Dissolution Enhancement of Ibuprofen Solid Dispersion Prepared with Vinyl Polymers by Fusion Method

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ABSTRACT
Solid dispersions of ibuprofen are prepared by the fusion method aiming to enhance its dissolution properties. Three vinyl polymers named Kollidone VA64, Povidone K12 and Povidone K30, are used in this work. In vitro dissolution studies were carried out to evaluate the dispersions. The outcome of the study indicated that the rate of dissolution of ibuprofen was considerably improved when formulated in solid dispersions with Povidone K12 and Povidone K30. Solid dispersions with Kollidone VA64 showed drug retarding capability and can be used to formulate sustained release dosage form.

Key words: Ibuprofen, Dissolution rate, Solid dispersion, Fusion method, Kollidone, Povidone.

INTRODUCTION
Fast onset of action is often desirable for ibuprofen, a widely used non-steroidal anti-inflammatory drug (NSAID) to be utilized in the treatment of mild to moderate pain and fever (Rainsford, 2003). The drug's rapid pharmacologic action can be obtained by tweaking its formulation so that the plasma drug concentration reaches optimum level within a short period of time (Buxton, 2006). Newa et al. stated that for existing dosage forms of ibuprofen, absorption of the drug is controlled primarily by its dissolution rate and because its high membrane permeability characteristic, extent of ibuprofen absorption approaches up to 100% upon dissolution.

Enhancing solubility and dissolution rate of poorly water-soluble drugs like ibuprofen is one of the striking areas of research in pharmaceutical field (Dhirendra et al., 2009). Various strategies have been utilized including prodrug formation (Murtha and Ando, 1994), complexation (Ghorab and Adeyeye, 2001), microcapsulation (Adeyeye et al., 1994), the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrines, nanoparticles, solid dispersions, self emulsifying drug delivery system (Shakhtshneider et al., 1996; Craig, 2002; Gao and Morozowich, 2006; Rane et al., 2007; Tang et al., 2007) etc, to overcome the problems associated with oral absorption and bioavailability issue. However ahead of all, solid dispersion is the most promising method to the scientists due to the ease of preparation, ease of optimization and reproducibility of the manufacturing method (Chiou and Reigelman, 1971; Ford, 1986; Law et al., 1991; Leuner and Dressman, 2000). Many methods like spray drying, co-precipitation, co-evaporation and freeze drying are used for solid dispersion manufacturing; however, costly equipments are required along with complicated procedures. Apart from these techniques, fusion method is a method of choice because it is environmentally friendly, cost effective, represents no stability nor toxicity problems and can be easily scaled up for commercial purpose (Uddin et al., 2010; Bhandari et al., 2007).

The aim of this study was to prepare different solid dispersions of ibuprofen by fusion method with three vinyl polymers: Kollidone VA64, Povidone K12 and Povidone K30 and characterize them by dissolution studies to evaluate the effect of these carriers on solubility profile of ibuprofen.
MATERIALS AND METHODS

Experimental material: ibuprofen RS was gift sample from Orobinder, India. Kollidone VA64, Povidone K12 and Povidone K30 were obtained from BASF, Germany. Reagent: Di-sodium hydrogen phosphate and Sodium hydroxide (Merck, Germany); all other ingredients used were of analytical grade. Equipment: USP dissolution tester-Apparatus-II (VEEGO, India); UV Spectrophotometer (UV mini-1204, SHIMADZU CORP., Kyoto, Japan); Digital pH meter (pH 211 Microprocessor pH Meter, HANNA Instruments, Romania); Electronic balance (AY 120, SHIMADZU CORP., Kyoto, Japan); Sieve (Endecott’s Test Sieve, Endecotts Limited, England); glass vials, water bath, dessicator etc.

Preparation of the solid dispersion
Fusion method was used for the preparation of solid dispersions of ibuprofen (Dhirendra et al., 2009; Vasconcelos et al., 2007). Required amount of drug and polymer (Table 1) were mixed in glass vials. The mixture was then heated till it was completely melted. The temperature was maintained to a range of 80°C-90°C. Continuous stirring during the melting was carried out to prevent the separation of the constituents. The melt was then rapidly solidified. The formulations were kept in a dessicator for further treatment. The solidified mass was then crushed, size reduced in a mortar and pestle and sieved through a 150 micron sieve. All glass vials were labeled with care and kept in dessicator. Samples for dissolution studies were taken from the vials.

Table 1: Different ratios of ibuprofen with Kollidone VA64, Povidone K12 and Povidone K30.

<table>
<thead>
<tr>
<th></th>
<th>KVA 1</th>
<th>KVA 2</th>
<th>KVA 3</th>
<th>KVA 4</th>
<th>KVA 5</th>
<th>PV12 1</th>
<th>PV12 2</th>
<th>PV12 3</th>
<th>PV12 4</th>
<th>PV12 5</th>
<th>PV30 1</th>
<th>PV30 2</th>
<th>PV30 3</th>
<th>PV30 4</th>
<th>PV30 5</th>
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</thead>
<tbody>
<tr>
<td>Ibuprofen (mg)</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
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<td>500</td>
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<tr>
<td>Kollidone VA64 (mg)</td>
<td>125</td>
<td>250</td>
<td>500</td>
<td>1000</td>
<td>2000</td>
<td>-</td>
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<td>Povidone K12 (mg)</td>
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<td>125</td>
<td>250</td>
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<td>1000</td>
<td>2000</td>
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<td>Povidone K30 (mg)</td>
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<td>125</td>
<td>250</td>
<td>500</td>
<td>1000</td>
<td>2000</td>
</tr>
</tbody>
</table>

Preparation of phosphate buffer pH 7.2
7.34gm di-sodium hydrogen phosphate and 1gm sodium hydroxide were weighed out and dissolved in small amount of distilled water, volume was adjusted to 1 liter with the same solvent to prepare 1 liter phosphate buffer. The pH of the buffer solution was adjusted using a pH meter.

In vitro dissolution Study
These studies were conducted at 37±0.5°C on an USP specification dissolution rate test type II apparatus (Paddle apparatus) with six sections assembly according to the USP 30 procedure (USP 30 and NF 25, 2007). For in vitro dissolution studies, phosphate buffer pH 7.2 was used as dissolution media. Water-bath temperature was fixed & confirmed to be 37±0.5°C before starting the experiment. The medium was preheated to 37°C and then a quantity of 800 ml was added to each vessel. The apparatus was then assembled and paddle rotation was started and adjusted at 100 rpm and the system was allowed to equilibrate for 15 minutes.

After that the paddle rotation was stopped and fixed amounts of solid dispersion containing 50mg equivalent ibuprofen from each batch were placed in the vessels. The apparatus was immediately operated at 100rpm. Each vessel, vessel position and corresponding sample result were assigned the same code. The duration of the experiment was 60 minutes for each set of sample.

10ml of sample was withdrawn from the media at pre-determined intervals of 5, 10, 15, 20, 30, 45, 60 minutes. Each and every time 10ml of dissolution sample was compensated by adding 10ml fresh phosphate buffer. The sample solutions were diluted and analyzed at 221nm for ibuprofen by
UV spectrophotometer. The amount of drug present in the samples was calculated from calibration curve constructed from the standard solution of USP reference standard test drug (Figure 1).

RESULTS AND DISCUSSION

Effects of Kollidone VA64, Povidone K12 and Povidone K30 on dissolution rate of ibuprofen solid dispersions are shown in figure 2, 3 and 4 respectively.

![Figure 1: Calibration curve of ibuprofen using phosphate buffer pH 7.2 as media.](image)

![Figure 2: Percent release of ibuprofen from solid dispersions prepared in different polymer ratios of Kollidone VA64.](image)

100% drug release from formulations prepared with KVA 64 was obtained within 15 minutes, 30 minutes and 60 minutes when ibuprofen to polymer ratio was 1:4, 1:2 and 1:1, respectively. However, formulations prepared with 2:1 and 4:1 drug to polymer ratio did not give 100% release of drug within 60 minutes dissolution time; 97.73% and 95.52% release of ibuprofen was obtained within 60 minute respectively (Figure 2).

Povidone K12 based ibuprofen solid dispersions released ibuprofen within 15 minutes, 30 minutes and 45 minutes when drug to polymer ratio was 1:4, 1:2 and 1:1 respectively. Both 2:1 and 4:1 ratio formulations took 60 minutes for 100% release of the drug (Figure 3).

Solid dispersions prepared with povidone K30 as polymer released 100% drug within 15 minutes for drug to polymer ratios of both 1:4 and 1:2. It also released ibuprofen by 100% within 30 minutes, 45 minutes and 60 minutes with drug to polymer ratio of 1:1, 2:1 and 4:1 respectively (Figure 4).

At lower concentration of KVA 64 (Ibuprofen:KVA 64=4:1) 100% release of ibuprofen was not obtained from KVA 64 based solid dispersions within 60 minutes (95.52%). Even 2:1 drug to KVA 64 ratio formulation was unable to give 100% drug release within 60 minutes dissolution time (97.73% release in 60 minutes). But when the drug to KVA 64 ratio was 1:4, 100% release of ibuprofen was obtained within 15 minutes. Povidone K30 gave a better dissolution profile in comparison to povidone K12. Povidone K30 based solid dispersions with the drug to polymer ratio of 1:2 and 1:4 released 100% ibuprofen within 60 minutes. Povidone K30 showed highest dissolution rate at 32% polymer concentration, povidone K12 at 50% polymer concentration and KVA64 at 65%. When %polymer was 65% all three polymers showed nearly same dissolution rate.
CONCLUSION

With the invention of many poorly water soluble drugs, enhanced dissolution rate i.e. improved oral bioavailability of oral solid dosage forms is a burning question these days. In our study we used fusion method to prepare solid dispersions of ibuprofen to increase their dissolution rate. Vinyl polymers (Kollidone VA64, Povidone K12 and Povidone K30) were used in the work. It is clear from the data obtained that a higher polymer concentration gave faster drug release for all the polymers used to prepare the solid dispersions. Again, for immediate release drug delivery systems, dissolution profiles obtained for Povidone K12 and Povidone K30 based solid dispersions are most encouraging because both they are capable of releasing cent percent of drug within a short period of time as discussed above. On the other hand, few of the Kollidone VA64 based preparations can be used to retard the drug release to some extent to develop time retarded drug delivery system.

REFERENCES


