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# Surfactant-Assisted Wet Granulation: A Simpler Approach to Improve Solubility and Sustain Ketoprofen Release

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***SUMMARY.*** **Ketoprofen granules were prepared by surfactant-assisted wet granulation (SAWG) using different concentrations of Soluplus®, polyethylene glycol (PEG) 6000 and 4000 grades and characterized for physicochemical and dissolution characteristics. FTIR examined any drug-excipients interactions. Granule size, percent yield, bulk and tap density, Hausner's ratio, and angle of repose of granules were found to be 571 ± 0.81 $\mu$m, 93.1 ± 0.84 %, 0.223 ± 0.01g/mL, 0.231 ± 0.002 g/mL, 1.098 ± 0.005, 33.81 ± 0.23º, respectively. Granules with 1% Soluplus® revealed highest solubility (3.09 mg/mL), but with 58.3% ketoprofen release until 12 h. Granules containing 5% PEG-6K demonstrated improved solubility as compared to pure drug, *i.e.* 2.81 mg/mL vs 0.010 mg/mL and release comparable to that of USP-stipulated sustained release pattern following Weibull model (β = 1.08) and showing erosion-controlled release. FTIR indicated no chemical interaction between ketoprofen and excipient in granule formulation. The SAWG successfully ameliorated ketoprofen solubility and sustained its release.**

*RESUMEN*. Se prepararon gránulos de ketoprofeno mediante granulación húmeda asistida por surfactante (SAWG) utilizando diferentes concentraciones de Soluplus®, polietilenglicol (PEG) 6000 y 4000 grados y se caracterizaron por sus características fisicoquímicas y de disolución. La interacción fármaco-excipiente se examinó por FTIR. El tamaño de los gránulos, el porcentaje de rendimiento, el volumen y la densidad del grifo, la proporción de Hausner y el ángulo de reposo de los gránulos fueron de 571 ± 0,81 $\mu$m, 93,1 ± 0,84%, 0,223 ± 0,01 g/mL, 0,231 ± 0,002 g/mL, 1,098 ± 0.005 y 33.81 ± 0.23º, respectivamente. Los gránulos con Soluplus® al 1% revelaron una solubilidad más alta (3.09 mg/mL), pero con un 58.3% de liberación de ketoprofeno hasta las 12 h. Los gránulos que contenían PEG-6K al 5% demostraron una solubilidad mejorada en comparación con el fármaco puro, es decir, 2,81 mg/mL frente a 0,010 mg/mL y una liberación comparable a la del patrón de liberación sostenida estipulado por la USP siguiendo el modelo de Weibull (β = 1,08) y mostrando erosión-liberación controlada. El examen por FTIR indicó que no hay interacción química entre ketoprofeno y excipiente en la formulación de gránulos. El SAWG mejoró con éxito la solubilidad del ketoprofeno y mantuvo su liberación.

## INTRODUCTION

About 60% of drugs, despite having high permeability are poorly water soluble, and categorized as biopharmaceutical classification system (BCS) class II drugs [1]. This poor solubility limits drug bioavailability, a pre-requisite for therapeutic activity [2]. For such drugs, the focus is to enhance their solubility and dissolution [3] in order to improve bioavailability and in parallel, reduce side effects. The current approaches for solubility enhancement have their own pros and cons. For instance, in micronization, high surface charge on small (micronized) particles may cause particle agglomeration which presents technical challenges [4]. Cyclodextrin inclusion complexes lead to dilution of system which may cause precipitation [5]. Amorphization [6] results in degradation of milled drug surfaces and subsequent suspension contamination [7]. Solid dispersions [8] may cause fast and instant drug dissolution due to enhanced wettability and dispersibility of drug particles [9]. Granulation, has been reported for enhancing solubility and in handling bioavailability issues of BCS Class II drugs [10].

*KEY WORDS:* dissolution, ketoprofen, polyethylene glycol, solubility, Soluplus®, surfactant-assisted wet granulation.

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Enhancement of dissolution with simultaneous control over release of a poorly soluble drug may demonstrate improved bioavailability, fluctuation-free plasma drug concentration, reduced dosing frequency, better drug efficacy, reduced gastrointestinal irritation/other dose-related side effects and improved compliance [11-13].

Ketoprofen, a potent non-steroidal anti-inflammatory drug is a BCS class II drug [14]. Low bioavailability [15], briefer half-life (0.5-2.0 h) [16] and association with gastric irritation [14] have made ketoprofen a candidate for a controlled release dosage form. Henceforth, this study was aimed to prepare ketoprofen granules with improved solubility and controlled release profile with a relatively simpler and novel approach of surfactant-assisted wet granulation (SAWG) employing Soluplus®, polyethylene glycol 6000 (PEG-6K) and polyethylene glycol 4000 (PEG-4K). Soluplus® (polyethylene glycol-polyvinyl-caprolactam-polyvinyl-acetate graft copolymer) and polyethylene glycol (PEG) are amphiphilic and hydrophilic polymers, respectively [17], act as solubilizers and surfactants [18], and to improve dissolution of BCS class II drugs [19].

## MATERIALS AND METHODS

### Chemicals

Ketoprofen and crospovidone were gifted by Fynk Pharmaceuticals LTD, Lahore and Mega Pharmaceuticals LTD Lahore, Pakistan, respectively. Hydroxypropylmethyl cellulose-K4M (HPMC) (NSF chemicals) were gifted from Sharooq Pharmaceuticals, Lahore, Pakistan. PEG-4K and PEG-6K (BDH Chemical Limited, UK), Avicel PH 102, Lactose DC and Soluplus®, sodium chloride, hydrochloric acid, sodium hydroxide and potassium dihydrogen phosphate (Sigma-Aldrich, UK) were purchased from the local market.

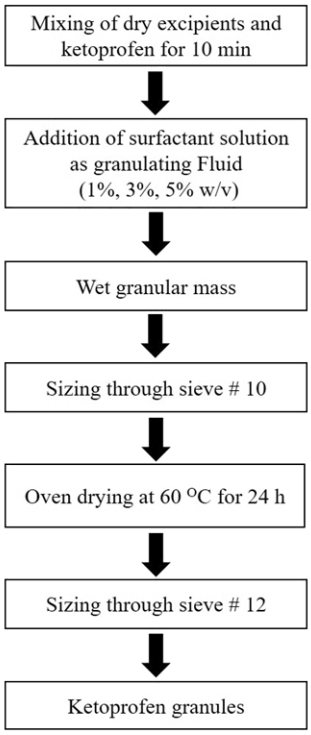


**Figure 1.** Study design for preparation of ketoprofen granules.

### Preparation of ketoprofen granules

Formulations G1-G9 were prepared by surfactant-assisted wet granulation method according to study design shown in Fig. 1. For granulation, the respective surfactants were prepared as 1, 3 and 5% (w/v) aqueous solutions. Fixed amounts of ketoprofen (50 %), Avicel® (7 %), lactose (12.5 %), crospovidone (6%), and HPMC-K4M (24%) were dry mixed for 10 minutes. To this dry mix, 10 mL separately of Soloplus®, PEG-4K and PEG-6K (Table 1) were mixed to formulate wet mass. For G10, a control granule formulation wet mass was prepared us-

| Code | Soluplus® (%) | PEG-6K (%) | PEG-4K (%) | Water (%) |
|---|---|---|---|---|
| G1 | 1 | - | - | - |
| G2 | 3 | - | - | - |
| G3 | 5 | - | - | - |
| G4 | - | 1 | - | - |
| G5 | - | 3 | - | - |
| G6 | - | 5 | - | - |
| G7 | - | - | 1 | - |
| G8 | - | - | 3 | - |
| G9 | - | - | 5 | - |
| G10 | - | - | - | q.s |

**Table 1**. Composition of ketoprofen granule formulations.

ing the same scheme (Fig. 1), but without addition of surfactant at 2nd step, using only water as wetting agent. The resultant mass of all formulations was passed through sieve # 10, dried for 24h at 60 °C (WTC, binder 78532 Tuttlingen, Germany) and passed through sieve # 12 to get uniform granules.

## Characterization of granules

### *Yield of granules*

Yield of ketoprofen granules was obtained on basis of amount of prepared granules in comparison to weighed amount of solid materials used using Eq. [**1**] [20].

$$Yield\,(\%) = \frac{Actual\,yield}{Theoretical\,yield} \times 100 \qquad [1]$$

### *Analysis of granule size*

Granules were separated into different size fractions using a mechanical sieve shaker (Sieve Shaker AS-200, Rotsh, Germany) having six sieves arranged one-on-other in such a way that lower sieve was with smaller sieve size than the sieve on it. The sieves were shaken for 10 minutes and particles remained on each sieve were weighed in three repeating cycles of sieve shaking to obtain average granule size and was calculated [21] using Eq. [**2**]

$$Average\,particle\,size = \frac{\%\,Weight\,retained \times Mean\,size}{100} \qquad [2]$$

### *Flowability of granule formulations*

To test flow properties of powders various tests, *i.e.,* bulk density, tap density, angle of repose, Carr's index and Hausner's ratio were conducted [22].

### *Bulk density*

Bulk density of ketoprofen granules was measured by taking sample (m) in 10 mL graduated cylinder, without tapping, and apparent volume ($V_0$) was recorded for unsettled granules. Bulk density in g/mL was calculated using Eq. [**3**]:

$$Bulk\,density = \frac{Mass\,of\,granules\,(m)}{Initial\,volume\,(V_0)} \qquad [3]$$

### *Tap density*

Ketoprofen granules were poured into 10 mL graduated cylinder and tapped for 20 times. The volume was labeled as bulk volume before tapping and as tap volume after 20 taps and tap density was calculated using Eq. [**4**]

$$Tap\,density = \frac{Mass\,of\,granules\,(m)}{Tap\,volume\,(v_t)} \qquad [4]$$

### *Angle of repose*

Ketoprofen granules (30 mL) were allowed to fall from the funnel through its diameter of 0.9 cm from an elevation of 10 cm. Determined the tangent of repose angle ($\alpha$) resulting from granule cone on surface using Eq. [**5**].

$$Tan\,(\alpha) = \frac{h}{r} \qquad [5]$$

where *h* and *r* are, respectively the height and radius of cone.

### *Carr's index*

Compressibility of granules was measured by Eq. [**6**].

$$Carr's\,index = \frac{Tap\,density - Bulk\,density}{Tap\,density} \times 100 \qquad [6]$$

### *Hausner's ratio*

Hausner's ratio of ketoprofen granules was calculated using Eq. [**7**].

$$Hausner's\,Ratio = \frac{Tap\,density}{Bulk\,density} \qquad [7]$$

## Compressional behavior

In-die Heckel model was employed to assess compressional behavior of granules for deformation under pressure. For each formulation, fixed amount of granules was compacted, using a hydraulic press equipped with flat faced dies, 13 mm in diameter, under 5 to 15 MPa compressional force. At each compaction pressure, the reduction in volume was measured using Eq. [**8**].

$$dD / dP = k\,(1–D) \qquad [8]$$

where *D* is compact's relative density at pressure applied, *P* and *k* (constant) is the measure of plasticity for a test material compressed and reflects the reciprocal of mean yield pressure, *Py*. Integration of Eq. [**8**] gives Eq. [**9**]:

$$ln\,(1) / (1–D) = KP + A \qquad [9]$$

A plot between *ln (1)/(1-D)* and *P* (compaction pressure) was plotted. The extrapolation of curve (*A*) gives the resistance to deformation of a material, known as mean yield pressure (*Py*) and was calculated by the reciprocal of the slope (*k*) [23].

## Solubility studies

An excess quantity of test granules was placed in glass-stoppered flasks having 25 mL of distilled water and shaken in an orbital shaker

(GFL 3015, Germany) at 37 °C at 50 rpm for 48 h. The supernatant was filtered through Whatman No. 41 filter paper and then concentration of drug was determined employing spectrophotometer (Shimadzu UV-2550 Koyoto, Japan) at 258 nm [24].

### *In vitro* drug release

Drug release was studied in USP Dissolution Apparatus I at 50 rpm. Two buffer media of pH 1.2 and 6.8, respectively mimicking pH of gastric and intestinal media [25] were used to obtain the release profiles, respectively for 2 and 10 h. Samples of 10 mL were taken at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, and 12.0 h while maintaining a constant volume (900 mL) in dissolution vessel by replenishing an equal amount of respective medium, already maintained at 37 ± 0.1 °C [26]. The samples were filtered, diluted if required, and analyzed for ketoprofen at 258 nm, with UV spectrophotometer. Percentage of drug released was calculated by standard calibration curve of pure drug in defined concentration regions, separately for both dissolution media.

### Release kinetics

Release kinetics was studied by fitting percent release data to zero order, first order, Higuchi, Hixson-Crowell, Korsmeyer-Peppas and Weibull models using DD Solver Ver 1.0. The highest $R^2$ and lowest Akaike information criterion (AIC) was used for the selection of kinetic model [27]. The diffusion exponential (n) resulting from Korsmeyer-Peppas model was used to understand release mechanism.

### Fourier transform infrared spectroscopy (FTIR)

Infra-Red spectra for pure drug, excipients and of different formulations were recorded on FTIR spectrophotometer (MB 3000, ABB Inc. Canada) using attenuated total reflectance (ATR) attached with FTIR to get resultant transmittance [28]. Spectrum was taken from wavelength of 500-4000 $cm^{-1}$.

## RESULTS AND DISCUSSION

The literature cites different approaches to ameliorate solubility of ketoprofen. The closely competing approaches to that used in this study are liqui-solid and kneading techniques. The liqui-solid technique requires adding of surfactants solution in drug solution and then transforming it to a solid mass [29]. In kneading the polymers are added in drug mixture, kneaded to form a paste, dried under vacuum followed by pulverization to solid dispersion [30]. Both above approaches involve multi-step formulation process for solubility enhancement. Contrarily, this study employed a relatively simpler and newer approach, the surfactant-assisted wet granulation (SAWG) which improved the solubility and parallelly, sustained the *in vitro* release of ketoprofen. In this study, G1 to G9 formulations were prepared with Soluplus® (G1-G3), PEG-6K (G4-G6), PEG-4K (G7-G9) with varied amounts (1%, 3%, and 5% w/v in water as a granulating solution while keeping the amount of ketoprofen and other ingredients fixed. The G10 (control) was prepared employing only water as granulating agent according to composition given in Table 1. Soluplus®, PEG-6K and PEG-4K have been employed to enhance solubility of drugs [19] specifically categorized in BCS class II [31]. The bifunctional character of Soluplus®, *i.e.,* ability to act as matrix polymer and solubilizing the insoluble drugs has effectively been utilized to enhance *in vitro* dissolution and *in vivo* absorption of poorly soluble drugs. Furthermore, Soluplus possesses appreciable wet and dry binding characteristics like PVP and Crospovidone [32]. Polyethylene glycols are also used to enhance the aqueous solubility or dissolution characteristics of poorly soluble drugs by making solid dispersions [33]. In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules [34]. To our best knowledge, both Soluplus® and PEG have not been used to enhance solubility of ketoprofen earlier by the method of granulation utilizing surfactant solution.

### Characteristics of ketoprofen granules

The physical characterization included % yield, granule size and flow properties, compressional behavior, solubility (Fig. 2-5) and *in vitro* dissolution are given in Table 2 and 3 and Fig. 6.

### Yield of granules

The yield of granules was within 73.55 to 96.00% (Fig. 2A). G6 (with 5% PEG-6K) showed maximum yield while G4 (1% PEG-6K) demonstrated the lowest yield. The yield below 40% is

| Code | Yield (%) | Granule size (µm) | Flowability properties | | | | |
|---|---|---|---|---|---|---|---|
| | | | Bulk density (g/ml) | Tap density (g/ml) | Angle of repose (θ) | Hausner' s ratio | Compressibility index |
| G1 | 82.40 | 571.88 | 0.222 | 0.276 | 11.39 | 1.241 | 19.44 |
| G2 | 83.05 | 570.49 | 0.190 | 0.250 | 17.44 | 1.313 | 23.80 |
| G3 | 83.15 | 567.99 | 0.211 | 0.282 | 15.94 | 1.338 | 25.26 |
| G4 | 73.55 | 571.04 | 0.171 | 0.184 | 22.11 | 1.078 | 7.26 |
| G5 | 80.30 | 559.52 | 0.233 | 0.245 | 31.38 | 1.055 | 5.23 |
| G6 | 96.00 | 563.47 | 0.184 | 0.203 | 25.86 | 1.102 | 9.21 |
| G7 | 88.65 | 568.95 | 0.247 | 0.280 | 24.37 | 1.133 | 11.72 |
| G8 | 94.35 | 563.28 | 0.245 | 0.272 | 34.06 | 1.109 | 9.81 |
| G9 | 93.50 | 572.21 | 0.209 | 0.230 | 34.06 | 1.098 | 8.90 |
| G10 | 90.50 | 564.47 | 0.248 | 0.284 | 24.62 | 1.142 | 12.42 |

**Table 2**. Physical characteristics of ketoprofen granules

| Time (h) | Ketoprofen release (%) from | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | G1 | G2 | G3 | G4 | G5 | G6 | G7 | G8 | G9 | G10 |
| 0.5 | 3.83 | 3.75 | 3.32 | 3.83 | 4.44 | 12.36 | 3.83 | 3.75 | 3.32 | 3.32 |
| 1 | 4.35 | 5.21 | 4.52 | 4.95 | 4.95 | 19.42 | 4.35 | 5.21 | 4.52 | 4.52 |
| 1.5 | 5.56 | 6.24 | 5.38 | 6.33 | 6.85 | 27.00 | 5.56 | 6.24 | 5.38 | 5.38 |
| 2 | 6.16 | 7.19 | 5.99 | 27.34 | 31.13 | 32.68 | 6.16 | 7.19 | 5.99 | 52.84 |
| 3 | 9.93 | 10.36 | 7.85 | 37.26 | 44.40 | 54.17 | 11.14 | 10.36 | 10.04 | 83.58 |
| 4 | 12.24 | 12.24 | 9.06 | 42.64 | 55.81 | 59.76 | 15.53 | 17.73 | 12.24 | 99.30 |
| 5 | 22.12 | 16.63 | 10.37 | 51.97 | 60.31 | 65.80 | 26.51 | 23.21 | 14.43 | |
| 6 | 25.41 | 20.91 | 14.43 | 57.02 | 69.31 | 76.23 | 33.09 | 26.07 | 19.70 | |
| 7 | 28.32 | 23.32 | 16.30 | 62.80 | 72.67 | 77.02 | 41.64 | 34.63 | 23.87 | |
| 8 | 30.90 | 26.18 | 17.29 | 65.69 | 76.23 | 78.20 | 45.17 | 46.04 | 29.36 | |
| 9 | 37.04 | 30.02 | 17.95 | 70.63 | 81.60 | 84.02 | 53.95 | 49.12 | 34.74 | |
| 10 | 42.97 | 32.98 | 20.91 | 73.48 | 91.37 | 88.85 | 64.92 | 55.59 | 44.07 | |
| 11 | 53.95 | 38.77 | 22.45 | 89.40 | 100.00 | 97.52 | 69.31 | 59.43 | 49.56 | |
| 12 | 58.34 | 46.00 | 27.60 | 95.10 | 101.00 | 100.00 | 78.09 | 63.82 | 53.95 | |

**Table 3**. Ketoprofen release from granule formulations.

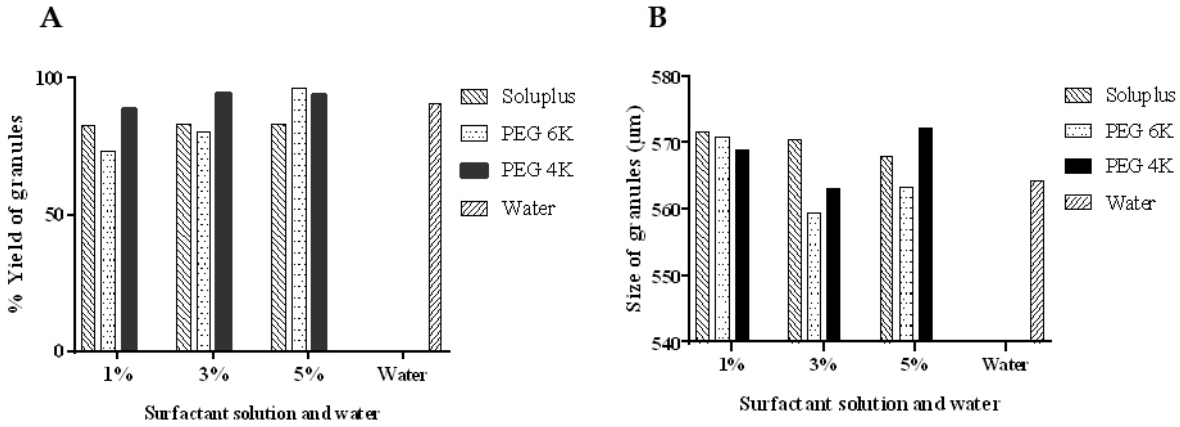


**Figure 2**. (**A**) Percent yield and (**B**) Size of G1-G10 granules.

considered as poor [35] thus, ketoprofen granules, G6 and G8-G10 showed excellent (> 90%) while G1-G3, G5, and G7 showed lesser but appropriate yield (> 80%).

**Size of ketoprofen granules**

The size of ketoprofen granule formulations ranged between 559.52 and 572.21 µm (Table 2 and Fig. 2B). Size of granules used in pharmaceutical industry lies between 0.2 and 5.0 mm suitable for packing as a dosage form or for mixing with other excipients prior to their compaction into tablets or filling into capsules. With this reference, all ketoprofen granules (G1-G10) were appropriate as dosage form as such, to be filled in capsules or compacted as tablets [36].

**Flowability of ketoprofen granules**

***Bulk and tap density***

Bulk and tap densities characterize the flow and compressibility behavior of materials. The bulk density for ketoprofen granules was within 0.171-0.248 g/mL, the lowest being for G4 and otherwise, for G7 (Fig. 3A). Tap density was between 0.184 g/mL (G4) to 0.284 g/mL (G3), Table 2 and Fig. 3B. All granules showed appropriate flow [22] and compressibility [37].

***Angle of repose***

The angle of repose values for ketoprofen granule formulations was 11.39 to 34.06° (Table 2 and Fig. 4A), all below 50 indicating appropriate flowability. The granule size, shape, nature of material and calculation method are the determinants for angle of repose. In the present study, the granules were less cohesive and moisture-free, reasons for free flowing [38].

***Hausner's ratio***

Hausner's ratio of all ketoprofen formulations (Table 2 and Fig. 4B) varied between 1.055 and 1.338. The formulations with Hausner's ratio > 1.25 are poorly flowing, < 1.25 flowing while values ≈1 are freely flowing [39]. Hence, all formulations, except G2 and G3 were shown to be freely flowing. Nevertheless, based on angle of repose, the above formulations inclusive of G2 and G3 exhibited good flowability which was not supported by Hausner's index (Table 2). This discrepancy might be attributed to use of different methods of calculation for flowability [40].

***Carr's index***

Carr's index for all formulation ranged between 25.26 and 5.23 (Fig. 4C). The formulation with Carr's index > 25 are poorly while < 15 are freely flowing [39]. G4-G10 showed good flowability according to the Carr's index while formulations G1 to G3 showed fair flowability. G2 and G3 showed poor flowability based on Hausner's ratio.

***Compressional behavior***

Heckel equation indicates compressibility, hardness, plasticity and deformability of materials (mechanical strength) [41]. Fig. 4D shows compression parameters, *i.e.,* mean yield pressure (Py) and constant (k) of all granule formulations. Low Py and high k indicate a softer, plastic and deformable material. Slow packing rate and granules of different size may yield high Py. In this study, the physical mix of excipients showed higher Py than that of pure drug and thus, would require more force for deformation.

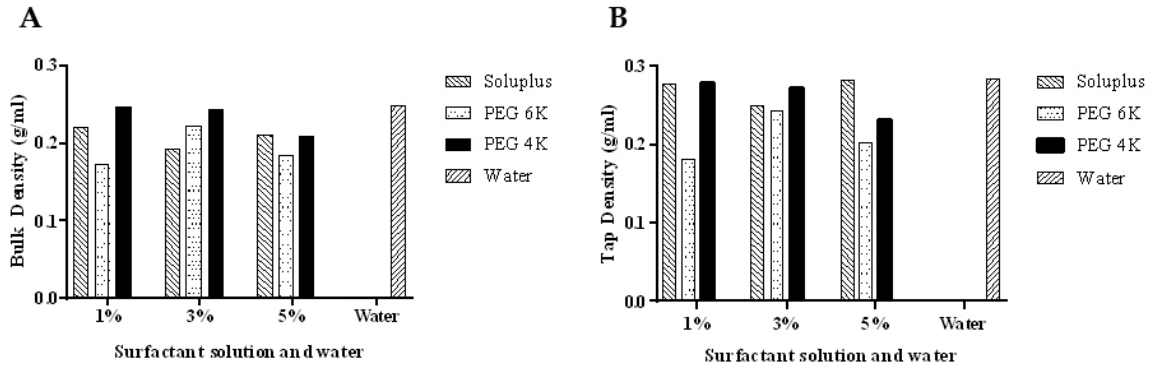


**Figure 3**. (**A**) Bulk density and (**B**) Tap density of G1-G10 granules.

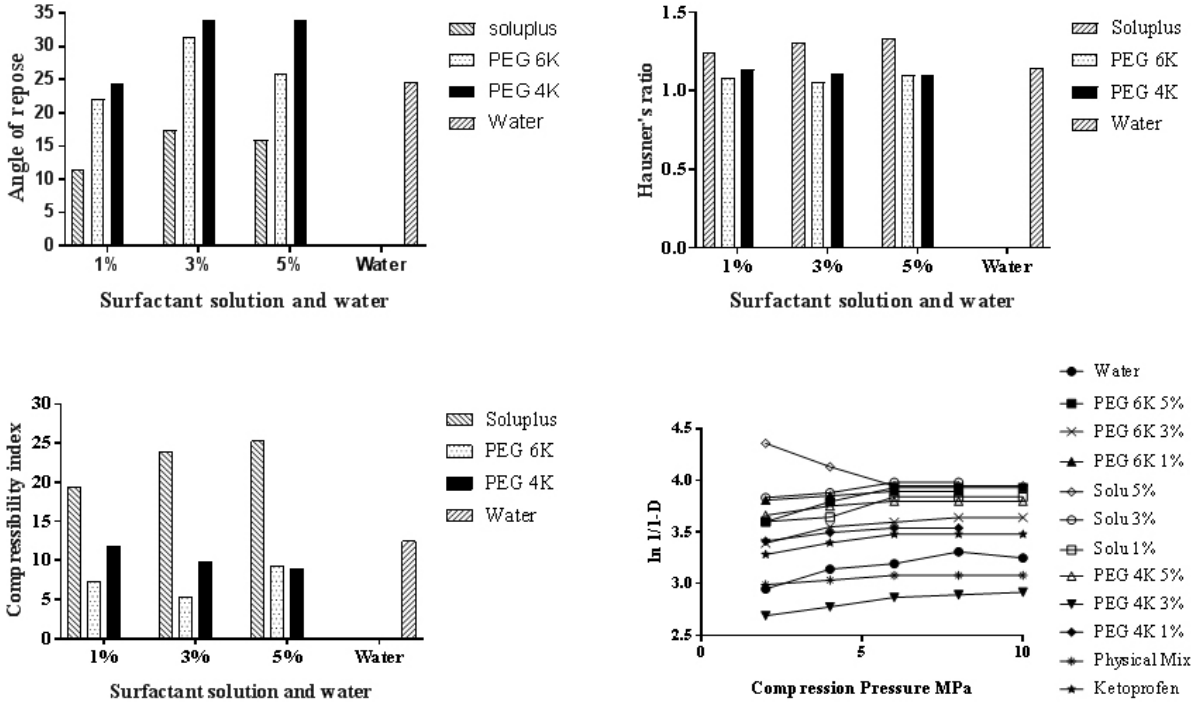


**Figure 4.** Flow and other properties: (**A**) Angle of repose, (**B**) Hausner's ratio, (**C**) Carr's compressibility index of G1-G10 granules, and (**D**) Heckel's plot of G1-G10 granules, physical mix and pure drug, ketoprofen.

G8 showed comparable Py to that of pure drug while G1-G3 and G6 showed lesser Py values than that of the pure drug indicating more suitability for compaction and high plasticity when presented as granules [23]. Rest of the 7 formulations showed higher Py values than that of the pure drug representing less plasticity. The above findings reflected that the surfactants used in this study improved the binding ability and plasticity of granules, in line with previous study wherein, the presence of surfactants due to formation of water soluble carriers/complex with poorly soluble drug was reported as the reason of enhanced solubility [42].

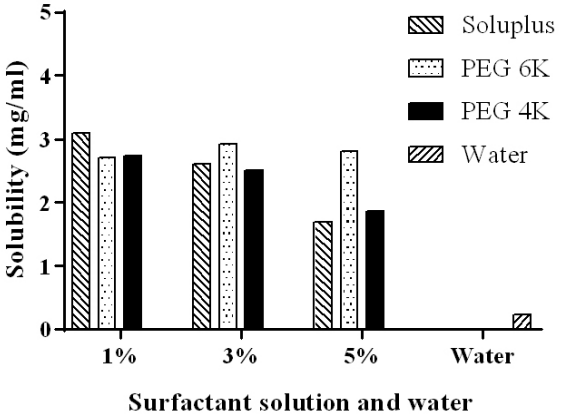


**Figure 5**. Solubility of G1-G10 Granules.

### *Solubility*

Ketoprofen solubility was increased but this enhancing magnitude was lesser at the increasing surfactants' concentrations from 1-5% (Fig. 5). The G1,G5 and G6 showed the highest solubility. The higher solubility was due to a better wettability of granules presenting larger surface area [24], formation of water soluble carriers or formation of complex with poorly soluble drug [42].

### *In vitro* release of ketoprofen granules

Formulations, except G10 showed an inadequate release in simulated gastric fluid (Table 3 and Fig. 6). However, in intestinal medium, both trends, fast and slow release of ketoprofen was observed. The G3 showed the lowest release, *i.e.,* 27% till 12 h while G5-G6 and G10 showed highest release (around 100%) in 12 h and 4 h, respectively. From G6, ketoprofen release of 19.42%, 32.68%, 59.76%, and 78.20% were within 15-40%, 25-60%, 35-75% and >70%, at 1, 2, 4, and 8 h, respectively, which USP has specified for sustained release formulations [25]. Similarly, G4 and G5 at all concentrations showed approximately a sustained release pattern. The G4-G6 showed enhanced release as the percent concentration of PEG-6K was in-

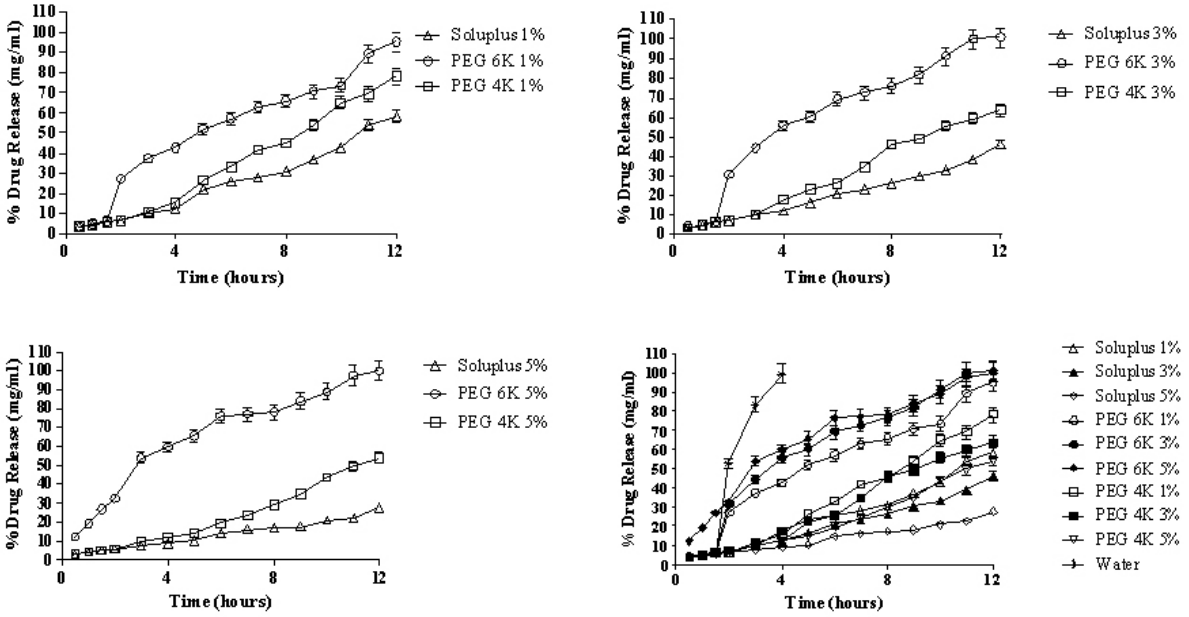


**Figure 6**. Dissolution profiles of G1-G10 granules.

creased. However, G1-G3 and G7-G9 showed decreased drug release with increased concentrations of respective surfactants. Release of ketoprofen from granules assumed the order; PEG-6K > PEG-4K > Soluplus®. Surfactants prominently influence drug solubility, dissolution and also drug residence time in intestinal fluid [43].

The solubility and dissolution rate are different phenomenon [44]. Solubility is a static and dissolution is a dynamic phenomenon [2] and poorly soluble drugs may exhibit fast dissolution rate and vice versa [44]. The G1, G5 and G6 showed enhanced solubility (3.09, 2.92, and 2.81 mg/mL, respectively) as compared to other surfactant-based formulations (1.69 to 2.73 mg/mL), G10 (0.23 mg/mL) and pure drug (0.010 mg/mL) as reported [45]. The G6 solubility co-related with higher release, *i.e.,* 100 % at 12 h but, despite higher solubility, G1 showed 58.34% release at 12 h. Furthermore, G10 despite its lowest solubility (0.23 mg/mL) showed highest release (99%) even at earlier time point, *i.e.,* at 4h. Higher solubility and higher drug release are due to good plasticity, mechanical strength and porosity of the surfactant-based granules (G1-G9), in line with the previous reports [46-48] as compared to granules prepared using water (G10).

## Release kinetics

The ketoprofen release followed Weibull model, characteristics of matrix type delivery systems. The model-derived ß value indicates progression and shape of dissolution curve, *i.e.,* $\beta > 1$ shows sigmoidal release with a lag time in initial phase, $\beta < 1$ gives steeper increase and $\beta = 1$ represents exponential rise in dissolution curve. The $\beta$ values of surfactant-based granules were above 1 thus, yielded sigmoidal curves, reflecting that the granules (G1 to G10) formed matrix. The n value derived from Korsmeyer-Peppas model for all, except G3-G6 was above 1, also supported the release mechanism as diffusion and erosion (super case II). The n value for G3-G6, between 0.566-0.838 showed anomalous transport [49]. Model fitted to the release data, and values of $\beta$ and n, derived, respectively from Weibull and Korsmeyer-Peppas models substantiated that the SAWG yielded matrix-embedded ketoprofen or polymer micelles dispersion of ketoprofen, consistent with the earlier reports [17,50].

## Fourier transform infrared spectroscopy (FTIR)

A representative FTIR chromatogram of G6 (containing PEG 6K 5%), selected based on good solubility, flow properties and drug release has been given (Fig. 7). FTIR spectra of ketoprofen exhibited peaks, specific to drug at 1689 $cm^{-1}$ (C=O stretching of acid), 1650 $cm^{-1}$ (C=O stretching of ketone), 1596 $cm^{-1}$, 1581 $cm^{-1}$ (C=C stretching of aromatic ring), 1442 $cm^{-1}$ (C-H deformation of $CH_3$ asymmetrical),

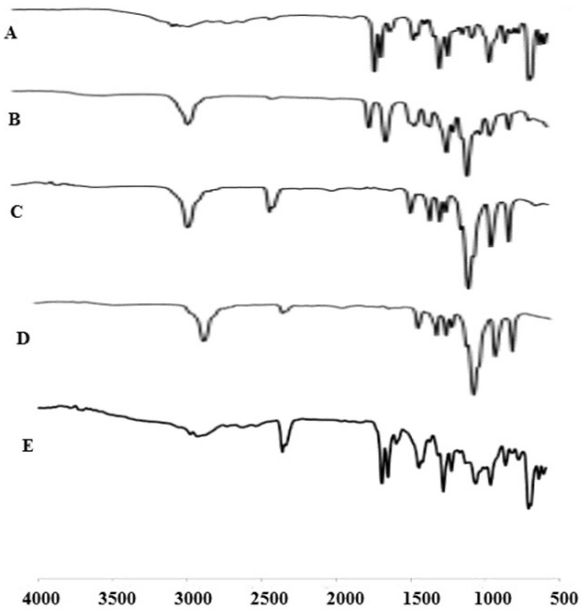


**Figure 7**. FTIR of (A) ketoprofen, (B) soluplus®, (C) PEG-6K, (D) PEG-4K, and (E) PEG 6K 5%.

1373 $cm^{-1}$ (C-H deformation of $CH_3$ symmetrical). Soluplus® spectra showed characteristic peaks at 2923 $cm^{-1}$, (aliphatic C-H stretching), 1740 $cm^{-1}$, and 1627 $cm^{-1}$ (C=O stretching). PEG revealed its characteristic peaks at 2877 $cm^{-1}$ (aliphatic C-H stretching), 1280 $cm^{-1}$ (C-O stretching), 1095-1141 $cm^{-1}$ (C-O-C) of ether, and O-H stretching at 3400 $cm^{-1}$ (Fig. 7). The characteristic peaks of ketoprofen functional groups were found in all granule formulations. The resultant FTIR spectrum neither showed any drug-excipient incompatibility nor denaturation of active ketoprofen in granules but showed drug-surfactant interaction through hydrogen bondings.

## CONCLUSION

The solubility of ketoprofen could be enhanced using SAWG approach with a possibility of controlling the release pattern of the drug. Highest solubility was found in granules prepared with 1% Soluplus®, which also retarded ketoprofen release up to 58.3% till 12 h. Granules prepared with 5% PEG-6K showed higher solubility and appropriate sustained release characteristics. Enhancement of the binding ability and plasticity of granules were the additional benefits of the SAWG. The granules could be further processed to develop unit dosage form, such as capsule or tablet formulations.

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