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Study of binary and ternary solid dispersion of ibuprofen for the enhancement of oral bioavailability

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ABSTRACT

To develop a novel ibuprofen loaded solid dispersion system (SDs) with enhanced dissolution rate, binary and ternary solid dispersion were prepared by co-precipitation method using poloxamer-407 only and mixture of poloxamer-407 with a second polymer such as HPMC 6cps, HPC, Kollicoat IR, Kollidon VA 64 respectively. In case of binary SDs, poloxamer 407 was used in three concentrations: 33%, 50% and 66.67% wt/wt of total SDs. In case of ternary SDs, poloxamer 407 was used at 15%, 25% 35% wt/wt of the total SDs content while maintaining the concentration of the second polymer at fixed amount (1gm). In vitro dissolution study was conducted in phosphate buffer of pH 6.8 for 1h. Release property of ibuprofen from two different SDs was investigated. And in case of both the systems, enhanced release property was found where the release was compared with pure ibuprofen powder. Enhanced release of ibuprofen from the optimized SDs was characterized in light of cumulative percent release, % release after 5 min of dissolution and release rate of the drug from different SDs. When the amount of carriers increased with a decrease in drug content, the release of ibuprofen was elevated. And it was found that almost two fold increase in the release of ibuprofen while 66.67% poloxamer was used.

Keywords: Solid dispersion, Ibuprofen, Co-precipitation, poloxamer-407, Dissolution.

INTRODUCTION

Solid dispersion system ((SDs) has been used to improve the solubility, dissolution rate and absorption of poorly water-soluble drugs (Sohn and Gibaldi, 1996) The enhancement of the dissolution rate of the drugs should be taken into greater consideration for increasing the bioavailability of poorly soluble drugs. Solid dispersion is one of the techniques for increasing the dissolution rate of the lipophilic drugs (Arias *et al.* 1994, Lee *et al.* 2005, Palmieri *et al.*, 2002) . It is a two-component system consisting of a hydrophilic carrier in which the drug is incorporated. The incorporated drug in the hydrophilic carrier can be either molecularly dispersed or occurred as nano-crystals or amorphous nanoparticles (Chiou and Riegelman, 1971). Co-precipitation is one of the effective techniques of SD where both drug and solid carrier solvent are dissolved in a common volatile solvent. The liquid solvent is removed by evaporation which results in amorphous precipitation of drug in a crystalline carrier (Brahmankar and Jaiswal, 1986; Kubo and Mizobe, 1997). The dissolution rate is affected by state and size of the particle and the carrier within which it is enclosed. Small size of the drug particles cause increased surface area which helps in enhancement of drug dissolution (Purvis *et al.* 2006, Yonemochi *et al.* 1999).

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Amorphous state of the drugs increases solubility of the drugs (Dai *et al.* 2007; Mura *et al.* 2002; Yonemochi *et al.* 1997; Kawashima *et al.* 1975) and hydrophilic carrier enhances wetting characteristics of the drugs which ultimately leads to increased dissolution rate of drugs (Chow *et al.* 1995).

Ibuprofen is absorbed rapidly and bound avidly to protein. But it does not show comprehensive therapeutic effect because of its poor solubility and dissolution, which leads to poor bioavailability of the drug (Vekama K 1980; Ahuja *et al.* 2007). Thus increasing the aqueous solubility and dissolution rate of ibuprofen is of therapeutic importance.

MATERIALS AND METHODS

Ibuprofen was received as a gift sample from Incepta Pharmaceuticals, Bangladesh. Methanol and Acetone (MERCK, Germany) Poloxamer 407 (Lutrol) (BASF, Germany), Kollicoat IR (BASF Germany), Kollidon VA 64 (BASF Germany), HPC (BASF Germany), Pet ether of 40-60 (MERCK, Germany) of laboratory grade were also used in the experiment.

Preparation of Solid Dispersion

Ibuprofen SDs was prepared by co-precipitation method. In case of ibuprofen binary SDs, ibuprofen and poloxamer were taken in vials according to table 1.

Table 1. Formulation of Ibuprofen binary and ternary solid dispersions.

Batch	Ibuprofen	Poloxamer 407	HPMC 6 cps	HPC	Kollicoat IR	Kollidon VA 64
I	0.3 g	0.7 g	-	-	-	-
II	0.5 g	0.5 g	-	-	-	-
III	0.7 g	0.3 g	-	-	-	-
IV	0.3 g	0.7 g	1 g	-	-	-
V	0.5 g	0.5 g	1 g	-	-	-
VI	0.7 g	0.3 g	1 g	-	-	-
VII	0.3 g	0.7 g	-	1 g	-	-
VIII	0.5 g	0.5 g	-	1 g	-	-
IX	0.7 g	0.3 g	-	1 g	-	-
X	0.3 g	0.7 g	-	-	1 g	-
XI	0.5 g	0.5 g	-	-	1 g	-
XII	0.7 g	0.3 g	-	-	1 g	-
XIII	0.3 g	0.7 g	-	-	-	1 g
XIV	0.5 g	0.5 g	-	-	-	1 g
XV	0.7 g	0.3 g	-	-	-	1 g

The drug-polymer mixture was dissolved in acetone by sonication for 15 min. Solvent was then evaporated completely with the help of cold air and stored in desiccator to ensure the evaporation of the residual solvent if present. After complete drying, SD formulations were withdrawn from the vials, grinded by mortar & pestle and preserved in the desiccator within the vials for further study. In case of ibuprofen ternary SDs, drug and poloxamer were first dissolved in acetone and then second polymer (HPMC 6 cps, HPC, Kollicoat IR, Kolidon VA 64) was added according to table 1. Rest of the procedures was similar to that of ibuprofen binary SD preparation.

Dissolution Studies

The dissolution was studied with accurately weighed amount of the formulations (containing approx. 25 mg of

ibuprofen) using a USP apparatus II in 900 ml of phosphate buffer (pH 6.8) for one hour (1h). The rotational speed of the paddle was set at 50 rpm at $37 \pm 0.5^\circ\text{C}$. Aliquots (5ml each) were withdrawn at predetermined time intervals of 10 minutes and sink conditions were maintained with fresh dissolution media. The samples were analyzed for drug content using a double beam UV spectrophotometer (model no. UV 1240 PC, Shimadzu Corporation, Koyto, Japan) at 221 nm. The release rates at different time intervals were then determined.

RESULTS

In-vitro release of ibuprofen

Graphical presentation of percent release of ibuprofen from the optimized SD formulations is shown in figure 1-5. All formulations that had poloxamer-407 showed better dissolution rate than those without having poloxamer-407. Three formulations were processed by using poloxamer-407 of three different strengths (33%, 50%, and 66.67%) with respect to total formulation. Formulations that contain 50% and 66.66% poloxamer-407 respectively showed better release than the formulation that has 33% poloxamer-407. Almost 100% ibuprofen was released within 1h in case of the formulation that contained 66.67% poloxamer-407 where as 88% drug was released for the formulation that contained 33% poloxamer-407. On the other hand only 54% drug was released within 1h for the formulation that had only ibuprofen.

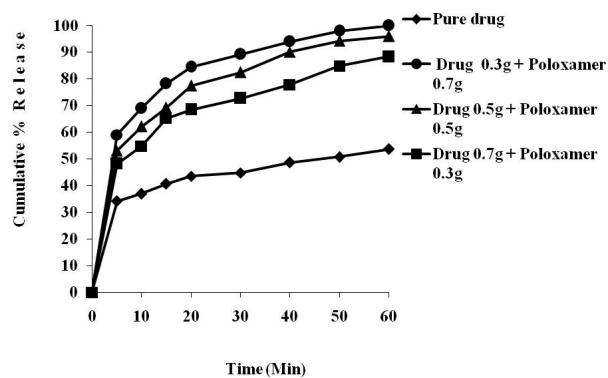


Fig 1: Release profile of ibuprofen from binary SD formulations comprising only drug and poloxamer-407.

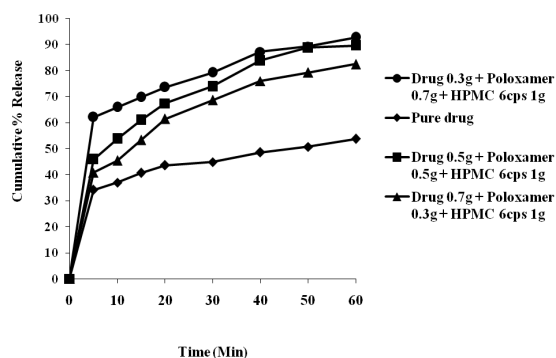


Fig 2: Release profile of ibuprofen from ternary SD formulations comprising drug, poloxamer-407 and HPMC 6cps.

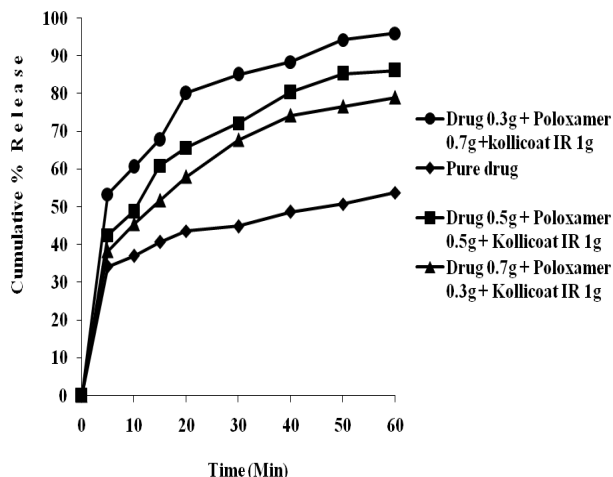


Fig 3: Release profile of ibuprofen from ternary SD formulations comprising drug, poloxamer-407 and Kollicoat IR.

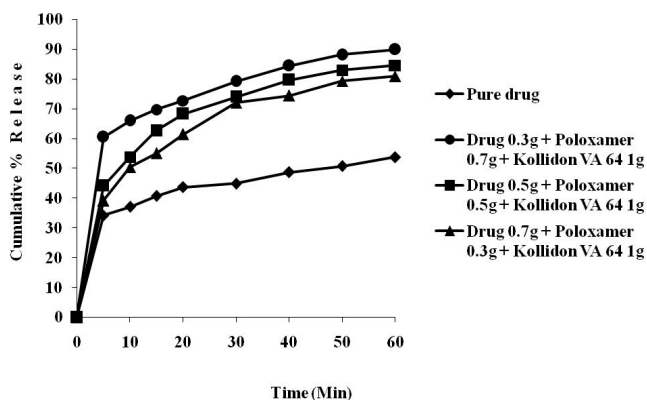


Fig 4: Release profile of ibuprofen from ternary SD formulations comprising drug, poloxamer-407 and Kollidon VA-64.

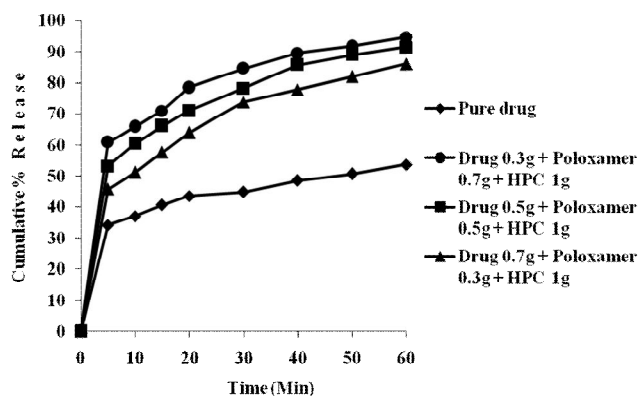


Fig 5: Release profile of ibuprofen from ternary SD formulations comprising drug, poloxamer-407 and HPC.

Again Effect of combination of Poloxamer 407 and second polymer on ibuprofen release was investigated with three different poloxamer-407 percentage : 15% (0.3 gm), 25% (0.5 gm), 35% (0.7 gm) where the percentage of poloxamer was calculated on total drug-polymer content and in all cases the amount of second polymer were remain same (1 gm).

As the poloxamer content in the formulation was increased, so release rate of the drug from SDs was also increased.

Release Rate of Ibuprofen Solid Dispersion from Different Formulations

Figure-6 shows that the rate was the highest for the formulation that contained highest amount of polymer. Here poloxamer was used with different percentage, where the percentage of poloxamer was calculated on total drug-polymer content and in all cases the amount of second polymer was constant (1 gm). The rate was determined (log % remaining / minute) for the formulations containing 15%, 25% and 35% poloxamer respectively. As the poloxamer-407 content increases, so does release rate.

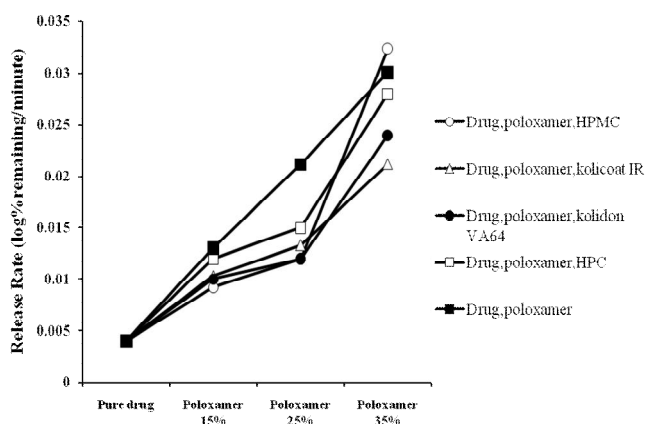


Fig 6: Release rate of ibuprofen from optimized binary and ternary SDs.

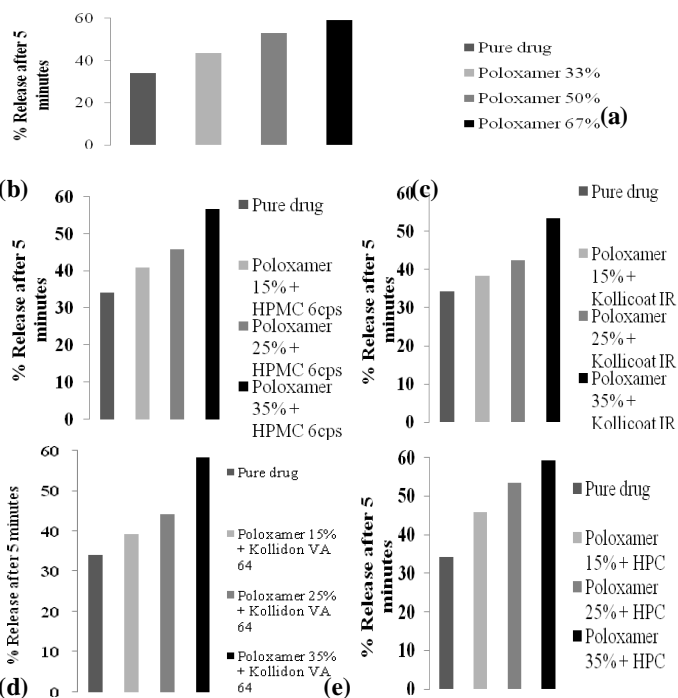


Fig 7: Percent release of ibuprofen after five minutes of dissolution consisting of a) Poloxamer (b) poloxamer+HPMC 6cps (c) poloxamer+Kollicoat IR (d) poloxamer+Kollidon VA64 (e) poloxamer+HPC.

Percent Release of Ibuprofen after Five Minutes of Dissolution

Only 34 % Ibuprofen was released for the first five minutes when it was used alone. Here poloxamer was used with different percentage, where the percentage of poloxamer was calculated on total drug-polymer content and in all cases the amount of HPMC 6cps were remain same (1 gm). As the poloxamer-407 content in the formula increased, so that release rate from the solid dispersion also increased.

DISCUSSION

The dissolution improvement of ibuprofen from drug-poloxamer-407 solid dispersion might be due to surface active property (lowering of surface tension between drug and solvent), critical micellar concentration of the polymer and improvement of wetting characteristics of the drug (Newa *et al.* 2007; Zhang *et al.* 2009). From the figure 1, it is clearly seen that as the poloxamer concentration was increased, percent release of the drug was also found to be increased accordingly.

Figure 2 shows the release profile of ternary SD of ibuprofen where HPMC was added in the formulations along with the poloxamer. In this case there is a decrease of contact angle noticed because of decreasing number of hydrophobic groups on the surfaces and molecules are re-organized themselves during solvent evaporation (Rane *et al.* 2009). Being a swell able hydrophilic polymer HPMC turn into gelatinized in the dissolution medium and this gelatinized polymer has water retentive characteristics that may enhance the wetting phenomena of the drug (Janssens *et al.* 2009).

Figure 3 shows the release profile of ternary SD of ibuprofen where Kollicoat-IR was added in the formulations along with the poloxamer. Kollicoat IR is a graft polymer composed of polyethylene glycol and polyvinyl alcohol and it shows the both properties of its component polymers. Since the interaction between the polymer and dispersed drug is likely to be complex so that there might some change of phase behavior is occurred (Juan *et al.* 2011). Normally amorphous substances exhibit higher solubility and dissolution rate in compare with thermodynamically stable crystalline forms as crystalline forms have weak internal bonding forces (Nada *et al.* 2005). Ibuprofen has poor solubility in water due to its needle like crystalline structure (Rajarajan *et al.* 2009). The dissolution rate of ternary SD was found to be effective in amorphous condition in compare with crystalline structure of the drug alone (Xu *et al.* 2007).

Figure 4 shows the release profile of ternary SD of ibuprofen where Kollidon VA-64 was added in the formulations along with the poloxamer. Ibuprofen in SDs along with Kollidon VA-64 as carrier attributed the drug changing into an amorphous state that ultimately exhibited the improve dissolution rates (Tiwari *et al.* 2008).

Figure 5 shows the release profile of ternary SD of ibuprofen where HPC was added in the formulations along with the poloxamer. The increase in dissolution of ibuprofen from the SDs might be ascribed to several reasons such as amorphous state condition takes place in lieu of crystalline behavior of the drug,

lowering of surface tension of the medium because of HPC and hence ensuing in better wetting properties of the hydrophobic drug.

CONCLUSION

This study was started to establish the possibility of preparing solid dispersions with improved aqueous solubility and dissolution rate, which will solve the difficulties in the development of pharmaceutical dosage forms of ibuprofen, poorly water soluble drug due to their limited water solubility, slow dissolution rate and low bioavailability. The dissolution rate was evaluated at different stage of the study by using different variables- e.g. HPMC 6cps, Poloxamer 407, Kollidon VA64, HPC and Kollicoat IR. Significant change of dissolution rate was recorded at different batch of the experiment. Solid dispersion preparation by the solvent co-precipitation method thus may be an ideal means of drug delivery system for poorly water soluble-drugs.

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STATEMENT OF CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

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