Original Article

# Investigation of Solid Dispersion Technique in Improvement of Physicochemical Characteristics of Ibuprofen Powder

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## Abstract

Ibuprofen solid dispersions were prepared by the solvent and fusion-solvent methods using polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), eudragit RS PO, eudragit RL PO and hydroxypropylmethylcellulose (HPMC) as carriers to improve physicochemical characteristics of ibuprofen. The prepared solid dispersions were evaluated for the flowability, solubility characteristics and dissolution behavior. Flowability studies of powders showed that solid dispersion technique improve flow properties compared with the physical mixtures. Solid dispersion technique found to be effective in increasing the aqueous solubility of ibuprofen. The dissolution of ibuprofen and polymers (PVP, HPMC, eudruagit and PEG-6000) were investigated using UV spectroscopy. Dissolution was carried out in phosphate buffer (pH 6.8) using a standard USP II dissolution apparatus. *In vitro* dissolution studies showed that in the dispersion systems containing eudragit or HPMC, dissolution of ibuprofen was retarded, which attributed to ionic interaction and gel forming, respectively. But solid dispersion containing PEG, as a carrier, gave faster dissolution rates than the physical mixtures. Finally, solid dispersion of ibuprofen:PEG 6000 prepared in 1:1.5 ratio showed excellent physicochemical characteristics and was found to be described by the zero order kinetic, and was selected as the best formulation in this study.

## 1. Introduction

When a drug is administered orally in a solid dosage form such as tablet or capsule, it must be released from the dosage form and dissolved in the gastrointestinal fluids before it can be absorbed. Therefore, the bioavailability of many poorly water soluble drugs is limited by their dissolution rates [1]. Ibuprofen, a nonsteroidal anti-inflammatory drug is poorly water soluble, and its oral absorption is dissolution rate limited [2]. Increase in dissolution of poorly soluble drugs by solid dispersion techniques presents a challenge to the formulation scientists [3-5]. The poor dissolution characteristics of relatively insoluble drugs has long been and still remains a problem to the pharmaceutical industry because the dissolution rate could be the rate-

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limiting process in the absorption of a drug from a solid dosage form [6].

Solid dispersion technique can be used to improve dissolution of poorly water-soluble drugs such as ibuprofen [2, 3]. Various polymers such as polyvinylpyrrolidone (PVP) [6, 7], HPMC [6], ethylcellulose [8] and polyethylene glycol (PEG) [8, 9] are common polymeric carriers in such systems [10]. The mechanisms underpinning the observed improvements in dissolution rate are not fully understood and rely on an understanding of the dissolution behavior of both components of the solid dispersion [10]. In the present work, the physicochemical characteristics of active pharmaceutical substances and excipients including particle size, flow rate and solubility during manufacturing process dictate the quality of the products. Thus, ibuprofen solid dispersions were prepared by solvent and fusion-solvent methods using PEG 6000, PVP, eudragit RS PO and RL PO and also HPMC as carriers to improve physicochemical characteristics of ibuprofen.

## 2. Materials and methods
### 2.1. Materials

Ibuprofen was from Shasum, India; PEG 6000, Tween 80 and sodium lauryl sulfate were obtained from Merck, Germany; PVP was purchased from Hopkin and Williams, England; eudrgit RS PO and eudragit RL PO was from Rohm, Germany; HPMC was from Dow Chemical, England. All other reagents were of analytical grade from local markets.

### 2.2. Assay of ibuprofen

Ibuprofen (0.45 g) was dissolved in 50 ml of methanol and then 0.4 ml of phenolphthalein solution was added to it. Titration was carried out with sodium hydroxide solution 0.1 M until red color was produced. A similar solution (blank) without ibuprofen was made and the required amount of sodium hydroxide solution was determined [11]. This test was repeated three times and the mean of the results of 3 determinations was used for ibuprofen purity.

### 2.3. Saturation solubility and phase-solubility studies

A modification method of solibility determination was used to determine the solubility of diffrent ibuprofen solid dispersions [12]. Weighed amounts of ibuprofen (pure drug), solid dispersions, and physical mixture, each sample equivalent to 0.5 g of ibuprofen, were separately introduced into 15 ml stoppered conical flasks containing 5 ml of phosphate buffer solution (pH 7.2). The sealed flasks were agitated on a rotary shaker for 72 h at 37 °C and equilibrated for 2 h. The supernatant solution was filtered through 0.45 μm membrane filter, and the filtrate was suitably diluted and analyzed on a UV spectrophotometer at 222 nm. Determinations were carried out in triplicate.

### 2.4. Preparation of physical mixtures

Physical mixtures of ibuprofen and polymers (PEG 6000, PVP, eudragit RS PO, euragit RL PO and HPMC) in powder form were mixed and passed through sieve mesh no. 35. The physical mixtures were prepared in the following ratios:
Ibuprofen: PEG 6000 in the ratios of 1:0.5; 1:1; 1:1.5 and 1:2.
Ibuprofen: PVP in the ratios of 1:1 and 1:2.
Ibuprofen: eudragit RS PO or eudragit RL PO, in the ratios of 1:0.5; 1:1 and 1:2.
Ibuprofen: HPMC in the ratios of 1:0.2 and 1:1.

### 2.5. Preparation of solid dispersions

Solid dispersions of ibuprofen and PEG were prepared by fusion-solvent method. The required amount of ibuprofen was dissolved in methanol. PEG 6000 was melted at 50-60 °C and added to the ibuprofen solution and mixed thoroughly [13]. Other solid dispersions containing HPMC, either kinds of Eudragit or PVP were prepared by solvent

method. The obtained mixtures were kept at 50-60 °C for 72 h and then the solutions were cooled at the room temperature to form solid [3]. The prepared solid dispersions were milled to pass through sieve mesh no. 35.

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Ibuprofen: PVP in the ratios of 1:1 and 1:2.
Ibuprofen: eudragit RS PO or eudragit RL PO, in the ratios of 1:1 and 1:2.
Ibuprofen: HPMC in the ratios of 1:0.2 and 1:1.

## 2.6. Preparation of solid dispersions containing surfactants

Eudragit RL PO has a higher water permeability and swelling characteristics than eudragit RS PO, because it contains a higher ratio of quaternary ammonium groups [17]. So, it was chosen for more investigation by using surfactants such as tween 80 or SLS to prepare solid dispersion. These kinds of solid dispersions were consisted of drug:polymer and surfactants. Only solid dispersions containing constant ratio of 1:1 eudragit RL PO: ibuprofen and different amounts of tween 80 (2%) or SLS (0.5 and 1%) were prepared and evaluated.

## 2.7. Evaluation of prepared solid dispersions

All prepared powders (physical mixtures and solid dispersions) were mixed with 1% magnesium stearate as lubricant. Flow properties of powders are important parameters in mixing and passing through hoper, especially during tabletting and capsule filling [14]. Therefore, for investigating prepared physical mixtures and solid dispersions, their flow property, angles of repose and compressibility's were determined and compared.

## 2.8. Flowability and volume flow rate determination

Flowability measurments of powders were conducted by Erweka apparatus model GT. The outlet funnel and nozzle of 15 mm were used in all tests. The time required to empty the complete sample from the hoper was measured. The measured value was normalized to 100 g and was corresponding to the flowability [15]. The test was repeated three times and the mean data was used as flowability value.

The volume flow rate were measured as the same, using 100 ml of the powders.

## 2.9. Determination of angles of repose
Determination of angles of repose are

**Table 1.** Saturated solubility of ibuprofen in different ratios of physical mixtures and solid dispersions.

| Composion | Ratio | Saturated solubility (mg/ml) | |
|---|---|---|---|
| | | **Physical mixture** | **Solid dispersion** |
| Ibuprofen: PEG | 1:0.5 | 5.01 ± 0.27 | 5.00 ± 0.15 |
| | 1:1 | 5.61 ± 0.28 | 5.17 ± 0.29 |
| | 1:1.5 | 4.70 ± 0.13 | 4.93 ± 0.22 |
| | 1:2 | 4.76 ± 0.31 | 5.08 ± 0.55 |
| Ibuprofen:Eudragit RS PO | 1:0.5 | 2.64 ± 0.04 | 3.30 ± 0.18 |
| | 1:1 | 2.32 ± 0.31 | 3.68 ± 0.21 |
| | 1:2 | 2.05 ± 0.19 | -* |
| Ibuprofen:Eudragit RL PO | 1:0.5 | 1.31 ± 0.06 | 2.26 ± 0.12 |
| | 1:1 | 0.97 ± 0.10 | 1.24 ± 0.04 |
| | 1:2 | 0.62 ± 0.03 | -* |
| Ibuporfen:HPMC | 1:0.2 | 3.56 ± 0.07 | 3.64 ± 0.10 |
| | 1:1 | 3.53 ± 0.09 | 3.79 ± 0.08 |

* The formulation was not made in this ratio.

relatively simple practical techniques for measuring resistance to particle movement [16]. It is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane. Such measurements give at least a qualitative assessment of the internal cohesive and frictional effects under low levels of external loading, as might apply in powder mixing, or in tablet die or capsule shell filling operations [16]. The angle of repose ($\theta$) were determined with same funnel as the flow rate determination (15 mm nozzle) using the equation 1:

$$Tan\ \theta\ =2\ h\ /\ D \qquad \text{Equation 1}$$

Where D is the diameter of a conical bed of the powder, and h is the powder bed height.

Approximately 15 g of powder was poured through a stainless steel funnel from a height of 6 centimeter onto a level bench top. The angle that the side of the conical heap made with the horizontal plane was recorded as the angle of repose. Lower angle of repose values represented better flow [18].

## 2.10. Compressibility determination

Approximately 100 ml of powder ($V_b$) was gently poured into a tarred graduated cylinder and the initial volume (bulk density, $d_b$) and weight of the material (M) was

recorded. The graduated cylinder was placed on a tap density tester (Erweka, model SVM202) and the final volume was recorded after 200 taps ($V_t$). The data obtained were used to calculate bulk density ($d_b$) and tap density ($d_t$) of the powders which were used to determine the percent compressibility index (I). Lower percent compressibility values represent better flow [19]. Percent compressibility index were determined using the equation 2:

$$I=100\times(\text{Tap density-Bulk density})/\text{Tap Density} \qquad \text{Equation 2}$$

## 2.11. Preparation of matrices

Flat-faced tablets, 12.7 mm diameter, were directly compressed on a Korch single punch tableting machine. Compaction was accomplished by direct compression of blends (physical mixtures and solid dispersions) containing equivalent to 300 mg ibuprofen. The hardness of the tablet was adjusted at 6-7 Kg. All the tests such as weight variation, content uniformity, hardness, friability, disintegration were carried out on matrices, but only dissolution test is reported.

## 2.12. Dissolution studies

Dissolution was determined by dissolution tester (Erweka type DT 800, Germany) and the USP XXII (apparatus II, paddle method).

**Table 2.** Angles of repose and compressibility determination from physical mixtures and solid dispersions containing ibuprofen.

| Composion | Ratio | Physical mixture | | Solid dispersion | |
|---|---|---|---|---|---|
| | | Angle of repose ($\theta$) | Compress (%) | Angle of repose ($\theta$) | Compress (%) |
| | 1:0.5 | 20.73 ± 1.46 | 10 | 25.20 ± 0.78 | 20 |
| Ibuprofen: PEG | 1:1 | 21.89 ± 0.63 | 10 | 15.24 ± 0.91 | 16 |
| | 1:1.5 | 21.89 ± 0.89 | 12 | 15.75 ± 0.20 | 16 |
| | 1:2 | 19.41 ± 0.84 | 12 | 27.27 ± 1.13 | 20 |
| Ibuprofen:Eudragit RS PO | 1:0.5 | 25.13 ± 1.14 | 18 | 35.26 ± 0.54 | 22 |
| | 1:1 | 25.08 ± 1.75 | 26 | 21.71 ± 0.93 | 16 |
| | 1:2 | 22.79 ± 1.09 | 24 | -* | -* |
| Ibuprofen:Eudragit RL PO | 1:0.5 | 31.86 ± 1.25 | 22 | 34.07 ± 1.14 | 22 |
| | 1:1 | 30.58 ± 0.28 | 20 | 17.59 ± 1.38 | 14 |
| | 1:2 | 25.05 ± 1.39 | 20 | -* | -* |

* Due to the difficulty to pass through funnel, omitted from investigation.

Dissolution studies was used at a rotation speed of 50 rpm, in 900 ml phosphate buffer (pH 7.2) maintained at 37 °C [3]. Samples of 5 mL were taken at 5, 15, 30, 45 and 60 min. and then one hour intervals. Immediately after taking samples, equal volumes of fresh dissolution medium were replaced to maintain a constant volume for drug dissolution. The concentration of ibuprofen was determined using UV spectroscopy at 222 nm. Dissolution studies were performed in triplicate for each batch of tablets.

### 2.13. Analysis of drug release

In order to investigate the mode of drug release from matrices, the data corresponding to 5 up to 80% release were fitted to Equation 3 [12].

$$Q = Kt^n \qquad \text{Equation 3}$$

Where Q is the percentage of drug released at time t, K is dissolution rate constant and "n" is the release exponent. The value of "n" indicates the release mechanism. For instance n=0.5 shows square root of time kinetics and n=1.0 shows zero-order release [12].

### 3. Results and discussion

Assay of ibuprofen powder used in this study was in the range of 101.5 to 104.8% purity. The maximum absorption of ibuprofen was obtained at 222 nm and maximum saturated solubility of ibuprofen in phosphate buffer solution (pH 7.2) was determined as $3.74 \pm 0.14$ mg/ml. Ghosh *et al*. [20] reported that the solubility of ibuprofen is pH dependent. They gave a solubility of ibuprofen of 0.075 g/l at pH 2.0, 0.35 g/l at pH 4 and 2.325 g/l at pH 6. The obtained results confirm the report of Ghosh *et al*. [20].

Table 1 shows the saturated solubility of ibuprofen from different solid dispersions. Solubility studies showed that the solubility of ibuprofen in PEG, increased up to 50% in comparison with pure ibuprofen (*p*<0.05). Similar findings was reported by Khan *et al*. [3], who claimed this phenomenon was due to water solubility of PEG. The solubility of ibuprofen decreased in the solid dispersions
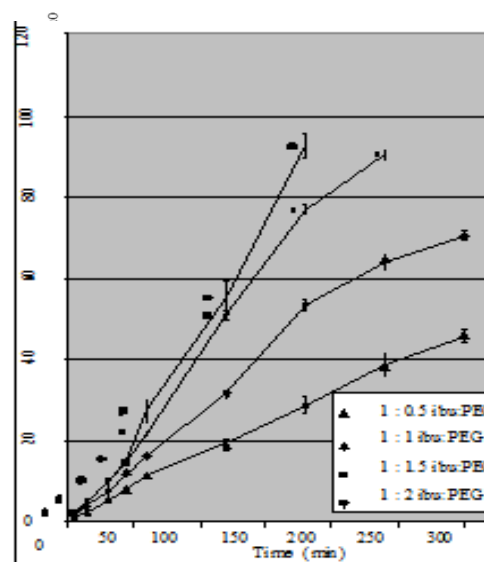


**Figure 1:** Rlease profile from matrice prepared by solid dispersion containing different ratios of ibuprofen: PEG.
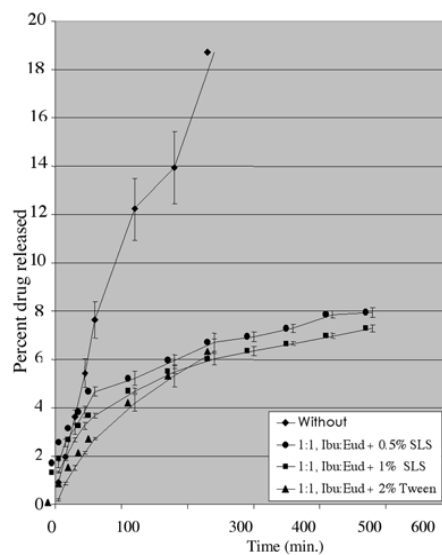


**Figure 2:** Release profile from matrice prepared by solid dispersion containing 1:1 ibuprofen: eudragit RL PO with 0.5 and 1% SLS or 2% tween 80 in comparison with matrices without surfactant.

**Table 3.** Release parameters from matrices containing ibuprofen and different ratios of PEG, eduragit and HPMC.

| Composion | Ratio | Physical mixture | | Solid dispersion | |
|---|---|---|---|---|---|
| | | K | n | K | n |
| Ibuprofen: PEG | 1:0.5 | 0.367 | 0.863 | 0.248 | 0.917 |
| | 1:1 | 0.388 | 0.878 | 0.460 | 0.893 |
| | 1:1.5 | 0.394 | 0.960 | 0.403 | 0.997 |
| | 1:2 | 0.927 | 0.838 | 0.179 | 1.200 |
| Ibuprofen:eudragit RS PO | 1:1 | 0.812 | 0.498 | 0.751 | 0.353 |
| Ibuprofen:eudragit RL PO | 1:1 | 0.351 | 0.717 | 0.635 | 0.416 |
| + 2% Tween | 1:1 | - | - | 0.230 | 0.572 |
| + 0.5% SLS | 1:1 | - | - | 1.170 | 0.314 |
| + 1% SLS | 1:1 | - | - | 0.913 | 0.339 |
| Ibuprofen: HPMC | 1:0.2 | 16.1 | 0.472 | 19.2 | 0.434 |
| | 1:1 | 0.317 | 0.610 | 0.757 | 0.459 |

using eudragit RS PO and eudragit RL PO (Table 1). The reduced saturated solubility of solid dispersions containing eudragit is due to ion interaction between ibuprofen and eudragit [17]. Heun *et al.* [17] reported that hydrophobic interaction energies for the eudragit RL fragments to all drugs were higher than that for the eudragit RS fragments, because of the double number of positively charged quaternary ammonium groups compared to eduragit RL. HPMC did not

significantly affect on phase solubility of ibuprofen, because HPMC solid dispersions produced a gel which reduced diffusion of ibuprofen from particles [7].

Flowability studies of powders containing PEG, showed that solid dispersion technique slightly improved flow properties compared with the physical mixtures. Physical mixtures and solid dispersions containing PVP produce a mass with a high viscosity which makes it impossible to continue investigation. Also, after 2 months, due to plastic characteristics, milling and size reduction was not possible, therefore, it omitted from investigation. The low flowability of solid dispersions containing PVP, is due to high ability to absorb water and its plasticity characteristics [21]. Similar finding was observed for ibuprofen:eudragit RL PO in the ratio of 1:2.

Determination of angles of repose and compressibility studies are shown in the Table 2, in which, it is seen that preparation of solid dispersion in the ratios of 1:1 and 1:1.5 of ibuprofen:PEG, promotes physiochemical properties compared with physical mixture ($p<0.05$).

The results of dissolution tests from tablets containing solid dispersions of PEG, are shown in Figure 1. It is seen that as the ratio of PEG from 0.5 to 2 increased, the release rate increased. Similar finding is observed for their physical mixture. The release kinetics
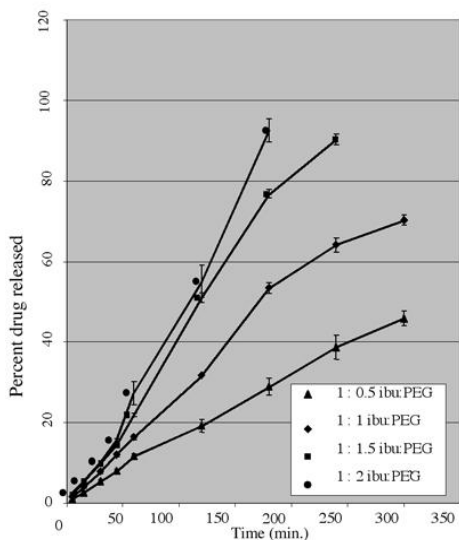


**Figure 3:** Rlease profile from matrice prepared by solid dispersion containing 1:1 of ibuprofen : PEG or eudragit RL PO, eudragit RS PO, HPMC and 1:1.5 of ibuprofen: PEG (best formulation).

for the these formulations was zero order with the value of "n" between 0.893 -1.200 (Table 3).

HPMC (due to gel formation) and eudragit (due to ionic interaction) caused slow release of ibuprofen. The release kinetics was observed as Higuchi model with the "n" value of around 0.5 (Table 3). Similar finding was reported by Sadeghi *et al*. [8], that solid dispersion systems of acetaminophen and eudragits resulted in decreasing drug release rate.

Addition of surfactants such as Tween 80 and SLS in the solid dispersions containing eudragit, caused decrease in release of ibuprofen (Figure 2). It is seen that the formulation without surfactant released about 18% of drug in 4 h, whereas, formulations containing SLS or Tween released only 8% of drug during 8 h. Ghosh *et al*. [20] using ibuprofen, starch, PVP and SLS, reported that the release rate of drug decreased as the SLS concentration increased from 0.01 to 0.05%.

Figure 3 shows the release pattern from different formulations containing ibuprofen: PEG, eudragit RS PO , eudragit RL PO or HPMC in the ratio of 1:1. It is seen that matrices prepared by 1:1 ibuprofen:HPMC had the lowest release rate. In this ratio only 10% of the drug released after 6 h, whereas formulation containing 1:1.5 of ibuprofen:PEG had a constant release rate of ibuprofen about 50 mg per hour that was found suitable for sustained release of the drug [21].

## 4. Conclusions

Ibuprofen solid dispersions were prepared using PEG, PVP, eudragit RS PO, eudragit RL PO and HPMC as carriers to improve physicochemical characteristics of ibuprofen. Solid dispersion technique found to be effective in increasing the aqueous solubility of ibuprofen. *In vitro* dissolution studies showed that in the dispersion systems containing eudragit

or HPMC, dissolution of ibuprofen was retarded, which attributed to ionic interaction and gel forming respectively. But solid dispersion containing PEG, as a carrier, gave faster dissolution rates than the physical mixtures. Finally, solid dispersion of ibuprofen:PEG 6000 prepared in 1:1.5 ratio showed excellent physicochemical characteristics and was found to be described by the zero order kinetic, and was selected as the best formulation in this study.

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