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Effect of Water Soluble Polymers on Dissolution Enhancement of Ibuprofen Solid Dispersion Prepared by Fusion Method

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ABSTRACT

The purpose of this study was to prepare and characterize solid dispersions of the NSAID Ibuprofen with PEG 6000, Poloxomer 188 and Poloxomer 407 with the intention of improving its dissolution properties. The solid dispersions were prepared by the fusion method. Evaluation of the properties of the dispersions was performed using dissolution studies. The results obtained showed that the rate of dissolution of Ibuprofen was considerably improved when formulated in solid dispersions with PEG 6000 and poloxomer 188. Solid dispersions with poloxomer 407 showed drug retarding capability which may trigger more research in the intension of exploiting this feature to prepare sustained release dosage form.

Key words: Ibuprofen, polyethylene glycol, poloxomer, solid dispersion, fusion method, dissolution

INTRODUCTION

Ibuprofen is a widely used non-steroidal anti-inflammatory drug (NSAID) utilized in the treatment of mild to moderate pain and fever (Moore, 2003). For any drug to exhibit its prompt pharmacologic action, its serum concentration has to reach optimum level within a short period of time (Buxton, 2006). Thus rapid ibuprofen absorption could be a prerequisite for the quick onset of its action (Rainsford, 2003). Because of its high membrane permeability characteristic, extent of ibuprofen absorption approaches up to 100% (Martinez et al*.,* 2002). Therefore, dissolution becomes the rate limiting step for absorption and the quick release of ibuprofen in the gastrointestinal tract following oral administration is desirable (Levis et al*.,* 2003; Matthias et al*.,* 2005; Newa et al*.,* 2008). 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). To overcome the problems associated with oral absorption and bioavailability issue, 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. 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 dying 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 (Bhandari et al*.,* 2007).

The aim of this study was to prepare different solid dispersions of Ibuprofen by fusion method with three water soluble polymers, polyethylene glycol (PEG 6000), Poloxomer 188 and Poloxomer 407 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. Poloxomer 188, Poloxomer 407 and PEG 6000 were obtained from BASF, Germany. **Reagent:** Di-sodium hydrogen phosphate and Sodium di-hydrogen phosphate (Merck, Germany); all other ingredients used were of analytical grade. **Equipment:** USP dissolution tester-Apparatus-II (VEEGO, India); UV Spectrophometer (UV mini-1204, SHIMADZU CORP., Koyoto, Japan); Digital pH meter (pH 211 Microprocessor pH Meter, HANNA Instruments, Romania); Electronic balance (AY 120, SHIMADZU CORP., Koyoto, 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℃-90℃. 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 PEG 6000, Poloxomer 188 and Poloxomer 407.

	PEG 1	PEG 2	PEG 3	PEG 4	PEG 5	PLX188 1	PLX188 2	PLX188 3	PLX188 4	PLX188 5	PLX407 1	PLX407 2	PLX407 3	PLX407 4	PLX407 5
Ibuprofen (mg)	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500
PEG 6000 (mg)	125	250	500	1000	2000	-	-	-	-	-	-	-	-	-	-
Poloxomer 188 (mg)	-	-	-	-	-	125	250	500	1000	2000	-	-	-	-	-
Poloxomer 407 (mg)	-	-	-	-	-	-	-	-	-	-	125	250	500	1000	2000

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 adjusterd 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℃ 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℃ before starting the experiment. The medium was preheated to 37℃ and then a quantity of 900ml 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 (Fig. 1).

RESULTS AND DISCUSSION

Effects of PEG 6000, poloxomer 188 and poloxomer 407 on dissolution rate of ibuprofen solid dispersions are shown in figure 2, 3 and 4 respectively.

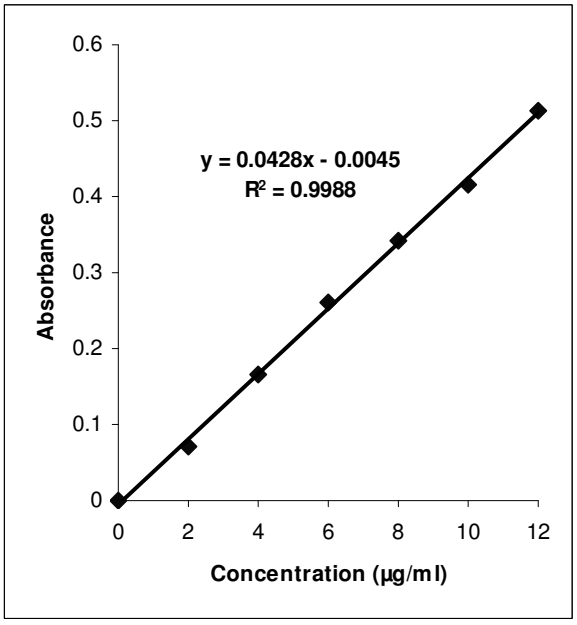

Figure 1: Calibration curve of Ibuprofen using phosphate buffer pH 7.2 as media.

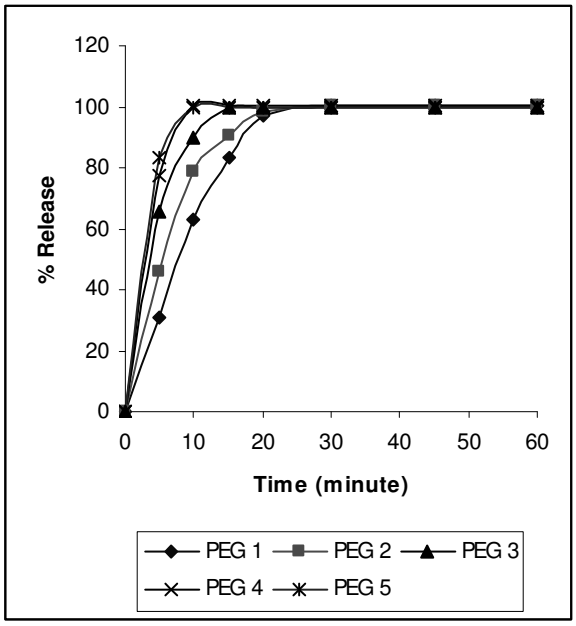

Figure 2: Percent release of ibuprofen from solid dispersions prepared in different polymer ratios of PEG 6000.

When PEG 6000 was used as polymer ibuprofen release from solid dispersions was found to be 100% within 15 minutes for 1:4, 1:2 and 1:1 drug to polymer ratios (PEG 3, PEG 4 and PEG 5). In this case no formulations took 60 minutes to release drug by 100%. Formulations containing 4:1 and 2:1 drug to polymer ratio (PEG 1 and PEG 2) offered 100% drug release within 45 minutes.

Incase of poloxomer 188, the release profile was almost same to PEG 6000 polymer based solid dispersions. Formulation PLX188 3, PLX188 4 and PLX188 5, having drug to polymer ratio of 1:4, 1:2 and 1:1 respectively, released 100% ibuprofen within 15 minutes. Other two formulations, PLX188 1 and PLX188 2 with 2:1 and 4:1 drug to polymer ratios respectively offered 100% drug release within 45 minutes.

Two formulations of solid dispersions containing poloxomer 407 as polymer gave 100% drug release within 15 minutes. They are PLX407 4 and PLX407 5 with ibuprofen to polymer ratios of 1:2 and 1:4 respectively. Solid dispersions with 1:1 drug to polymer ratio (PLX407 3) took 30 minutes to release ibuprofen. No formulation required 60 minutes to release 100% ibuprofen. Formulations of 2:1 and 4:1 drug to polymer ratio took 45 minutes to release drug by 100%.

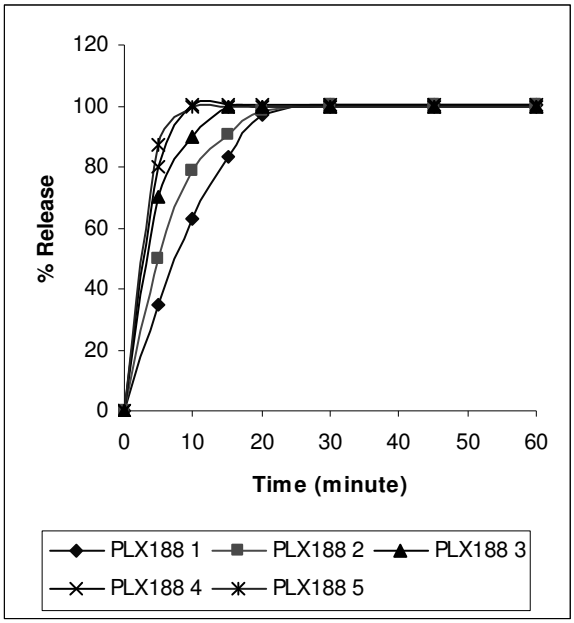

Figure 3: Percent release of ibuprofen from solid dispersions prepared in different polymer ratios of Poloxomer 188.

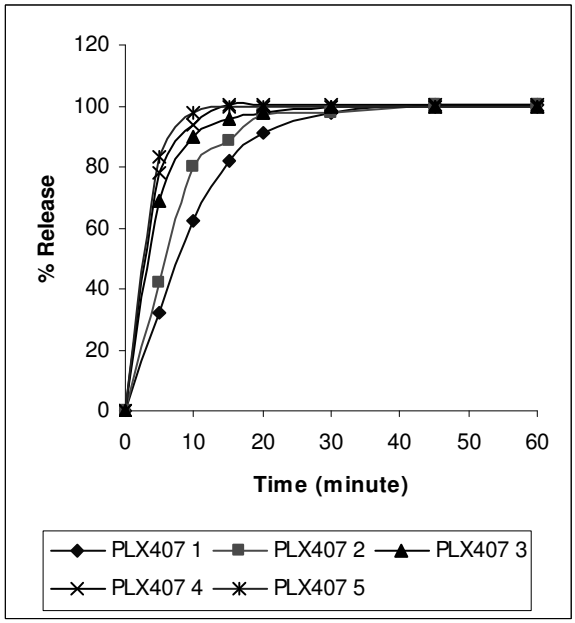

Figure 4: Percent release of ibuprofen from solid dispersions prepared in different polymer ratios of Poloxomer 407.

Upon comparing the release profiles of ibuprofen solid dispersions of different polymer based, it can be found that when drug to polymer ratio was 1:4 all formulations released 100% drug within 15 minutes. It is clear from the data obtained that a higher polymer concentration gave faster drug release in case of all three polymers used to prepare the solid dispersions. For immediate release drug delivery systems, dissolution profiles obtained for poloxomer 188 and PEG 6000 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 poloxomer 407 based preparations can be used intentionally to retard the drug release to some extent to give time retarded drug delivery system.

CONCLUSION

Solid dispersions are of immense importance now-a-days in the development of poorly water soluble drugs in oral solid dosage forms with enhanced dissolution rate and thus improved oral bioavailability. In our experimental protocol we used fusion method to prepare solid dispersions of ibuprofen. Water soluble polymers (PEG 6000, poloxomer 188 and poloxomer 407) 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, from the discussion it can be concluded that solid dispersion systems have a potential usage as controlled release drug delivery system with careful use of different polymers at various ratios. More works have to be carried out to bring this theory into practice.

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