2].

The percent of ibuprofen released from different systems after two hr dissolution was calculated and summarised in Table-1. The results show that the amount and manner of sugar addition have a potential on the percent of the drug release from solid dispersions and physical mixture.
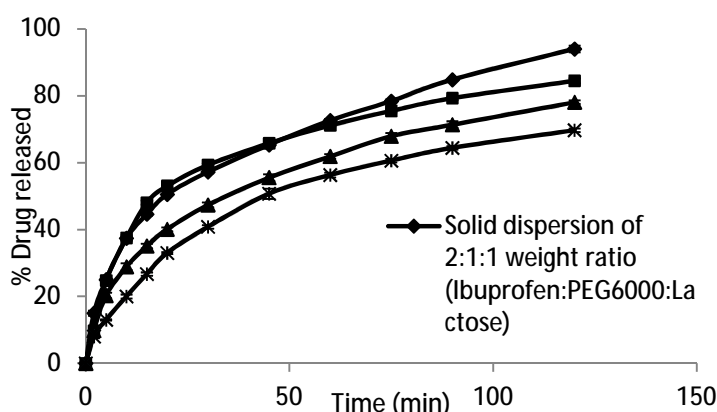

Figure-8: Impact of the method of inclusion of lactose in solid dispersion on the release profile of drug from solid dispersion and from physical mixture. Values are mean ±SD, n = 3.

Table-1: Percent of drug released from different systems after 2 hr dissolution

System Ibuprofen:PEG6000:lactose	Percentage of ibuprofen released after 2hr
Solid dispersion of 2:1:1	94
Physical mixture of 2:1:1	84.5
Solid dispersion of 2:1+1	78
Ibuprofen powder	69.7

Conclusion:

From the results of this study, it can be concluded that the amount of carrier and addition of fast dissolving sugars during solid dispersion preparation have a great effect on the release of ibuprofen from solid dispersions. However, physical mixing of the drug with polyethylene glycol 6000 and fast dissolving sugar showed an enhancing effect to the dissolution of the drug in the early stage of dissolution similar to that obtained via solid dispersion.

The overall enhancement of drug dissolution by incorporating fast dissolving sugars in the solid dispersion was explained by in situ pore creation, which facilitates penetration of the dissolution medium into the system and so improved release of the drug.

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