

Study of Binary and Ternary Solid Dispersion of Spironolactone Prepared By Co-Precipitation Method for the Enhancement of Oral Bioavailability

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ABSTRACT

The study was designed to formulate novel spironolactone, a BCS class II drug loaded solid dispersion system (SDs) with improved dissolution rate. For this purpose 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. To prepare binary SDs poloxamer 407 was used in three concentrations: 33%, 50% and 66.67% wt/wt of total SDs, whereas in case of ternary SDs, poloxamer 407 was used at 15%, 25% 35% wt/wt of the total SDs content and the concentration of the second polymer is maintained at fixed amount (1gm). In vitro dissolution study was carried out in a USP type II dissolution apparatus in 0.1 N hydrochloric acid solution for 1 hour. Release property of spironolactone from two different SDs was examined. Both the systems showed improved release profile compared with pure spironolactone powder. Enhanced release of spironolactone 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 spironolactone was elevated. And it was found that almost two fold increase in the release of spironolactone while 66.67% poloxamer was used.

INTRODUCTION

Water insoluble drugs comprise nearly one-third of drugs in development and one-half of these fail in trials because of underprivileged pharmacokinetics (Savic *et al.*, 2006). Poorly water soluble drugs belong to BCS class II and Class IV group of compounds (Amidon *et al.*, 1995). In the process of absorption of drug from oral route, dissolution is the rate limiting step for lipophilic drugs. Therefore improving of dissolution is of great importance in order to ensure maximum therapeutic effect of these drugs. Solid dispersion system (SDs) is

defined as a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent, or melting solvent method. Solid dispersion system has been used to improve the solubility, dissolution rate and absorption of poorly water-soluble drugs (Sohn and Gibaldi, 1996). 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 SDs. In this method both drug and solid carrier solvent are dissolved in a common volatile solvent. Therefore amorphous precipitation of drug in a crystalline carrier takes place as a result of evaporation that removes the liquid solvent (Brahmankar and Jaiswal, 1986; Kubo and Mizobe, 1997).

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The dissolution rate is affected by state and size of the particle and the carrier within which it is enclosed. The reduction of particle size to nearly molecular level results in improves dissolution (Patro and Choudhary, 2005). As the soluble carrier dissolves, the insoluble drug is exposed to dissolution medium as very fine particles leading to an increase in both surface area and solubilization for fast dissolution and absorption (Purvis *et al.* 2006, Yonemochi *et al.* 1999). Solubility of the drugs increases as a result of amorphous state 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 (Chow *et al.*, 1995).

Spironolactone 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 (Ahuja *et al.* 2007). Thus increasing the aqueous solubility and dissolution rate of spironolactone is of therapeutic importance.

MATERIALS AND METHODS

Spironolactone 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

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

Dissolution Studies

The dissolution was studied with accurately weighed amount of the formulations (containing approx. 25 mg of spironolactone) using a USP apparatus II in 0.1 N hydrochloric acid solution 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 242 nm. The release rates at different time intervals were then determined.

RESULTS

In-vitro release of spironolactone:

Graphical presentation of percent release of spironolactone 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% spironolactone was released within 1h in case of the formulation that contained 66.67% poloxamer-407 where as 92% drug was released for the formulation that contained 33% poloxamer-407. On the other hand only 44% drug was released within 1h for the formulation that had only spironolactone.

Again Effect of combination of Poloxamer 407 and second polymer on spironolactone 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). Release rate of the drug from SDs was improved as the poloxamer content in the formulation was increased,

Release Rate of Spironolactone 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.

Percent Release of Spironolactone after Five Minutes of Dissolution

Only 16 % Spironolactone 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 second polymer (HPMC 6 cps, HPC, Kollicoat IR, Kolidon VA 64) were remain same (1 gm). As the poloxamer-407 content in the formula increased, so that release rate from the solid dispersion also increased.

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

Batch	Spironolactone	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

DISCUSSION

The dissolution improvement of spironolactone from drug-poloxamer-407 solid dispersion might be due to lowering of surface tension between drug and solvent as well as decreased crystallinity of the product (Kalaiselvan *et al.*, 2006). Also critical micellar concentration of the polymer and improvement of wetting characteristics of the drug might be played a crucial role in dissolution enhancement of the drug (Newa *et al.* 2007; Zhang *et al.* 2009).

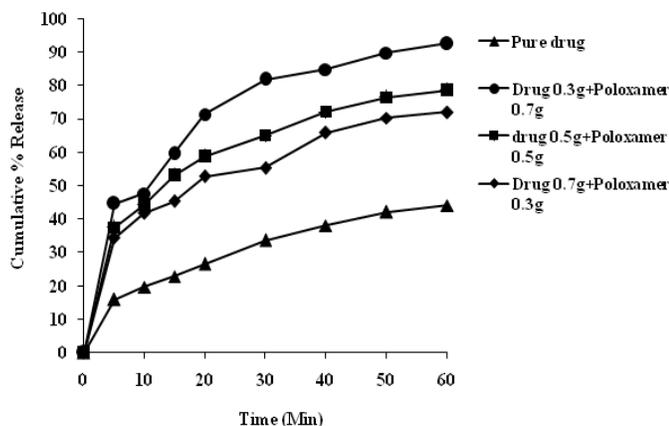


Fig. 1: Release profile of spironolactone from binary SD formulations comprising only drug and poloxamer-407.

From the figure 1, it is evident that percent release of the drug is proportional to poloxamer concentration added with the formulation. On the other hand, Figure 2 shows the release profile of ternary SD of spironolactone where HPMC 6 cps, a hydrophilic polymer was added in the formulations along with the poloxamer. The reason behind the improve aqueous solubility of ternary SD of spironolactone with HPMC might be explained by the fact of enhancement of the wetting phenomena of the drug due to gelatinized behavior of HPMC polymer (Janssens *et al.* 2009). Another reason could be assigned that the number of hydrophobic groups on the surfaces of the drug decreased and the molecules were re-organized themselves during solvent evaporation which resulted in decrease of contact angle (Rane *et al.* 2009).

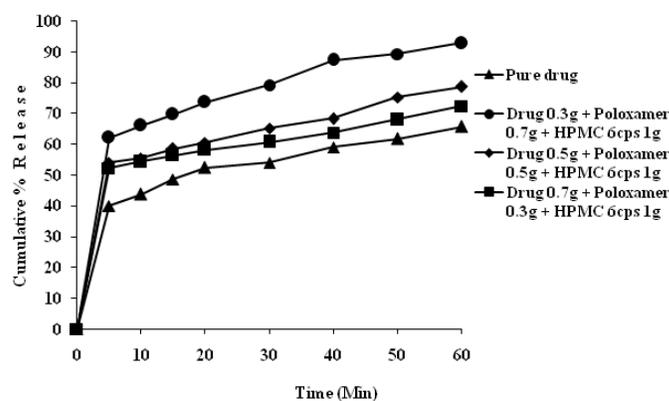


Fig. 2: Release profile of spironolactone from ternary SD formulations comprising drug, poloxamer-407 and HPMC 6cps.

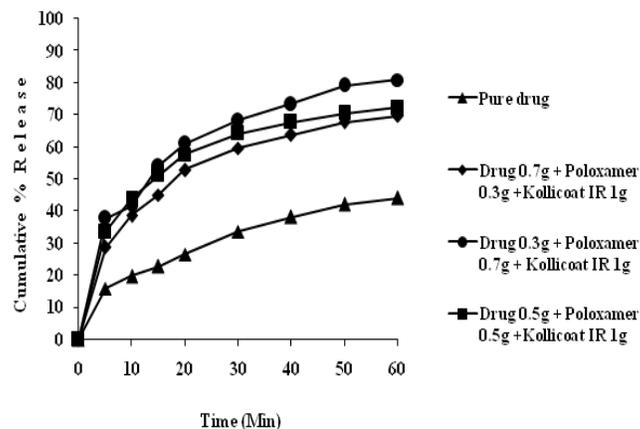


Fig. 3: Release profile of spironolactone from ternary SD formulations comprising drug, poloxamer-407 and Kollicoat IR.

The release profile of ternary SD of spironolactone where Kollicoat-IR was added in the formulations along with the poloxamer is shown in Figure 3. Polyethylene glycol and polyvinyl alcohol together with form Kollicoat IR, a graft polymer. Due to complex formation between the dispersed drug and graft polymer there might have chance of alteration of phase behavior of the drug (Juan *et al.* 2011). Higher solubility and dissolution rate is observed in amorphous substances in

comparison to thermodynamically stable crystalline forms. This might be attributed to the fact that crystalline forms have weak internal bonding forces (Nada *et al.* 2005). On the other hand Intermolecular hydrogen bonds work on between drug and carrier (Tantishaiyakul *et al.*, 1996).

Spironolactone has poor solubility in water due to its needle like crystalline structure (Rajarajan *et al.*, 2009). The release profile of ternary SD of spironolactone where Kollidon VA-64 was added in the formulations along with the poloxamer is shown in figure 4.

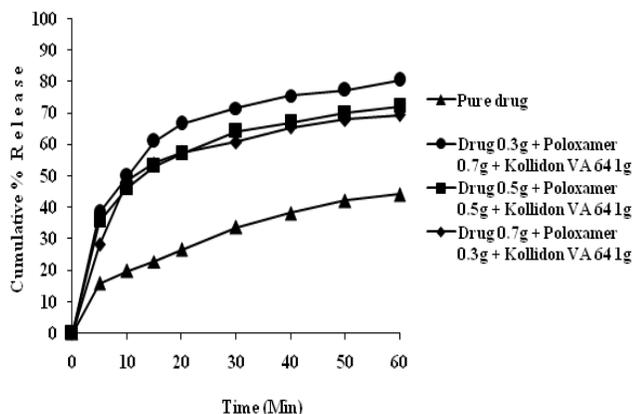


Fig. 4: Release profile of spironolactone from ternary SD formulations comprising drug, poloxamer-407 and Kollidon VA-64.

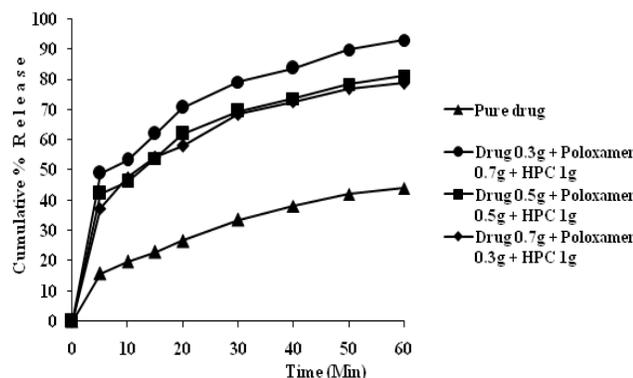


Fig. 5: Release profile of spironolactone from ternary SD formulations comprising drug, poloxamer-407 and HPC.

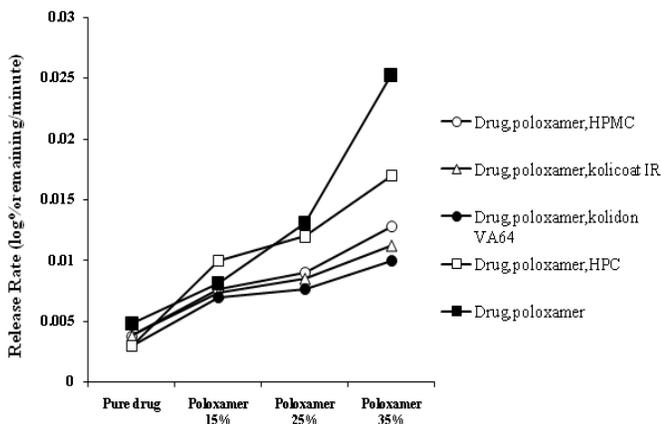
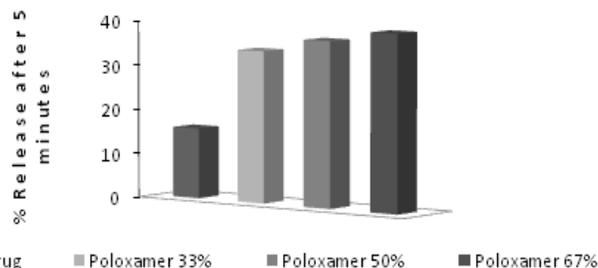


Fig. 6: Release rate of spironolactone from optimized binary and ternary SDs.

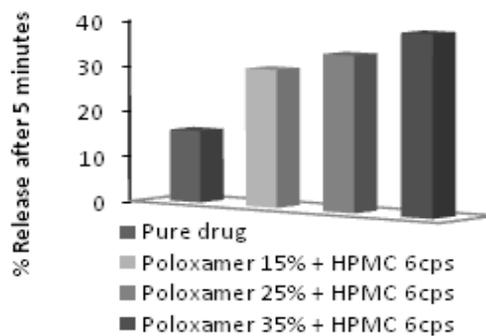
According to Karatas *et al.* (2005) conversion of crystalline drug into amorphous form causes higher aqueous solubility. Spironolactone in SDs along with Kollidon VA-64 as carrier attributed the drug shifting into an amorphous state and that ultimately results in improve dissolution rates (Xu *et al.*, 2007; Tiwari *et al.* 2008; Zahedi and Lee, 2008).

The release profile of ternary SD of spironolactone where HPC was added in the formulations along with the poloxamer is shown in Figure 5. The increase in dissolution of spironolactone from the SDs might be attributed to the amorphous state condition which takes place instead of crystalline behavior of the drug. The wetting properties are greatly increased due to the surfactant property of the HPC polymer which causes decreased interfacial tension between the medium and the drug and ultimately higher dissolution rates achieved. The presence of carrier may also prevent aggregation of fine drug particles, thereby providing a larger surface area for dissolution.

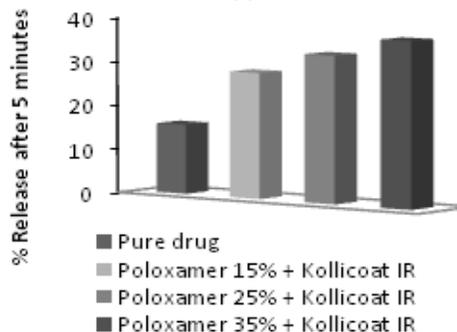
Inhibition of crystal growth due to the presence of carrier polymers facilitates faster dissolution (Betageriet and makarla, 1995).



(a)



(b)



(c)

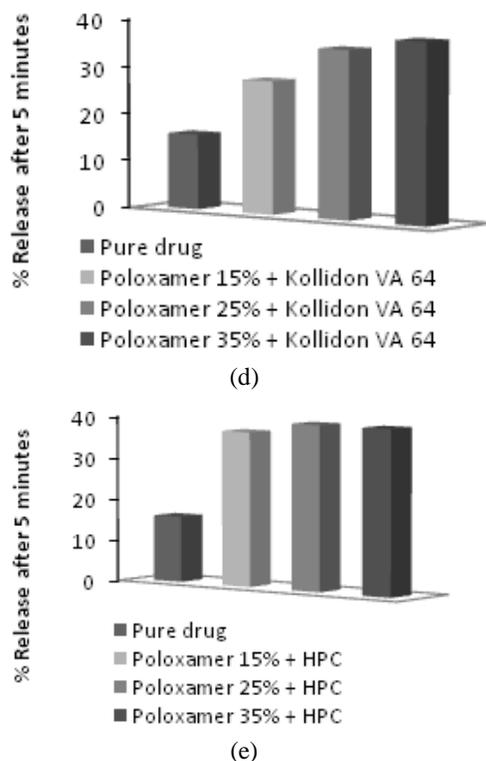


Fig. 7: Percent release of spironolactone after five minutes of dissolution consisting of (a) Poloxamer (b) poloxamer+HPMC 6cps (c) poloxamer +Kollicoat IR(d) poloxamer+Kollidon VA64 (e) poloxamer+HPC.

CONCLUSION

This study is an opportunity of preparing solid dispersions with improved aqueous solubility and dissolution rate, which will solve the difficulties in the development of pharmaceutical dosage forms of spironolactone. In a nutshell, 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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