Original Research Article

Development of a binary carrier system consisting polyethylene glycol 4000 - ethyl cellulose for ibuprofen solid dispersion

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Abstract

Background and Objective: One of the established strategies to improve solubility and dissolution rate of poorly water-soluble drugs is solid dispersion (SD). Polyethylene glycol (PEG) is used as common carrier despite its stability problem which may be overcome by the addition of hydrophobic polymer. The present research aimed to develop an SD formulation with ibuprofen, a poor water-soluble BCS Class II drug as active pharmaceutical ingredient (API) and PEG 4000-ethyl cellulose (EC) as binary carrier.

Methods: Melt mixing SD method was employed using a ratio of API: binary carrier (1:3.5 w/w) (SD_{PE}). Another SD was prepared using only PEG (SD_P) as a carrier for comparative study. The developed formulation was evaluated using optical microscopy, scanning electron microscopy (SEM), determination of moisture content, differential scanning calorimetry (DSC), *in vitro* dissolution test, attenuated total reflection-Fourier transform infrared spectroscopy (ATR-FTIR) and flow properties.

Results: SEM and DSC indicated the conversion of crystalline ibuprofen to fine partly amorphous solid dispersion, which was responsible for the increase in dissolution rate of SD than a physical mixture. The release characteristics within 1 h from the higher to the lower value were the SD_{PE} > SD_P > physical mixture. Flow property evaluation using the angle of repose showed no difference between SD and PM. However, by Carr index and Hausner ratio, the flow properties of SD_{PE} was excellent.

Conclusion: The SD formulation with the PEG 4000-EC carrier can be effective to enhance *in vitro* dissolution of ibuprofen immediate release dosage form.

Keywords: Binary carrier system, ethyl cellulose, ibuprofen, polyethylene glycol 4000, solid dispersion

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INTRODUCTION

A drug should have a certain degree of water solubility to exert its pharmacological effect. Many potent drug candidates are lack of marketability due to their poor water solubility.[1] As per a recent report, 40% of the marketed drugs and 90% of the drugs under development are estimated to be poorly soluble molecules.[2] Over the years, different techniques (e.g., salt formation, micronization,

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complexation, emulsions, nanosuspensions, solid–lipid nanoparticle, etc.[3]) have been employed to enhance the solubility and dissolution of poorly water-soluble drugs. Apart from these, solid dispersion (SD) or amorphous dispersion is one of the commonly employed approaches toward solving solubility issues.[4] Polymeric carrier, an important component of an SD system plays a major role to formulate a successful solid dispersion. A number of high molecular weight hydrophilic polymers have been introduced as carriers for SD (e.g., polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), poloxamer, hydroxylpropyl methyl cellulose and Soluplus®, etc.).[5-7] PEG, chemically ethylene oxide polymer is commonly used as SD carrier in various formulations.[8-11] PEG as SD carrier bears the advantages of low melting point, fast solidification potential, capacity to form a solid drug solution, low cost, and low toxicity.[9] However, it also has a few limitations such as high moisture absorbing low stability, less ability to retain the amorphous form of the drug for a long time. To overcome these limitations, some other polymer another polymer needs to be included with PEG to prepare a binary carrier system. Researchers formulated a felodipine SD using PEG-PVP binary carrier system to improve drug solubility.[10] They have used low molecular weight liquid PEG along with PVP to form a low melting point binary carrier. PEG 1500 was used with different polymer separately such as PVP K30, PVP-vinyl acetate, Eudragit EPO in a fixed ratio to evaluate the best stable polymer blend for SD of carbamazepine and nifedipine.[9] It was shown that PEG-PVP vinyl acetate resulted in highest stability for the formulation. All these combined carriers SD systems commonly used hydrophilic polymers while the use of the hydrophobic polymer is very rare unless for controlled release.[12,13] Ethyl cellulose (EC), a commonly used hydrophobic polymer is better known as a coating element or component of sustained or controlled release matrix system. The use of EC in SD formulation was studied to achieve this controlled release pattern.[14] However, the inclusion of EC with hydrophilic polymer for immediate release SD formulation was never considered before. If EC is incorporated in a binary carrier with PEG, then it may reduce the high moisture absorption tendency of the carrier which will eventually lead to better stability of the SD system. In that case, the binary carrier system will possess the beneficial effect of PEG in the improvement of drug solubility coupled with better stability due to the presence of EC. Based on this hypothesis, the present research aimed to design and develop an SD formulation that includes an active pharmaceutical ingredient (API) and PEG-EC binary carrier. Other advantages expected from such SD formulation include ease of preparation by one step melt mixing method, SD powder with better flowability, etc. However, the question was whether EC exhibits any negative impact on enhancement of drug dissolution in SD formulation. dissolution of the drug from SD Ibuprofen was used as a model API for the work which was solid dispersed by melt mixing method to prepare immediate release granules followed by evaluation of solubility enhancement other relevant characterizations and evaluation of flow properties. Ibuprofen, a nonsteroidal analgesic is widely used as a model API in SD formulations due to its poor aqueous solubility, good applicability, compatibility with a lot of excipients, and low cost.[15]

MATERIALS AND METHODS

Materials

Ibuprofen was purchased from Swapnroop Drugs and Chemicals, Aurangabad, India. Polyethylene glycol (PEG 4000) and Ethylcellulose (EC) were purchased from Merck KGaA, Germany and Shanghai Honest Chem Co Ltd., China, respectively. All other chemicals and reagents used for the study were generously contributed by the Department of Pharmaceutical Technology, Kulliyyah of pharmacy, IIUM, Malaysia.

Methods

As PEG is a "hygroscopic" material,[16] all SD materials and samples containing PEG were stored in a double plastic pack with airtight seal to minimize the environmental exposure.

Preparation of solid dispersion

SD was prepared by simple melt mixing method as described by Yadav *et al.*[17] The compositions of the SD formulations are described in Table 1. PEG 4000 was melted in a water bath (<60°C), then ibuprofen was added to the molten mass with constant stirring. EC was added to it after the complete dispersion of ibuprofen in PEG. The beaker was then immediately transferred to an ice bath (<5°C) and the solidified mass was then kept for overnight drying under desiccator. The dried mixture was pulverized using mortar-pestle then the resulted SD granules was screened through 500 μm sieve and stored in an airtight container at room temperature till further process.

Characterization of the developed solid dispersion

Characterization of the prepared SD was done to determine the physical state of the SD and to evaluate the improvement of dissolution of the developed formulation.

Attenuated total reflectance-Fourier transform infrared spectroscopy

Attenuated total reflectance-Fourier transform infrared spectroscopy study was carried out by a PerkinElmer

Table 1: Compositions of solid dispersion formulations

SD formulation code	Components (ratio by weight)		
	Drug (ibuprofen)	PEG 4000	EC
SD_{PE}	1	1.5	1
SD_{P}	1	2.5	-

SD: Solid dispersion, PEG: Polyethylene glycol, EC: Ethyl cellulose

IR spectrometer. Approximately 50–70 mg of each sample (API, polymers, PM, or SDs) was clamped on ATR diamond crystal at force <90 units and scanned with 4000–400/cm IR range. The generated IR spectrums and functional groups were compared to evaluate incompatibilities or interaction between the API and the polymeric carriers in PM and SD, if any.

Differential scanning colorimetry

The thermograms of API, polymers, PM and SD_{PE} samples were derived by Differential Scanning Calorimeter (1-STARe, Mettler Toledo) for determination of melting points and presence of interaction. Each sample (5–10 mg) was enclosed in an aluminum crucible and exposed to the temperature range of 10°C –200°C under a constant nitrogen flow (10–20 ml/min). A closed aluminum crucible without sample was used as a blank.

Optical microscopy

Physical state of the samples was observed under a compound light microscope (Leica DM750, Singapore). The images were captured at 100× magnification with the help of the system software (LAS EZ, Singapore) followed by visual comparison to identify their differences.

Scanning electron microscopy

A scanning electron microscopy (SEM) analysis was carried out with gold coating and scanned using ZEISS EVO 50 scanning electron microscope to determine the crystal shape of pure drug and the surface morphology of SD sample. The SEM micrographs were then analyzed and compared to determine the nature of the samples.

In vitro dissolution

In vitro dissolution studies were carried out for SD_{PE}, SD_{P}, and PM by United States Pharmacopeia type I (basket type) dissolution test apparatus as per the method described in the literatures.[15,18] The parameters for the test were: 500 ml of the medium (pH 6.8 phosphate buffer), 50 RPM stirring rotation per minute at 37°C ± 0.2 by taking 1 ml of aliquots during 15, 30, and 60 min sampling intervals. SD_{PE}, SD_{P}, and PM used for dissolution study were equivalent to 50 mg of ibuprofen for each basket. Immediately after taking the aliquots, an equal volume of fresh medium was replaced in the respective basket. The aliquots were filtered through 0.22 μm syringe filter and measured for the absorbance at 221 nm by UV spectrophotometer (Schimadzu 1800, Japan) after subsequent dilution with the dissolution medium.

Preformulation studies

Although there are various preformulation studies for solid dosage forms such as tablet, capsule, powder, or granules;[19] in our research, we have analyzed moisture content and flow property only as the scope of this research was not extended to the final dosage form.

Moisture content

Preweighed PM and the SD samples were kept on the aluminum tray of the Halogen Moisture Analyzer (Mettler-Toledo) and heated with a controlled rate. Then, moisture content was determined by its software using loss on drying concept.[20] In addition to moisture analyzer, PM and both SDs were placed in an open glass beakers for 1 week at ambient temperature to evaluate the moisture absorption nature by calculating the weight difference between 1st day and 7th day.

Flow property

Determination of bulk density (ρ_{BD}) and tapped density (ρ_{TD}) followed by calculation of Carr index (CI) and Hausner ratio (HR) indicate the flow behavior of a powder sample.[21,22] The densities (ρ_{BD} and ρ_{TD}) were measured by tapping method as described in the USP.[22] Samples (100 ± 0.1 g) of PM and SDs were poured into separate 100 ml measuring cylinders for bulk volume measurement. Tapped volume was measured after tapping the cylinder for 750 taps by tap density tester (Copley scientific, JV 1000). Then, ρ_{BD} and ρ_{TD} were calculated respectively to derive CI and HR by following equations.

$$CI = \frac{\rho TD - \rho BD}{\rho TD} \times 100 \quad (1)$$

$$HR = \frac{\rho TD}{\rho BD} \quad (2)$$

In addition, angle of repose (AOR) was studied for flow property as per the USP.[22] This method involved pouring the samples through a glass funnel for measurement of diameter or height of the formed cone at the bottom. Two different modes of AOR determination were followed; fixed base method and fixed height method to categorize the type of flow with respect to the standard table.

RESULTS

Applicability of polyethylene glycol and ethylcellulose in melt mixing method

PEG 4000 is a low melting point polymer (61.84°C) as shown by our differential scanning calorimetry (DSC) study [Figure 1]. Therefore, the method of SD preparation was employed at around 60°C at which ibuprofen is also

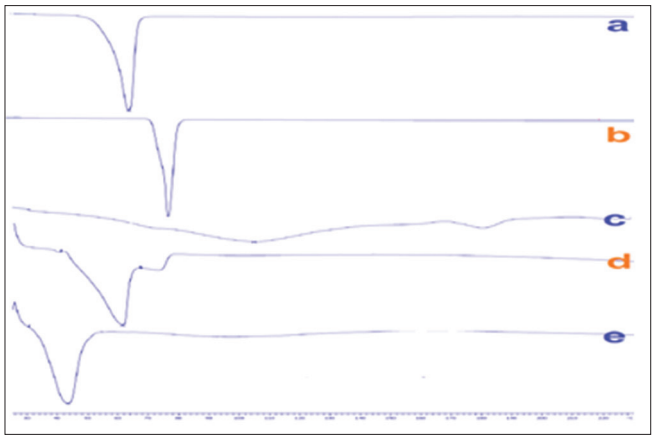

Figure 1: Differential scanning calorimetry thermograms of all samples ([a]: PEG 4000, [b]: ibuprofen, [c]: EC, [d]: PM, [e]: SD_{PE})

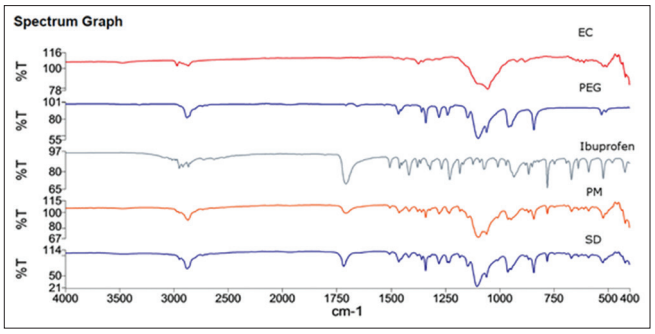

Figure 2: Fourier-transform infrared spectroscopy spectra of all samples

stable and dissolved in the molten PEG 4000. Preparation of SD_{PE} was easier to collect from the glass apparatus and lesser drying time was required when compared to SD_P. The physical nature of SD_P was also waxy. EC bearing relatively higher melting temperature could not be used alone for melting method of SD preparation containing any API.[23]

Attenuated total reflectance-Fourier transform infrared spectroscopy study

The IR spectrums of SD_{PE} and PM with the same composition were compared with pure ibuprofen as well as each of the components of the binary carrier [Figure 1]. The ibuprofen IR spectra presented sharp peaks due to C = O stretching of isopropanoic group at wavenumber 1720/cm, C-O stretching at 1123/cm and due to CO-H in-plane bending at 1230/cm. PEG 4000 showed peaks at wavenumber of 2883/cm and 1098/cm due to C-H stretching and C-O stretching, respectively. EC had a distinct peak at 3500/cm which was accountable for–OH groups present with the closed ring structure of the polymer unit. Besides these, multiple asymmetric peaks or band from 2900 to 2850/cm were for–CH stretching. The peak at 1374/cm might be for–CH_3 bending and at 1054/cm for C-O-C stretching. All the API, PEG, and EC characteristic peaks resemble to the previously published reports.[13,24] All those characteristic peaks were present in PM spectrum without significant shifting which indicated that no interaction occurred among the ingredients.[25] A comparative ATR-FTIR study between the SD_{PE} and PM also showed no significant change in characteristic peaks of ibuprofen in SD formulation indicating no interaction or incompatibility between the active and inactive components of the system.

Determination of drug crystallinity by differential scanning calorimetry

DSC thermograms of pure ibuprofen, PEG 4000, EC, PM, and SD_{PE} are shown in [Figure 2]. Ibuprofen exhibited a sharp endothermic peak at 78°C as the melting point. PEG 4000, despite its semi-crystalline nature, showed an endothermic peak at 61.84°C. Thus, it is easier to use for melt mixed SD. EC, being amorphous nature showed the broad endothermic band at around 100°C–110°C. PM showed an endothermic peak at 61.50°C merging with another endothermic peak at the almost same region of ibuprofen melting peak. During DSC analysis of PM, ibuprofen has become partly soluble in molten PEG and partly remained as crystal causing the presence of both PEG and ibuprofen merged melting peaks. SD thermogram showed an endothermic peak at 41.70°C, but the absence of ibuprofen peak; which might indicate some interactions between ibuprofen and PEG or EC. However, this is contradictory with the FTIR results. In a binary system consisting of a crystalline drug and a crystalline polymer, chances of eutectic system formation is high provided the drug is soluble in the molten polymer at the melting point of the polymer or above and vice versa.[26] Although in this research, the system was ternary, EC remained completely insoluble which could be further proved by the presence of a broad endothermic band at the same melting region in SD, PM as well as in pure EC. Hence, it can be considered that PEG 4000 and ibuprofen are the two contributing element to the physical nature or state of the system. Moreover, PEG was shown to form eutectic system with different drugs by various researchers.[27]

Microscopic nature of solid dispersion

From optical microscopic images [Figure 3a-c], it can be observed that ibuprofen in pure form exists as elongated crystals. In PM, the crystals were visible as black spots on the image within the PEG 4000 and EC. In the microscopic image of SD_{PE}, ibuprofen crystals were not visible which indicated that most of the ibuprofen was soluble in molten PEG rather than remaining as crystal. Optical microscopy results can only be considered as preliminary broad findings. There was also a chance of dispersion of ibuprofen in the polymeric carrier in reduced particle size

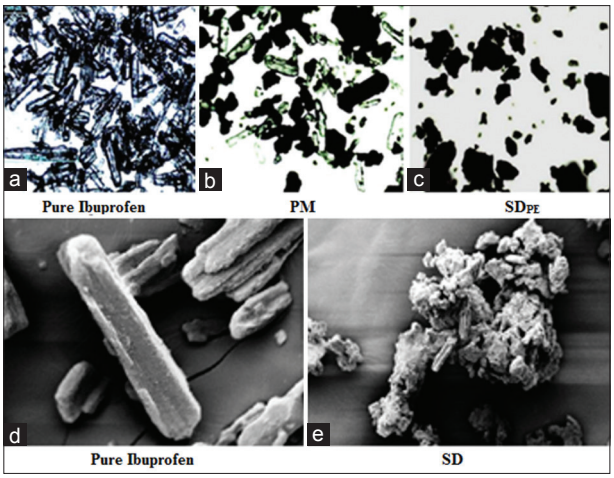

Figure 3: Microscopic images of all samples (a – c: optical microscopic image of ibuprofen, PM and SDPE respectively; d & e: SEM micrograph of ibuprofen and SDPE respectively)

to such an extent that optical microscopy is not capable to magnify. SEM study might support one of the views.

The SEM micrographs [Figure 3d - e] showed the presence of ibuprofen crystal in the PM. The SD_{PE} showed the presence of PEG and amorphous EC dispersed together but the absence of ibuprofen crystals. Surface property of the SD_{PE} and the PEG are almost similar as per visual comparison between SEM micrographs.

In vitro dissolution

The result of *in vitro* dissolution is represented by the plot between cumulative percent release vs. time [Figure 4]. The results showed SD_{PE} granules gave a cumulative percent drug release (CPDR) of >95% in 1 h for immediate release which is higher than PM (76.1% ±2.2) and SD_p granules (83.9% ±5.1). The standard deviations of CPDR at each time point from SD_p were as high as ± 7.64 which indicated poor acceptability of SD_p granules. However, SD_{PE} exhibited better *in vitro* release profile despite containing hydrophobic EC. Thus, this research proved that the presence of EC at 28.5 wt% (as per composition of SD_{PE}) does not adversely affect the drug release from SD granules containing PEG 4000 (42.9 wt%). It can be assumed that EC contributed to the better granule stability and flow property with no negative effect on drug release.

Applicability of solid dispersion to final dosage form

Applicability of the developed SD granules to be used for final dosage form (e.g., tablet or capsule) should have low or moderate moisture content and good flow property. The moisture content analysis showed that SD_{PE} and PM had a moisture content of 1.01% ± 0.01 and 1.39% ± 0.45, respectively. This result was comparable with the moisture absorption from atmospheric exposure. The moisture

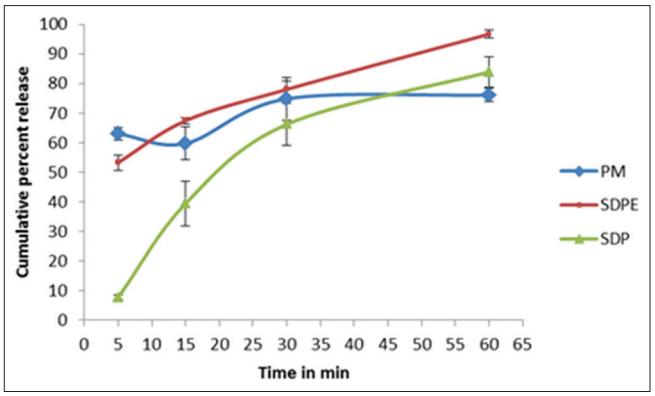

Figure 4: *In vitro* dissolution study of all samples

content calculated on weight/weight basis revealed that SD_{PE} had absorbed the lowest amount of moisture (0.30%) in 7 days than PM (2.60%) and SD_p (1.20%). Another important preformulation test is flow property analysis of the granules or powder. The results of CI, HR, and AOR studies were tabulated in Table 2.

DISCUSSION

During solid dispersion, PEG 4000 acted as a plasticizer in the binary carrier system and nullified the requirement of high temperature along with EC. Moreover, the presence of EC shortened the drying time and made the SD_{PE} less waxy in nature compared to PEG 4000 alone.

In FTIR analysis, the peak at 2900–2850/cm of EC was found absent in SD as well as in PM where the masking effect by the sharp and intense peak of PEG at 2883/cm might be responsible. The intensities of all the characteristic ibuprofen peaks are less compared to SD or PM. The reason might be the lesser proportion of drug in the SD sample compared to the pure drug sample or part of the drug was converted to amorphous from crystalline state. However, the presence of C = O carbonyl stretching at 1720/cm in the SD definitely indicates the presence of ibuprofen crystals in the formulation.[15,18]

Ibuprofen was completely soluble in molten PEG and formed strong two-phased eutectic system due to its low melting point. The minor phase (drug) starts to grow in the interstitial spaces of the major phase (polymer) causing the significant reduction of drug particle size in the eutectic system.[28] The eutectic system formation accountable here depended largely on the ratio of two phases. Ibuprofen and PEG 4000 ratio used in this research (1:1.5) might be above the eutectic point. When this molten mixture was cooled, ibuprofen started solidifying in faster rate which caused the increased thickness of liquid part until the eutectic point. When it reached the eutectic point, the

Table 2: Results of flow property analysis

Flow indicator	SD_{PE}	PM
AOR (fixed base method)	31±1.86	33±1.55
AOR (fixed height method)	32.3±1.50	32±2.05
CI	4.13±1.14	11.65±0.92
HR	1.04±0.01	1.13±0.01

SD: Solid dispersion, PM: Physical mixture, AOR: Angle of repose, CI: Carr index, HR: Hausner ratio

remaining liquid part, containing mostly PEG and partly or no ibuprofen become solidified and forms a very fine dispersion. The melting endotherm of SD at 41.70°C in DSC analysis was probably for the eutectic system melting temperature. However, these thermograms indicated that ibuprofen might not be converted to amorphous from crystalline but rather remained as very fine dispersion which was accountable for enhancing solubility and dissolution.

The SEM micrographs of the samples indicated the solidified PEG with dispersed or absorbed ibuprofen where the absence of ibuprofen crystal proves the formation of an SD system.

Both of the SDs showed better drug dissolution than PM which proved that ibuprofen SD definitely improves the drug dissolution. Enhancement of aqueous solubility after SD was obtained due to either conversion of the crystalline drug to amorphous form or to very fine dispersion and solid solution.[15,18] In this case, the chances of amorphous ibuprofen formation were less as evidenced by FTIR and DSC study. Rather it showed possibilities of fine dispersion of drug into PEG carrier. When the SD contacted with an aqueous medium, PEG started the wetting, then the dispersed drug particles came out. Due to the fine nature and enhanced surface area. The solubility and dissolution of the drug were increased. Two notable issues observed were; initial high drug release of PM compared to both SDs and lower cumulative percent drug release from SD_p despite the presence of no hydrophobic carrier like EC. The first issue can be explained by the density of materials. SDs were packed granules where PM was loosely packed. For PM, immediate wetting occurred on contact with medium resulted in faster initial drug release rate compared to SDs. Regarding the second issue, the presence of only PEG caused very waxy nature of SD_p, thus sticking to the wall of basket occurred during the dissolution test. This might attribute to the lower release rate of the drug.

The difference in moisture absorption between SD_{PE} and SD_p was due to the presence of EC. For SD_{PE}, the hydrophobic nature of EC lessen the moisture absorption compared to SD_p which contained only PEG. Difference between SD_{PE} and PM might be due to the packing of bed. Loosely packed bed of PM was more susceptible to moisture absorption than tightly packed SD granules. This moisture content study proved that the presence of EC can overcome the stability related issue of PEG due to hygroscopicity.

No significant difference was seen for AOR results between SD_{PE} and PM where AOR values of both samples were within "31–35" which is categorized as "good flow."[22] Since AOR was not a very inclusive test and there were high chances of human error and variations. By CI and HR, SD_{PE} sample exhibited better flow property than PM. The lower the CI and HR, the better the flow property.[21] SD_{PE} sample was categorized in "excellent" flow class with CI values below 5 and HR values <1.05, whereas PM was in "good" flow class with CI and HR values below 11 and 1.13.[22] The uniform size and shape of SD granule gave good flow property compared to poor flow PM powder. Since, Nonuniform size distribution, uneven shapes, low particle sizes are contributing factors of poor flow property.

CONCLUSION

An immediate release ibuprofen granule was formulated with a binary carrier composed of PEG 4000 and EC with desired *in vitro* dissolution profile, low moisture absorbing property and good applicability to the final dosage form. Dissolution rate was increased by SD of ibuprofen. EC contributed to lower the hygroscopicity of the SD despite containing a high amount of PEG. The *in vitro* drug release profile was consistent and satisfactory with respect to the desirability of immediate release dosage form (>90% within 1 h). The formulation might be converted to a final dosage form by either compression into a tablet or filling into a capsule.

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Conflicts of interest

There are no conflicts of interest.

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