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RESEARCH ARTICLE

COMPARATIVE IN VITRO DISSOLUTION STUDY OF SPIRONOLACTONE FROM BINARY AND TERTIARY SOLID DISPERSION: MODEL DEPENDANT AND INDEPENDENT APPROACHES

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ABSTRACT:

In this study binary and ternary solid dispersions (SDs) of spironolactone were prepared by solvent evaporation technique using Poloxamer 407, kollicoat IR, kollidon VA 64 and PEG 6000 as carrier. In binary solid dispersion drug –carrier weight ratio was 1:5, 1:10, 1:15 and 1:20. In ternary solid dispersions drug was dispersed with mixture of PEG 6000 and Kollidon VA 64 in the ratio 1/2/10, 1/3/10, 1/4/10, 1/5/10. The solid dispersions were investigated for drug loading and dissolution behavior. Solid dispersions were found effective to enhance the solubility of spironolactone in water significantly. Evaluation of the properties of the SDs was also performed by using Fourier-transform infrared (FTIR) spectroscopy and X-ray diffraction (XRD) studies. The FTIR spectroscopic studies showed the stability of spironolactone and absence of well-defined spironolactone -poloxomer 407 interaction. The XRD studies indicated the amorphous state of spironolactone in SDs of spironolactone with poloxomer 407. Dissolution data of SDs were compared by using both model dependant and model independent technique. No significant difference in % DE (dissolution efficiency) was found among the ternary SDs. But in case of binary SDs drug release was found to depend on the nature and amount of carrier. So, Solid dispersion technique may be an effective technique to enhance dissolution rate of spironolactone.

Key words: Spironolactone. PEG 6000, solid dispersion, poorly water soluble, Poloxamer 407

INTRODUCTION

Poorly water-soluble drugs exhibit many difficulties in the development of pharmaceutical dosage forms due to their limited water solubility, slow dissolution rate and low bioavailability[1]. Nowadays, pharmaceutical technology provides many approaches to enhance the dissolution rate of poorly soluble drugs. Physical modifications often aim to increase the surface area, solubility and/or wettability of the powder particles and are therefore focused on particle size reduction or generation of amorphous states [2]. There are many ways to increase the aqueous solubility of such compounds, including micronization, salt formation and formulation of the drug as a solid dispersion (SD). For many compounds, however, decreasing the particle size may not lead to a significant or adequate increase in bioavailability. Salt formation may also be problematic, particularly with neutral compounds and weak acids. Solid dispersion involves at least two different solid components, generally a hydrophilic matrix and a hydrophobic drug; the matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [3].

Solid dispersion method has been widely employed to improve the dissolution rate, solubility and oral absorption of poorly water soluble drugs [4-5]. Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature along with various hydrophilic carriers, such as polyethylene glycols, polyvinylpyrrolidone, hydroxypropyl methylcellulose, gums, sugar, mannitol and urea [6].

Spironolactone (SPN) is K^+- sparing diuretics, an antagonist of aldosterone, a mineralocorticoid, competing for intracellular aldosterone receptors in the cells of the distal tubule [7]. It is used in the treatment of primary hyperaldosteronism (adrenal adenomas or bilateral adrenal hyperplasia) and or refractory edema associated with secondary aldosteronism (cardiac failure, hepatic cirrhosis, nephritic syndrome and severe ascites). Spironolactone added to standard therapy substantially reduces morbidity and mortality and ventricular arrhythmias in patient with heart failure [8].

The objective of this work was to investigate the improvement in the aqueous solubility and dissolution rate of spironolactone by preparing solid dispersion with various polymers such as poloxomer 407, kollicoat IR, kollidon VA 64 and polyethylene glycol 6000 (PEG 6000).

Dissolution data were compared by using both model dependant (Zero order model, First order, Hixson-Crowell cube root law and Higuchi square root law) and model independent (difference factor (f1), similarity factor (f2), dissolution efficiency (%DE) and multiple comparison Bonferroni test) [9-14].

MATERIALS AND METHODS

Spironolactone was collected from Incepta Pharmaceuticals Ltd, Bangladesh. Poloxamer 407 (BASF, Germany) kollicoat IR(BASF, Germany), kollidon VA 64 (BASF, Germany) and PEG 6000 (LOBA India) were procured from commercial sources. All other chemicals and reagents used in this study were of analytical grade.

Preparation of solid dispersion

Solid Dispersions of spironolactone in Poloxomer 407, Kollicoat IR, Kollidon VA 64 and PEG 6000 in different weight ratios (1:5, 1:10, 1:15 and 1:20) were prepared by

solvent evaporation method and denoted as POL, KIR, KVA and PEG 1/5, 1/10, 1/15, 1/20 respectively. Spironolactone was dissolved in sufficient amount of acetone and the carrier was added. The solvent was then completely evaporated at 40-45º C and the resulting residue was dried under vacuum for 3 h, stored in desiccators at least overnight, ground in a mortar, and passed through a #100 sieve.

Ternary solid dispersion using mixture of polymer was also prepared in the same way. PEG 6000 (less effective carrier in case of binary solid dispersion) was mixed with Kollidon VA 64 (highest effective carrier in case of binary solid dispersion) in the ratio 1/2/10, 1/3/10, 1/4/10, 1/5/10(Drug/ Peg 6000/ Kollidon VA 64) and denoted as PKVA 1/2/10, 1/3/10, 1/4/10, 1/5/10.

Determination of drug content in solid dispersions

To determine the potency SD equivalent to 10 mg spironolactone was taken and dissolved in 100 ml methanol as per assay method described in BP for spironolactone tablet[15]. Then the solution was filtered and assayed by Shimadzu UV/Visible double beam spectrophotometer at 238 nm. Finally the amount of drug in each formulation was calculated.

In Vitro Dissolution Data

The in-vitro dissolution tests were performed for the pure spironolactone and solid dispersions, using USP dissolution test apparatus type II (paddle type) using 900 ml of purified water as dissolution medium. As the drug is practically insoluble in water as mentioned in BP[15], we used this media to compare the dissolution profile of pure drug with that of prepared binary and ternary solid dispersion. The temperature of the medium was maintained at 37^0C±0.5°C throughout the experiment. The samples containing 25 mg of spironolactone or its equivalent solid dispersions were placed in the dissolution medium. Paddle was used at a stirring rate of 75 rpm. A 10 ml aliquot was withdrawn at predetermined time intervals of at 10, 20, 30, 40, 50 and 60 minutes and then 10 ml of fresh dissolution medium was replaced to maintain the constant volume of dissolution medium. From the samples collected, 1 ml was diluted with dissolution medium and the absorbance of the diluted solutions were measured at 238 nm using Shimadzu UV/Visible double beam spectrophotometer (Shimadzu, Japan) against dissolution medium as blank. Percentage of drug release was calculated using the equation obtained from the standard curve prepared in the media.

Comparison of dissolution data by Model Dependent Methods

To study the release kinetics, data obtained form in vitro drug release study were tested with the following mathematical model.

Zero order equation

The equation assumes that the cumulative amount of drug release is directly related to time. The equation may be as follows:

$C = K_0 t$---------- (1)

Where, K_0 is the zero order rate constant expressed in unit concentration/time and t is time. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

First order equation

The release behavior of first order equation is expressed as log cumulative percentage of drug remaining vs time. The equation may be as follows[16]:

$Log\ C = Log\ C_0 - kt / 2.303$ ---------- (2)

Where,

C = The amount of drug un-dissolved at t time,

C_0 = Drug concentration at $t = 0$,

k = Corresponding release rate constant.

Higuchi square root law

The Higuchi release model describes the cumulative percentage of drug release vs square root of time. The equation may be as follows [17]:

$Q = K\sqrt{t}$ ---------- (3)

Where, Q = the amount of drug dissolved at time t. K is the constant reflecting the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time.

Hixson-Crowell cube root law

It is the law that represents idea about the evaluation of drug release pattern changes with the surface area and the diameter of the particles[18]. It is mentioned as the cube root of the percentage of drug remaining in the matrix vs time. The equation is as follows

$Q_0^{1/3} - Q_t^{1/3} = k_{HC} \times t$---------- (4)

Where,

Q_0 = Initial amount of the drug in the tablets

Q_t = The amount of drug release in time t

k_{HC} = The rate constant for the Hixson-Crowell cube root law

Comparison of dissolution data by Model Independent Methods

Data obtained form in vitro drug release study were tested with the different model independent technique (dissolution efficiency (%DE) difference factor (f1), similarity factor (f2), and multiple comparison Bonferroni test)

Dissolution efficiency (%DE) was employed to compare the drug release from different solid dispersion. Dissolution efficiency is the area under the dissolution curve within a time range (t1 - t2) expressed as a percentage of the dissolution curve at maximum dissolution, over the same time frame[19]. This was calculated from the equation:

$$DE = \frac{\int_{t_1}^{t_2} y \cdot dt}{y_{100} \times (t_2 - t_1)} \times 100$$

Where y is the percentage dissolved at time t

Difference factor (f1) and similarity factor (f2) were calculated to find out similarity of solid dispersion. Difference factor f1 is the percentage difference between two curves at each point and is a measurement of the relative error between the two curves. The similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. The following equations were used to calculate difference factor f1 and similarity factor f2:

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{i=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

Where n is the number of time points, Rt is the dissolution value of reference product at time t and Tt is the dissolution value for the test product at time t.

Similarity factor f2 has been adopted by FDA (1997) and the European Agency for the Evaluation of Medicinal Products (EMEA, 2001) by the Committee for Proprietary Medicinal Products (CPMP) to compare dissolution profile [20-22]. Two dissolution profiles are considered similar and bioequivalent, if f1 is between 0 and 15 and f2 is between 50 and 100 (FDA, 1997).

Multiple comparison techniques provide a detail picture of exactly which treatments differ from one another. We used Bonferroni test, most commonly used post hoc test, to find out the holmologous group with in ternary SDs. SPSS version 12.0 is used to perform the test.

Fourier-Transform Infrared Spectroscopy

Fourier-transform infrared **(**FT-IR) spectra were obtained by using an FT-IR spectrometer-430 (Jasco, Japan). The samples (spironolactone or SDs) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powder at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 4 cm-1, from 4000 to 500 cm-1.

X-ray diffraction

X-ray powder diffraction patterns were obtained at room temperature using a D 8 ADVANCE X-ray diffractometer (BRUKER, Germany) with Cu as anode material and graphite monochromator, operated at a voltage of 35 kV and 20 mA current. The samples were analysed in the 2θ angle range of 5°–70° and the process parameters were set as: scan step size of 0.02° (2θ), and scan step time of 0.5 degree/min.

RESULTS AND DISCUSSION

Physical appearance and Potency of prepared solid dispersion

The spironolactone solid dispersions were prepared employing solvent evaporation method. All solid dispersions were white fine powders. No discoloration was observed during preparation of SD. Prior to in-vitro dissolution study the prepared solid dispersion was subjected to potency test. Three measurements were performed and Potency ± SD of different SD with pure drug is shown in table1. Potency of spironolactone was between 95-101%.

Table 1: Potency of pure drug and prepared SDs

Sl. No.	Item	% Potency ± SD (n=3)
1	Pure Drug	100.25±0.21
2	POL1/5	99.25±0.34
3	POL1/10	99.75±0.42
4	POL1/15	100.2±0.51
5	POL1/20	95.25±0.28
6	KVA 1/5	96.75±0.35
7	KVA 1/10	100.25±0.13
8	KVA 1/15	97.25±0.54
9	KVA 1/20	99.35±0.45
10	PEG 1/5	98.57±0.66
11	PEG 1/10	99.25±0.64
12	PEG 1/15	99.35±0.65
13	PEG 1/20	100.57±0.75
14	KIR 1/5	96.65±0.75
15	KIR 1/10	100.18±0.81
16	KIR 1/15	97.62±0.85
17	KIR 1/20	99.49±0.92
18	PKVA 1/2/10	99.55±0.95
19	PKVA 1/ 3/10	99.85±0.12
20	PKVA 1/4/10	100.03±1.05
21	PKVA 1/5/10	99.52±0.62

Dissolution profile of Spironolactone from binary Solid Dispersion

Binary Solid Dispersion of spironolactone was prepared with Poloxomer 407, Kollicoat IR, Kollidon VA 64 and PEG 6000 in different weight ratios (1:5, 1:10, 1:15 and 1:20). Drug releases from these solid dispersions are shown in figure 1-4.

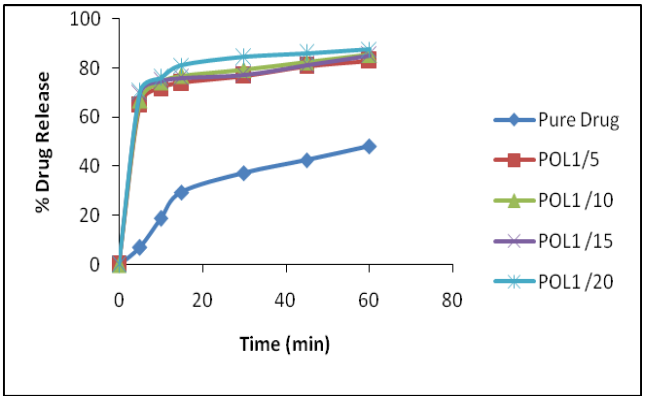

Figure 1: Average % drug release (n=6) from SD containing Poloxomer 407

Drug release from pure drug powder was very slow. Only 7% drug was released within 5 minutes. Drug release was increased with time but finally only 48.31% drug was released after one hour.

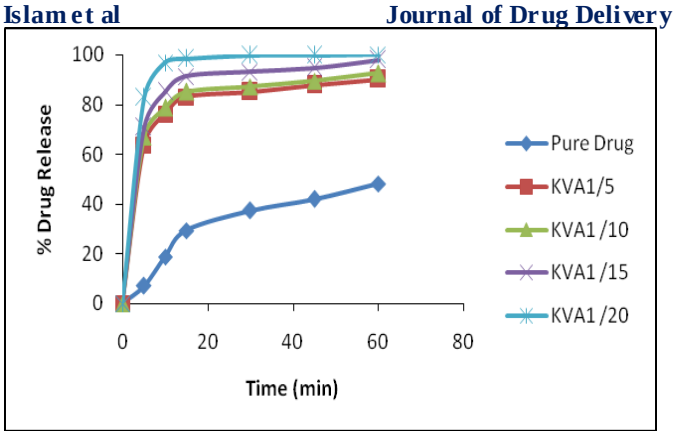

Figure 2: Average % drug release (n=6) from SD containing Kollidon VA 64

In vitro dissolution studies indicate that drug release from SDs was faster from their pure drug. Drug release from SDs was found to depend on the nature and amount of carrier.

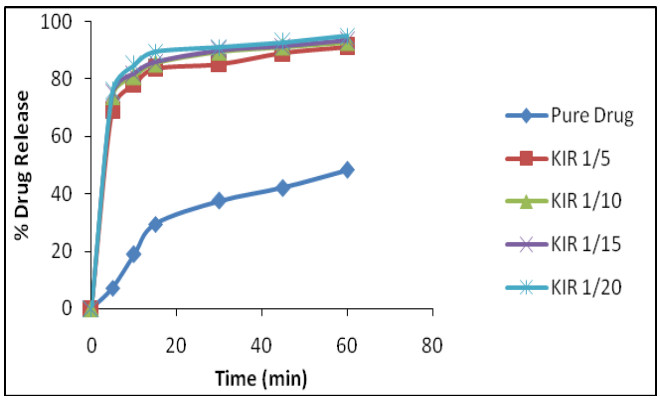

Figure 3: Average % drug release (n=6) from SD containing Kollicoat IR

Figure 1-4 show the in vitro release profile of spironolactone from SDs containing various carriers in different ratio. The percent release of spironolactone was found to be increased proportionately with the gradual increase in the amount of carrier (Poloxomer 407, Kollicoat IR, Kollidon VA 64). The improvement in the in vitro drug release profile may be due to the reduction of particle size of spironolactone and hence improving drug wettability and significantly better dissolution. With 5 minutes 60-80% drug was released from solid dispersion containing Poloxomer 407, Kollicoat IR, Kollidon VA 64. About 10 fold increase of drug release was found in this formulation.

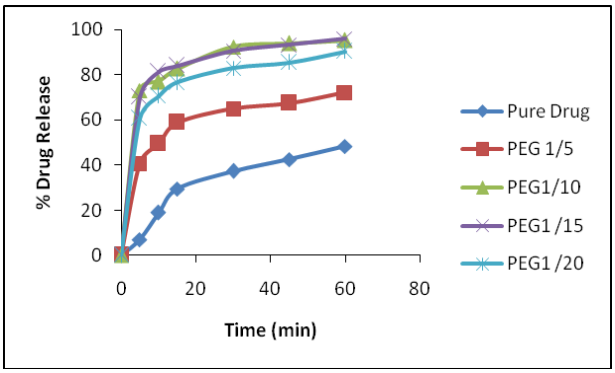

Figure 4: Average % drug release (n=6) from SD containing PEG 6000

Solid dispersion containing PEG 6000 also improves the dissolution rate of spironolactone than that of the pure drug due to its hydrophilic nature (Figure 4). As the relative proportion of PEG 6000 increased, spironolactone dissolution rates rose up to an extent after that dropped which could be attributed to the localization of higher amounts of carrier itself.

Dissolution profile of Spironolactone from Ternary Solid Dispersion

Ternary Solid Dispersion of spironolactone was prepared with mixture of Kollidon VA 64 and PEG 6000 in different weight ratios.

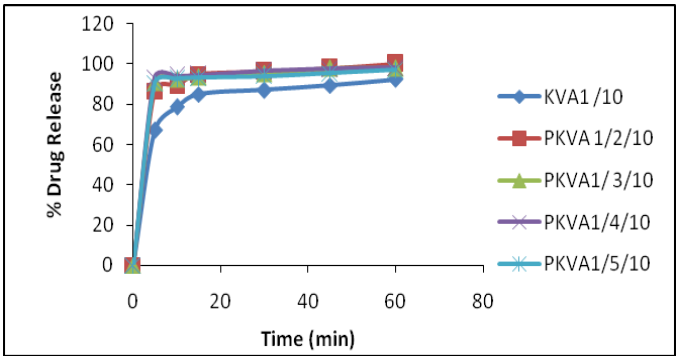

Figure 5: % drug release from SD containing PEG 6000 and Kollidon VA 64

Ternary solid dispersions were found more effective to increase the dissolution rate than binary solid dispersion. Figure 5 shows the release profile of spironolactone from SD containing both PEG 6000 and kollidon VA 64. The amount of kollidon VA 64 was kept constant however, the percentage of PEG 6000 changed gradually (15.38%, 21.48% 26.66% and 31.25%) respectively. The formulation containing lowest amount of PEG 6000 showed maximum drug release rate (100.23% after one hour) whereas other formulation containing more amount of PEG 6000 released less amount of drug that could be attributed to the localization of higher amounts of carrier itself.

Drug release kinetics

In this study total 16 binary SDs and 4 ternary SDs were prepared by solvent evaporation method. dispersion containing 1/5 drug polymer ratio were analyzed by Zero order model, First order, Hixson-Crowell cube root law and Higuchi square root equation as example. Y-equation (Y = aX+b) and correlation co-efficient (R^2) of selected binary solid dispersion and all ternary solid dispersion are shown in Figure 4 .The data shows that only pure drug follows 1st order, Higuchi release model but in case of SDs, R^2 values were less than 0.693(Table 2). This may be due to the slow release rate of pure drug and higher release rate of SDs.

On the other hand all the ternary solid dispersions along with the respective mother binary SD (KVA 1/10) were analyzed with the same model. Y-equation (Y = aX+b) and correlation co-efficient (R^2) of ternary solid dispersion are shown in table 3.The data shows that none follows the model. This may be due to the higher drug release rate from the ternary SDs.

Table 2: Y-equation (Y = aX+b) and correlation co-efficient (R^2) from different plots of selected binary SDs

Item	Zero Order		1st Order		Higuchi Model		Hixson-Crowell Model	
	Y equation	R^2	Y equation	R^2	Y equation	R^2	Y equation	R^2
POL1/5	y = 0.814x + 45.38	0.39	y = -0.008x + 1.678	0.599	y = 8.831x + 27.72	0.664	y = 0.037x + 2.735	0.272
KVA1/5	y = 0.931x + 47.47	0.425	y = -0.012x + 1.648	0.693	y = 9.971x + 27.82	0.704	y = 0.039x + 2.774	0.287
KIR 1/5	y = 0.910x + 49.46	0.399	y = -0.013x + 1.622	0.689	y = 9.859x + 29.79	0.677	y = 0.767x + 2.042	0.515
Pure Drug	y = 0.760x + 8.313	0.865	y = -0.004x + 1.965	0.917	y = 6.662x - 1.557	0.961	y = 0.043x + 1.561	0.577

Table 3: Y-equation (Y = aX+b) and correlation co-efficient (R^2) from different plots of selected ternary SDs

Item	Zero Order		1st Order		Higuchi Model		Hixson-Crowell Model	
	Y equation	R^2	Y equation	R^2	Y equation	R^2	Y equation	R^2
KVA1 /10	y = 0.939x + 49.22	0.413	y = -0.014x + 1.626	0.714	y = 10.11x + 29.17	0.693	y = 0.039x + 2.808	0.282
PKVA 1/2/10	y = 0.914x + 59.20	0.322	y = -0.025x + 1.432	0.794	y = 10.32x + 37.69	0.594	y = 0.038x + 2.987	0.251
PKVA1/ 3/10	y = 0.849x + 61.08	0.279	y = -0.020x + 1.340	0.657	y = 9.857x + 39.98	0.543	y = 0.037x + 3.019	0.237
PKVA1/4/10	y = 0.828x + 62.55	0.26	y = -0.020x + 1.250	0.589	y = 9.759x + 41.38	0.521	y = 0.037x + 3.042	0.231
PKVA1/5/10	y = 0.820x + 61.06	0.265	y = -0.016x + 1.321	0.529	y = 9.619x + 40.27	0.527	y = 0.037x + 3.018	0.232

Model independent analysis of dissolution data

% DE indicates the overall performance of the carrier in drug release. % DE of all the prepared SDs along with pure drug were calculated (n=6) and shown in table 4. The results indicate that ternary solid dispersion is more effective to increase the dissolution rate as % DE is more than 90%. On the other hand, in binary solid dispersion dissolution efficiency was found to depend on the nature of polymer. % DE of KIR 1/5, KVA 1/10, KVA1 /15, KVA1 /20 were found higher in case of 1/5, 1/10, 1/15 and 1/20 drug-carrier ratio respectively.

Table 4: Dissolution efficiencies (%DE) of SDs

Sl. No.	Item	% DE (n=6)
1	Pure Drug	32.97±0.95
2	PEG 1/5	59.47±1.12
3	POL1/5	73.59±1.05
4	POL1 /15	74.95±2.62
5	POL1 /10	75.62±1.28
6	PEG1 /20	77.01±0.95
7	POL1 /20	79.27±0.83
8	KVA1/5	79.96±0.74
9	KIR 1/5	81.23±1.45
10	PEG 1 /10	81.98±2.66
11	KIR 1/10	83.91±1.64
12	KIR 1/15	84.43±2.65
13	PEG1 /15	84.52±1.75
14	KVA1/10	84.76±2.75
15	KIR 1/20	86.16±1.75
16	KVA1 /15	87.38±2.75
17	PKVA1/5/10	90.29±0.81
18	PKVA1/ 3/10	91.35±1.85
19	PKVA 1/2/10	91.55±3.12
20	PKVA1/4/10	92.25±2.65
21	KVA1 /20	94.35±1.75

Percent drug release of SDs of 1/5 drug-carrier ratio was compared by difference factor (*f1*) and similarity factor (*f2*). POL 1/5 was used as reference to calculate the f1 and f2 as %DE of POL 1/5 were more than PEG 1/% but less than KIR 1/5 and KVA 1/5. Table 5 shows the f1, f2 values of different solid dispersion in respect of POL 1/5 as a reference. Here different polymer with same drug polymer ratio was used for comparison. For KVA1/5 and KIR 1/5, f2 were more than 50 and f1 were less than 15. So they are similar with the reference. But pure drug and PEG 1/5 are not similar with the reference.

Table 5: Calculated difference factor (*f1*) and similarity factor (*f2*) of binary SDs

Solid Dispersion	f2	f1
POL1/5	100.00	0.00
KVA1/5	58.55	8.20
KIR 1/5	55.57	9.85
PEG 1/5	38.18	21.75
Pure Drug	17.10	59.37

Table 6 shows the f1, f2 values of different ternary solid dispersion in respect of PKVA 1/2/10 as a reference. KVA 1/10 is the mother binary SDs for all the prepared ternary SDs, so it was also included for the comparison. For all the ternary solid dispersion, f2 were more than 50 and f1 were less than 15. So, all the ternary SDs is similar in respect of drug release. But binary SD, KVA 1/10 is not similar with the reference ternary SD (f2 = 46.54).

The findings can also be proved by multiple comparison Bonferroni test. SPSS version 12.0 was used for multiple comparisons. % DE at 60 min time of different SDs was used for this comparison. No significant difference was found among the ternary SDs. But mean difference of binary SD, KVA 1/10 and reference was significant at the .05 level. (Table 7)

Table 6: Calculated difference factor (*f1*) and similarity factor (*f2*) of ternary SDs

time	f2	f1
PKVA 1/2/10	100.00	0.00
KVA1 /10	46.54	11.62
PKVA1/ 3/10	78.93	2.17
PKVA1/4/10	72.51	2.39
PKVA1/5/10	75.95	2.94

Table 7: multiple comparison Bonferroni test result

R-SD	T-SD	Mean Difference (R-T)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
PKVA 1/2/10	KVA1 /10	9.57000(*)	0.500	0.000	7.993	11.147
PKVA 1/2/10	PKVA1/ 3/10	0.200	0.500	1.000	-1.377	1.777
PKVA 1/2/10	PKVA1/4/10	-0.700	0.500	1.000	-2.277	0.877
PKVA 1/2/10	PKVA1/5/10	1.260	0.500	0.203	-0.317	2.837

R-SD = References solid dispersion, T-SD = Test solid dispersion
**** The mean difference is significant at the .05 level.***

Fourier-Transform Infrared Spectroscopy Study

Fourier-transform infrared (FT-IR) spectroscopy was used to characterize possible interactions between the drug and the carrier in solid state. The IR spectrum of SD (POL 1/5) was compared with the standard spectrum of spironolactone. FT-IR spectra of spironolactone showed characteristic peaks at wave numbers 1768.75, 1680.99, 1435.06, 1273.04, 1126.45cm^{-1}. Pure poloxomer 407 showed characteristic peaks at wave numbers 3445.59, 1663.63, 2887.49, 1466.87, 1350.19, 1448.61cm^{-}1.SD of spironolactone with poloxomer 407 contains characteristic peaks of spironolactone(1768.75 45cm^{-1}) and poloxomer (2887.49, 1465.93 45cm^{-1}). A combine peak at (3442.03 cm^{-1}) was also observed. IR spectra of spironolactone and POL 1/5 are shown in figure 6-7. From this study, it can be conclude that, there was no chemical interaction in this SD formulation.

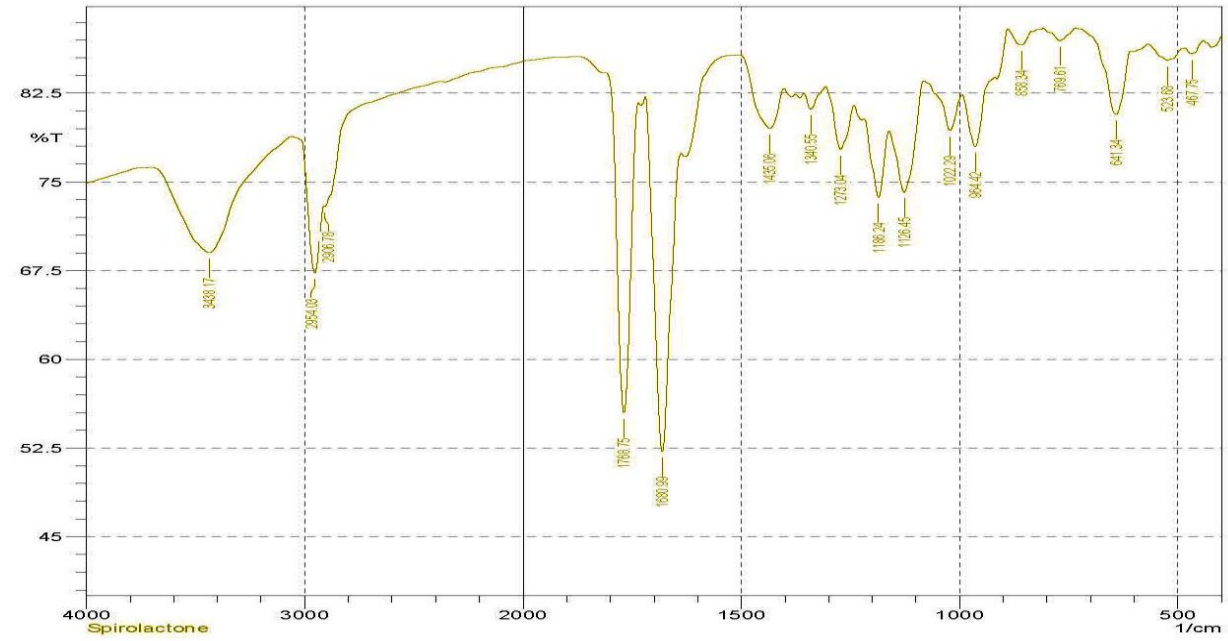

Figure 6: FTIR Spectrum of Spironolactone

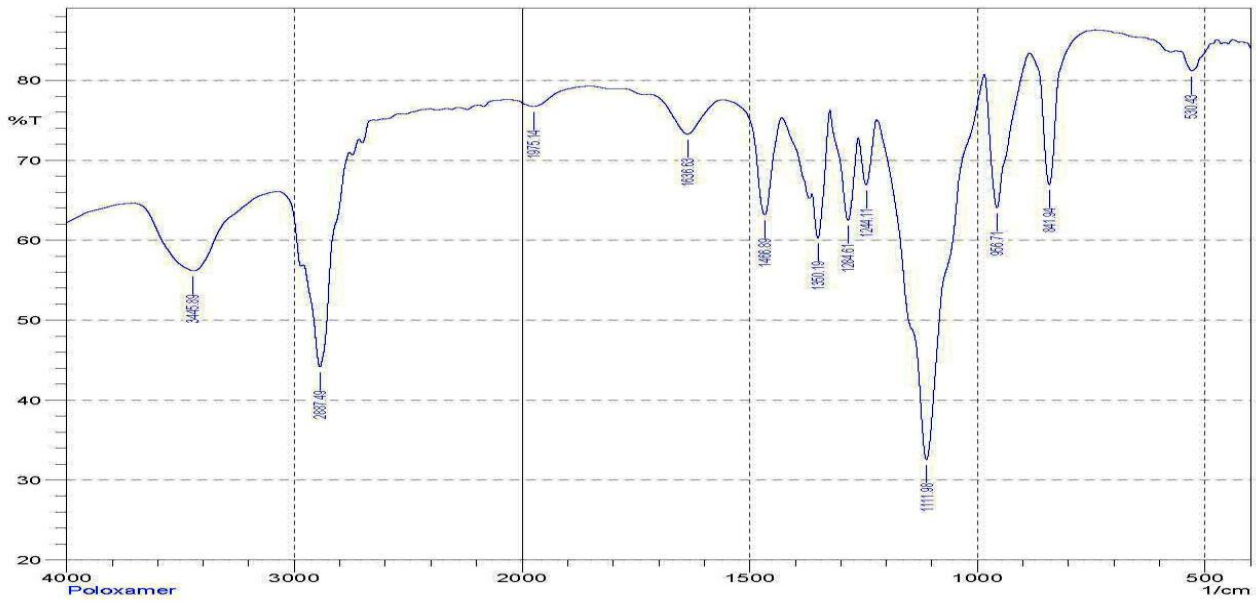

Figure 7: IR spectrum of poloxomer 407

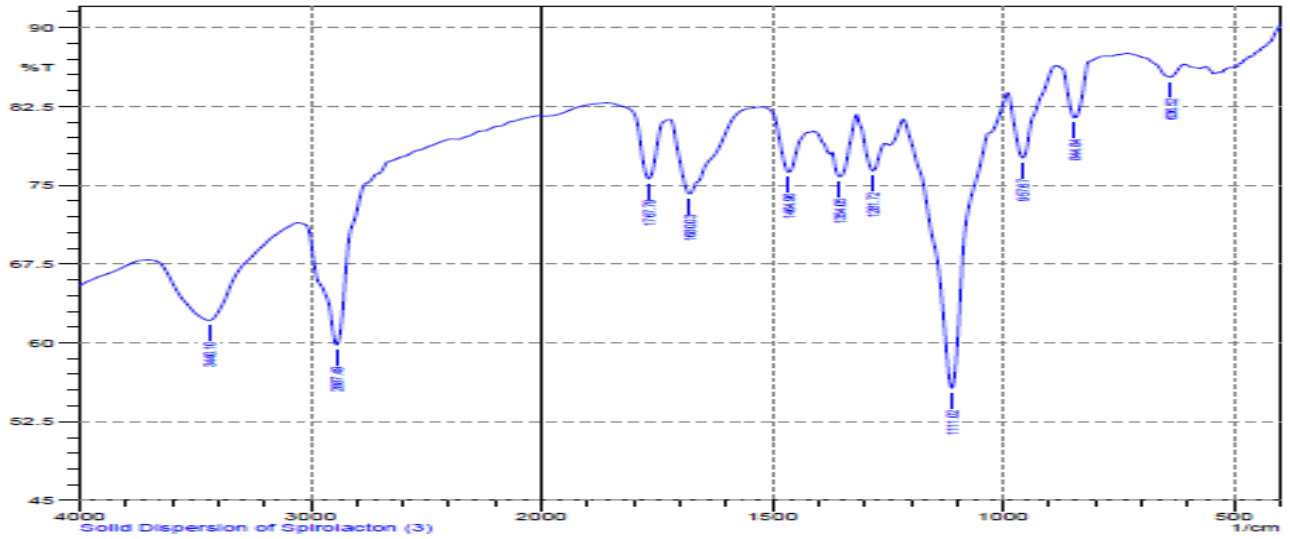

Figure 8: FTIR Spectrum of Solid Dispersion of Spironolactone (POL 1/5)

X-ray diffractions (XRD)

The solid state characterization of drug and SD were investigated using XRD to find out crystalline nature of spironolactone and solid dispersion (POL 1/5). The diffraction spectrum of pure spironolactone showed that the drug was crystalline in nature as it was demonstrated by numerous peaks. Numerous diffraction peaks of spironolactone were observed at 20 of 9.18, 16.66, 17.3, and 20.28 (Figure 9) indicating crystalline spironolactone. Some changes in the peak positions of spironolactone were observed in SDs (POL 1/5). The prominent peaks in the SD were 6.5, 11.44, 15.64, 20.6, and 21.72. Peak intensity was also decreased in SD. Highest peak intensity in case of pure spironolactone was 2010 counts, on the other hand it was only 1185 in case of SD.

The relative reduction of diffraction intensity of spironolactone in SD preparations at these angles suggests that the size of the crystals was reduced. The results of this study imply that spironolactone is present in partially amorphous or microcrystalline form in the SDs.

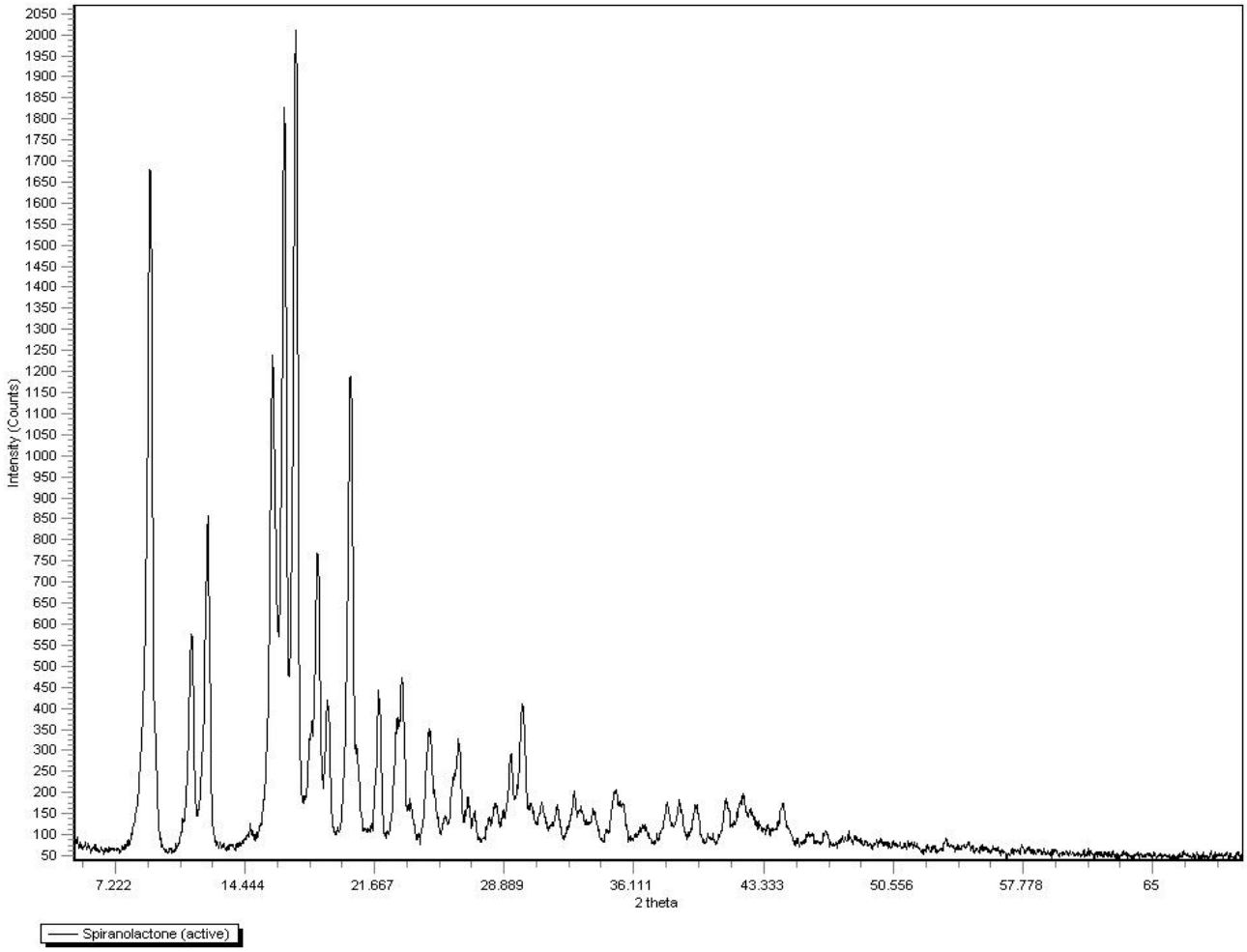

Figure 9: X-ray diffraction (XRD) patterns of Pure Spironolactone

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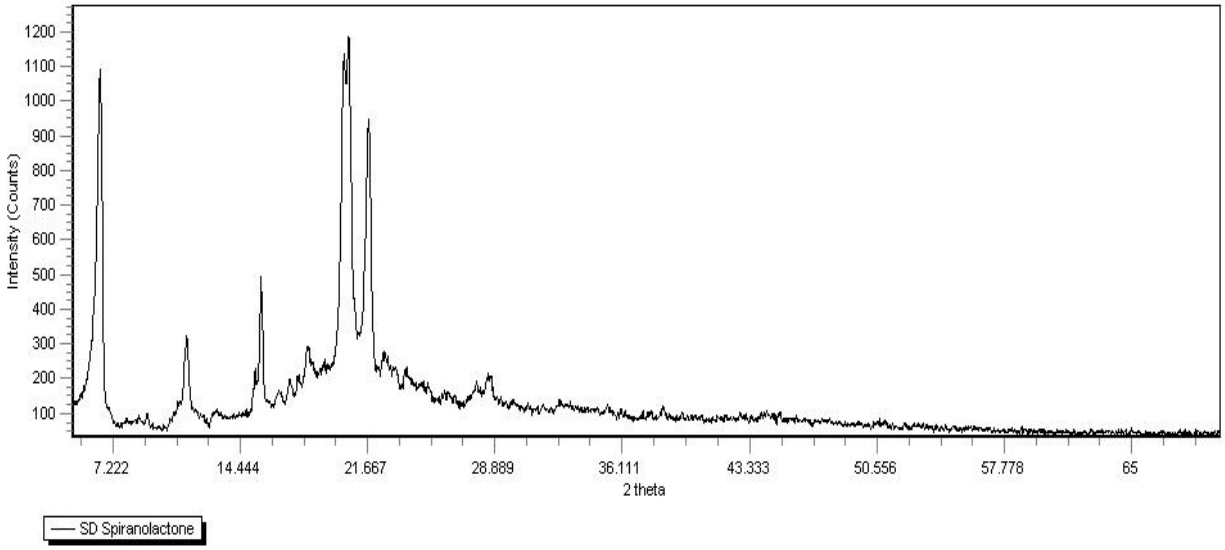

Figure 10: X-ray diffraction (XRD) patterns of 1:5 of Spironolactone and poloxomer

CONCLUSION

Solid dispersions of spironolactone with different carriers in different ratios were prepared to improve dissolution characteristics. . Solvent evaporation method was employed to prepare solid dispersions. In vitro dissolution studies showed that solid dispersions of water insoluble drug with different carriers were effective in increasing the dissolution of spironolactone and gave greater release rate than pure drug. Dissolution data analyzed by model dependant and in dependant technique proves that binary SDs of poloxomer 407 is similar with IR, kollidon VA 64. On the other hand, all ternary SDs were similar. But, binary SD (KVA 1/10) was not similar with the ternary SDs. So, ternary SDs is more effective to increase the spironolactone release rate. However, in vivo study is required for final selection of carrier.

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REFERENCES

1. Najmuddin N, Khan T, Mohsin AA and Patel V, Enhancement of dissolution rate of Ketoconazole by solid dispersion. *Int J Pharm Pharm Sci.* 2010, **2**, 132-136.
2. Patel T, Patel LD, Patel T, Makwana S and Patel T, Enhancement of dissolution of Fenofibrate by solid dispersion technique. *Int. J. Pharm. Sci.* 2010, 1, 127-132.
3. Kamalakkannan V, Puratchikody A, Masilamani K and Senthilnathan B, Solubility enhancement of poorly soluble drugs by solid dispersion technique- A review. *J. Pharm. Res.* 2010, 3, 2314-2321.
4. Tanaka N, Imai K, Okimoto K, Jeda SR, Ibuki YT, Higaki K and Kimura T , Developments of novel sustain –release system disintegration controlled matrix tablet (DCMT) with solid dispersion granules of nicladipine (II): In vivo evaluation. *J. Controlled Release*. 2006, 122, 51-56.
5. Duncan QMC, The mechanism of drug release from solid dispersions in water- soluble polymers. *Int. J. Pharm*. 2002, 231, 131-144.
6. Dingra D, Bhandari A, Sharma RB, Ranjana G and Sachin G, Enhancement of dissolution rate of slightly soluble drug Clomophen Citrate by solid dispersion. *Int. J. Chem Tech Res.*2010, 2, 1691-1697.
7. Rang HP, Dale MM, Ritter JM and Moore PK, *Pharmacology*. Elsevier Science Ltd, U. K. 2003, p. 364.
8. Brunton LL, In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Jackson, E. K. Eds), Mcgrow-Hill, U. S. A. 2006, Chapter 28, pp. 762.
9. Costa P, Lobo JMS. Modeling and comparison of dissolution profiles, *Eur. J. Pharm.Sci*., 2001, 13, 123-133.
10. Shah VP, Lesko LJ, Fan J, Fleischer N, Handerson J, Malinowski H, Makary M, Ouderkisk L, Roy S, Sathe, P, Singh GJP, Tillman L, Tsong Y, Williams RL. FDA guidance for industry: dissolution testing of immediate release solid oral dosage forms, *Disso. Technol.*, 4, 1997, 15-22.
11. Costa P, An alternative method to the evaluation of similarity factor in dissolution testing, Int. J. Pharm., 2001,220, 77-83.
12. Moore JW, Flanner HH. Mathematical comparison of dissolution profiles, Pharm. Technol., 1996, 20, 64-74.
13. Guideline for Industry. Immediate Release solid oral dosage forms scale-up postapproval changes (SUPAC) In vitro dissolution testing, US Department of Health and Human Services, Food and Drug Administration (1995).
14. Yuksel N, Kanık AE, Baykara T. Comparison of in vitro dissolution profiles by ANOVA-based model-dependent and independent methods, Int. J. Pharm., 2000,209, 57-67.
15. British Pharmacopoeia CD version 2; The British Pharmacopoeia Commission; London; 2009
16. Wagner JG, Interpretation of present dissolved-time plots derived from in vitro testing of conventional tablets and capsules. *J. Pharm. Sci*., 1969; 58: 1253 – 1257.
17. Higuchi T: Rate of release of medicaments from ointment bases containing drugs in suspension. *J. Pharm. Sci.*, 1961; 50: 847-875.
18. Hixon AW and Crowell JH: Dependence of reaction velocity upon surface and agitation. *Ind. Eng. Chem.*, 1931; 23: 923-931
19. Anderson NH, Bauer M, Boussac N, Khan-Malek R, Munden P and Sardaro M : An evaluation of fit factors and dissolution efficiency for the comparison of in vitro dissolution profiles. *Journal of Pharmaceutical and Biomedical Analysis* 1998, 17 (4-5), 811-822.
20. US Food and Drug Administration, Center for Drug Evaluation and Research, 1997, Guidance for industry: Dissolution testing of immediate release solid oral dosage forms (http://www.fda.Gov/cder/guidance/1713bp1. pdf)
21. US Food and Drug Administration, Center for Drug Evaluation and Research, 2000, Guidance for industry- Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutical classification system (http://www.fda.gov/cder/guidence/3618fnl.pdf).
22. European Agency for the Evaluation of Medicinal Products (EMEA),(2001) Notes for Guidance on the Investigation of Bioavailability and Bioequivalence. Available at http://www.emea.europa.eu/pdfs/human. /ewp/140198en.pdf.

