



Dissolution study of Spironolactone by using solid dispersion technique

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Original Research Article

ABSTRACT

The main objective of the current study was to formulate poorly water soluble drug Spironolactone by using solid dispersion technique in order to achieve a better dissolution rate which would further help in enhancing oral bioavailability. Solid dispersions were prepared using two methods; solvent method and fusion method. Solid dispersion was prepared by using polymers, such as Hydroxy propylmethyl cellulose (HPMC 6cp), Hydroxy propyl cellulose (HPC), Sodium carboxymethylcellulose (Na-CMC), Povidone K12, Povidone K30, Poloxamer 407. Solid dispersions containing Spironolactone with HPC (96.81%), HPMC 6cp (93.05%), Poloxamer 407 (90.84%) and Na-CMC (89.93%) provided higher release rate than the release rate of solid dispersion containing only Spironolactone (35.27%), and Spironolactone with Povidone K12 (76.17%), Povidone K30 (67.92%). So the present study revealed that the solid dispersion may be an ideal means of drug delivery system for poorly water soluble drugs. Further study in this field was required to establish these drug delivery systems so that in future it can be used effectively in commercial basis.

Keywords: Solid dispersion, Spironolactone, dissolution, bioavailability.

INTRODUCTION

Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. Recently more than 40% NCEs (new chemical entities) developed in Pharmaceutical Industry are practically insoluble in water. These poorly water soluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity (Murray et al., 1997).

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and

dissolution may be the rate determining step for the onset of therapeutic activity. Solid dispersion, which was introduced in the early 1970s, is essentially a multi-component system, having drug dispersed in and around hydrophilic carrier(s). In order to improve the solubility and bioavailability of poorly water soluble drugs many methods are used. The solid dispersion approach has been widely used for improvement solubility, dissolution rate and hence bioavailability. Solid dispersion (SD) is one of such methods and it involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method (Chiou and Riegelman, 1971). The technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide (Babu et al., 2003), ketoprofen (Rogers and Anderson, 1982), tenoxicam (El-Gazayerly, 2000),

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nifedipine (Vippagunta et al., 2002), nimodipine (Babu et al., 2002). SD technology has been successfully used for improving the solubility of the drugs and hence bioavailability, e.g., tenoxicam, tacrolimus (Yamashita et al., 2003), indomethacin (Makiko et al., 2005), ibuprofen (Loganathan et al., 2000), nilvadipine (Hirasawa et al., 2009).

Therefore, the improvement of drug solubility

MATERIALS AND METHODS

Materials: Spironolactone (Zhejiang Shenzhou Pharmaceutical Comp. Ltd., China), Methanol (MERCK, Germany), Acetone (MERCK, Germany), Distilled water (University Laboratory), HPMC 6cp (Samsung, Korea), HPC (Samsung, Korea), Povidone K30 (F. MARK), Povidone K12 (F. MARK), Poloxamer 407 (BASF), NaCMC (Samsung, Korea), Lactose (Mingel,

Table 1: Formulation for the preparation of Spironolactone solid dispersions using various excipients.

Ingredients	SPL- HPMC	SPL- HPC	SPL-NaCMC	SPL-Pov K12	SPL-Pov K30	SPL-Polo
Spironolactone	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg
Acetone	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml
HPMC 6cps	500 mg					
HPC		500 mg				
NaCMC			500 mg			
Povidone K12				500 mg		
Povidone K30					500 mg	
Poloxamer 407						500 mg

thereby its oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system. There are numerous approaches available and reported in literature to enhance the solubility of poorly water soluble drug. The techniques are

Germany), Paraffin liquid (MERCK, India).

METHOD

Preparation of Solid Dispersion by Solvent Method

At first Spironolactone (500 mg) was weighed

Table 2: Formulation for the preparation of Spironolactone solid dispersions by fusion method using different concentration of Poloxamer 407.

Ingredients	SPL- Polo A	SPL- Polo B	SPL- Polo C	SPL- Polo D	SPL- Polo E
Spironolactone	500 mg	500 mg	500 mg	500 mg	500 mg
Poloxamer 407	200 mg	400 mg	600 mg	800 mg	1000 mg
Acetone	5 ml	5 ml	5 ml	5 ml	5 ml

chosen on the basis of certain aspects such as properties of drug under consideration, nature of excipients to be selected and nature of intended dosage form. This present work is intended to discuss the various traditional and novel techniques for solubility enhancement of hydrophobic drugs for oral pharmaceutical formulation (Boles Ponto and Schoenwald, 1990; Ozdmir and Ordu, 1998).

accurately in an analytical balance and taken into dry and clean glass vials. Then Acetone (5 ml) was added (Patel MM and Patel DM, 2006) on each vial. Then each polymer (500 mg) was dissolved in the solvent using a vortex mixer to make a polymer solution (Table 1). Drug, polymer and solvent combination was dried by using hair dryer until solid dispersion was formed. The solvent

Table 3: Correlation coefficient (R²) values for the formulation of solvent evaporation method.

Product Formulation	Correlation coefficient (R ²) value			
	Zero order plot	First order Plot	Hixon Crowel Plot	Higuchi Plot
SPL-HPMC	0.914	0.910	0.631	0.984
SPL-HPC	0.903	0.818	0.611	0.988
SPL-NaCMC	0.943	0.959	0.605	0.978
SPL-Povidone K12	0.966	0.961	0.674	0.981
SPL-Povidone K30	0.928	0.895	0.621	0.963
SPL-Poloxamer 407	0.923	0.959	0.605	0.987

evaporated completely. Finally the formulations were withdrawn from vials, crushed in mortar and pestle, passed through 150 micron sieve. Then the resulted samples were weighed and transferred in fresh vials with proper labeling and its double amount of

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Table 4: Correlation coefficient (R²) values for the formulation of fusion method.

Product Formulation	Correlation coefficient (R ²) value			
	Zero order plot	First order Plot	Hixon Crowel Plot	Higuchi Plot
SPL-HPMC	0.904	0.920	0.601	0.981
SPL-HPC	0.898	0.808	0.604	0.982
SPL-NaCMC	0.903	0.939	0.602	0.971
SPL-Povidone K12	0.906	0.901	0.607	0.983
SPL-Povidone K30	0.908	0.885	0.621	0.979
SPL-Poloxamer 407	0.913	0.949	0.608	0.989

lactose was added on each vials as adsorbent and mixed well. Formulations were kept in desiccators until the dissolution started.

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Preparation of Solid Dispersion by Fusion Method

At first 500 mg of the model drug, Spironolactone was accurately weighted and taken in glass vials and 5 ml Acetone was added as solvent to dissolve each vial and heated on a water bath containing paraffin liquid to melt the ingredients at the temperature of 120°C. At this time, stirring was performed to make sure a homogenous mixing of the drug in the solvent. When the drug was completely dissolved in the solvent, then 500 mg of each polymer (HPMC 6cps, HPC, NaCMC, Povidone K12, Povidone K30, Poloxamer 407) were weighed accurately and mixed with the solution containing drug and solvent (Table 2). Drug, polymer and solvent combination was cooled with constant stirring to homogeneously disperse the drug throughout the matrix.

In vitro dissolution study of Solid Dispersion

In-vitro dissolution was carried out in a USP XXX apparatus 2 (Paddle Apparatus) in 900 ml of distilled water for 1 hour at 37±0.5°C and at a rotational speed of 50 rpm. Dissolution samples were withdrawn at predetermined intervals and were filtered through 0.45 μm filters. The drug content was determined spectrophotometrically at max = 238 nm in the filtrate either directly or after appropriate dilution with the dissolution media.

RESULT AND DISCUSSION

Effects of Spironolactone, poorly water soluble drug, Solid Dispersions using various Excipients. After dissolution, we found from the Table1 that the percent release (%) of drug for seven formulations within 1 hour were 35.27%, 93.05%, 96.81%, 89.93%, 76.17%, 67.92% and 90.84% of SPL (drug only), SPL-HPMC, SPL-HPC, SPL-NaCMC,

Figure 1: Effect of different excipients on Spironolactone solid dispersion dissolution rate
 dissolution condition: distilled water; RPM: 100; 37°C ± 0.5°C.

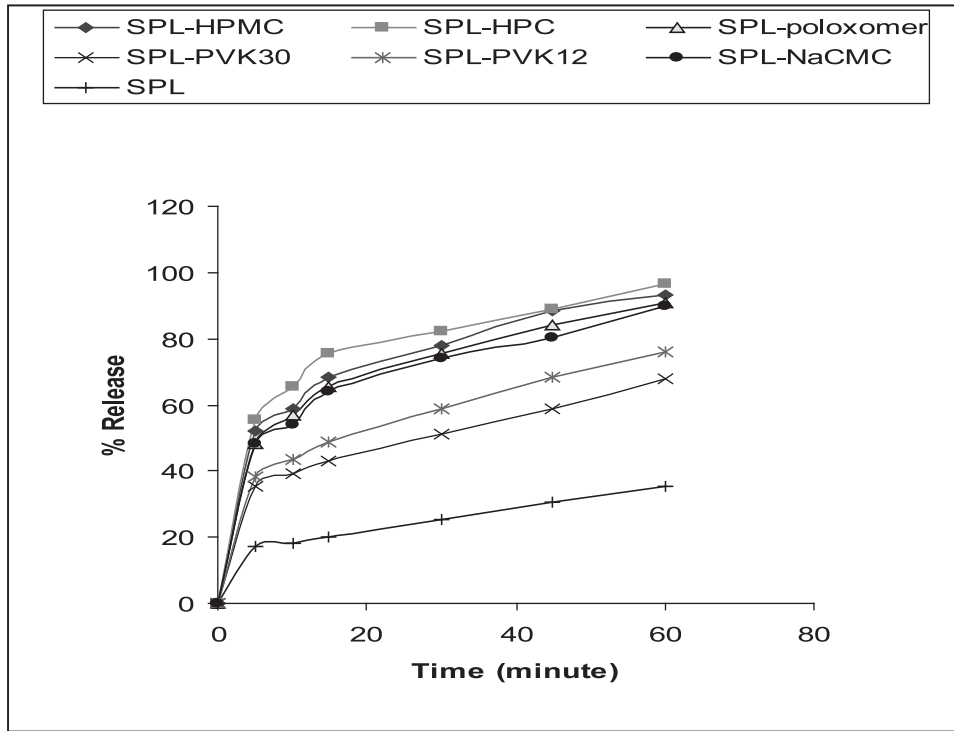
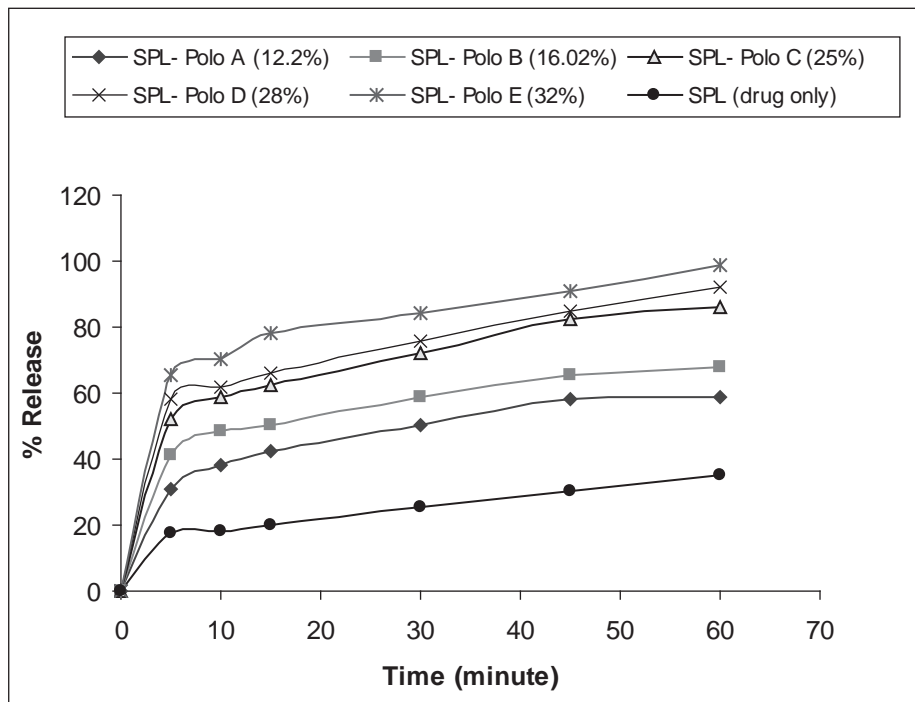


Figure 2: Effect of different concentrations of Poloxamer 407 on Spironolactone solid dispersion dissolution rate
 dissolution condition: distilled water; RPM: 100; 37°C ± 0.5°C.



SPL-Povidone K12, SPL-Povidone K30 and SPL-Poloxamer respectively (Figure 1). So the dissolution studies showed the % release of pure Spironolactone from the solid dispersions was only 35.27%. Here the formulations SPL-HPC, SPL-HPMC, SPL-Poloxamer 407, SPL- NaCMC have shown higher % release respectively.

So it can be said that there was an appeal difference between the release rate of only Spironolactone and solid dispersion containing Spironolactone with different excipients. Solid dispersions containing Spironolactone with HPC, HPMC 6cp, Poloxamer 407 and NaCMC provided higher release rate than the release rate of solid dispersion containing only Spironolactone, Povidone K12, Povidone K30.

Effects of Spironolactone Solid dispersions using Different Concentrations of Poloxamers 407

Spironolactone solid dispersions were prepared by fusion method according to Table 2. Here formulations contained drug and different concentrations of Poloxamer 407. The drug and different concentrations of Poloxamer 407 were coded as - SPL-Polo A, SPL-Polo B, SPL-Polo C, SPL-Polo D, SPL-Polo E respectively. The release of different concentrations of Poloxamer 407 has shown 12.2%, 16.02%, 25%, 28% and 32% of SPL-Polo A, SPL-Polo B, SPL-Polo C, SPL-Polo D, SPL-Polo E respectively. Distilled water was used as dissolution medium. So the dissolution studies showed the percent release of drug for six formulations within 1 hour were 58.80%, 67.73%, 87.91%, 93.42%, 96.16% and 34.84% of SPL-Polo A, SPL-Polo B, SPL-Polo C, SPL-Polo D, SPL-Polo E, SPL (drug only) respectively (Figure 2). So the dissolution studies showed the percent release of pure Spironolactone from the solid dispersions was only 34.84%. It can be said that the percent release of drug was increased when increased the concentrations of Poloxamer 407. So, it can be represented as the modified drug release delivery system where Poloxamer 407 was used as the release modifier.

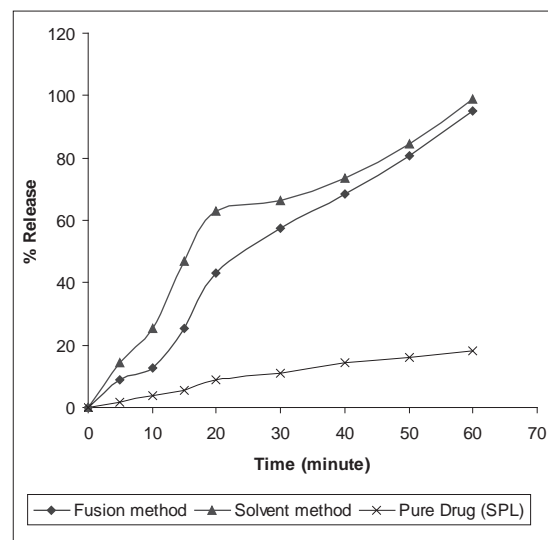
The comparison of percent release between

fusion and solvent evaporation method has been shown in Figure 3. The correlation coefficients values of the trend lines of the graphs showed that formulation of Solvent evaporation method (SPL-HPMC, SPL-HPC, SPL-NaCMC, SPL-Povidone K12, SPL-Povidone K30 and SPL-Poloxamer) and Fusion method (SPL-HPMC, SPL-HPC, SPL-NaCMC, SPL-Povidone K12, SPL-Povidone K30 and SPL-Poloxamer) method best fits in Higuchian release pattern. The values of the correlation coefficients (R^2) for solvent evaporation method and fusion method have been shown in the Table 3 and Table 4 respectively. It is difficult at this stage to explain in details the actual mechanism of release since, the polymer degradation starts during the dissolution period. However the possible reason of increased dissolution rate of Spironolactone was the use of carriers for which the wettability and spreadability of the precipitated drug occur by reducing aggregations in the readily soluble state.

CONCLUSION

In this experiment an attempt has been taken to evaluate Spironolactone release from the different polymer-drug loaded formulation of Solid dispersions. Observations of In-vitro dissolution of the solid dispersion of Spironolactone using distilled water as the

Figure 3: Comparison of percent release curve of spironolactone with different formulation methods.



media to study the drug release efficiency from the solid dispersion. These distorted solid dispersions may cause a wide variation in drug release pattern.

Spironolactone is a potassium-sparing diuretic, acts as a competitive antagonist to aldosterone. Spironolactone is poorly water-soluble drug and the present study was aimed to enhance the dissolution property of Spironolactone. So this study was endeavored to observe release pattern of drug from the solid dispersion of Spironolactone by using different polymers, such as HPMC 6cps, HPC, NaCMC, Povidone K12, Povidone K30, Poloxamer 407. The variables affecting drug dissolution was matrix property, hydrophilic excipients loading from the solid dispersion and also depend on the physicochemical property of the drug molecule. The major problem of poorly water soluble drugs especially for new molecules is bioavailability. Thus the main target is to increase the solubility of poorly water soluble drugs. So the present study reveals that solid dispersion may be an ideal means of drug delivery system for poorly water soluble drugs. Further study in this field is required to establish these drug delivery systems so that in future it can be used effectively in commercial basis.

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