

Improving the dissolution properties of spironolactone using liquisolid technique

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Abstract

In this study the effect of liquisolid technique on the dissolution profile of spironolactone was evaluated. Different formulations of spironolactone liquisolid compacts were prepared using various amounts of non-volatile vehicles (Poly ethylene glycol 400 and glycerin). The ratio of microcrystalline cellulose (as carrier) to silica (as coating powder material) was 20 for all formulations. After preparing tablets by direct compression with constant compression load, the release profiles were evaluated by USP paddle method. Differential scanning calorimeter (DSC) and resolution data over a wide spectral range. Fourier transform infrared spectroscopy (FTIR) were used to evaluate any interaction between spironolactone and other ingredients. The liquisolid tablets exhibited significantly higher dissolution rates in comparison with conventionally direct compressed tablets. Furthermore results showed dissolution rate enhancement of liquisolid tablets by increase in the amounts of non-volatile vehicles. Differential scanning calorimetry showed that, the drug has got solubilized in the liquid vehicle. FT-IR spectroscopy studies of pure spironolactone, liquisolid compacts, glycerin and PEG400 supported solubilization of the drug in the liquid vehicle too. The FT-IR spectra also showed that no interactions have been occurred between spironolactone and other ingredients. In conclusion the liquisolid technique can be a suitable method in order to prepare rapid release tablets of poorly water-soluble drugs such as spironolactone.

Keywords: Spironolactone, liquisolid technique, dissolution rate, PEG 400

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Introduction

Drug dissolution is a critical step in drug absorption from the gastrointestinal tract, especially in poorly water-soluble drugs (1, 2). Therefore several techniques have been used in order to enhance the dissolution property of these poor water soluble drugs, such as formation of water

soluble salts, formation of water soluble pro-drugs, particle size reduction, formation of water-soluble molecular complexes, solid dispersion, co-grinding, microencapsulation, liquisolid compact (1,3). All of these methods have their own advantages and defects. for example in formation of water

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soluble salts technique, epigastric irritation may be induced due to the alkaline nature of the salts (4) or the second technique, formation of water soluble pro-drugs, can't be used for some drugs or need so much money to be established (5), in micronization method particle size reduction in fine hydrophobe-drugs may increase the tendency for agglomeration which reduce the surface area and consequently reduce the dissolution rate of the drug (6). Among these various methods, liquisolid technique has been shown to be a most promising technique by several researchers including Spireas et al (7-9), Jarowski (10), Nokhodchi et al (11, 12), Elkordy et al (13-15).

In liquisolid technique poorly water-soluble drugs dissolved or suspended in a non-volatile, water-miscible, inert and high boiling point (13,14) liquid vehicle to establish a liquid medication, a liquid medication may also be formed by mixing oily drugs with liquid vehicle (14,16). Thereafter the liquid medication can be converted in to dry looking, non-adherent and free-flowing powder with readily compressing property by blending with carrier and coating excipients. It have been suggested that particles with porous surface and high absorption property may be used as the suitable carrier in this technique (17) such as cellulose, starch and lactose (13, 16). Once the carrier material saturated with liquid, incorporation of the liquid medication in to the carrier material, a thin liquid layer is formed around the particle (16, 18). By the fact that increasing the moisture content of this excipient results in decreasing the flow property of the powders, the coating material is required to overcome this problem (11, 15). Coating material should be a very

fine and highly adsorptive powders (mostly silica) to cover the surface, adsorb the excessive moisture and so maintain the powder flow ability (13,15). Spironolactone is a selective aldosterone antagonist which mostly use for treating edematous conditions (19, 20). This drug has a low water solubility and dissolution rate which may reduce its bioavailability (21, 22). To improve this undesirable property, in this project several formulations of spironolactone through liquisolid technique with different types of vehicle were prepared and studied.

Materials and methods

Materials

Spironolactone was obtained from Behdasht Kar Pharmaceutical Company, Iran. Microcrystalline cellulose (Avicel PH 102) was obtained from FMC Biopolymer (Ireland). Ethanol 96% was obtained from Jahan Teb, Iran. Nm-sized amorphous silicon dioxide was obtained from Mingtai Chemical (Taiwan). Starch 1500 was obtained from colorcon (England). Glycerin, Poly ethylene glycol 400 (PEG 400) and magnesium stearate were obtained from Merck (Germany).

Preparation of conventional tablet and liquisolid compacts

For the purpose of producing spironolactone conventional tablet, the powder of the drug mixed with the mixture of microcrystalline cellulose and silica (with the ratio of 20:1 respectively). The mixing process was performed in a cubic mixer (Erweka, Germany) for a period of 10 minutes. Then the disintegrating agent (starch) with the ratio of 10% w/w was added to the mixture and mixed for ten minutes. Thereafter Mg stearate as a lubricating

agent (1% w/w) was mixed with the previous mixture for 5 minutes. After all, the final mixture was compressed on a 10 mm punch and die using a single punch tableting machine (Korsch, Germany). This formulation was denoted as conventional direct compression tablet (CDCT). Each tablet of this formulation contains 25 mg of spironolactone, 150 mg of coarse granular microcrystalline cellulose, and 7.5 mg of nm-sized silica.

For preparing several liquisolid compacts of spironolactone, which were denoted as LS-1 to LS-14 (table 1), the powders of spironolactone were dispersed in different types of vehicle with different ratios, to produce liquid medications. This mixing was performed in a mortar. PEG 400 and glycerin were the liquid vehicles that used in this project. Then the binary mixture of carrier and coating material (microcrystalline cellulose and silica respectively) with the ratio of 20:1 were added to the liquid medication to produce powders with acceptable flow and compression properties (8). Depending on the ratio of the drug and the liquid vehicle in the liquid medication used, different liquid load factor (the liquid load factor, L_f , is the weight ratio of the liquid medication and carrier powder in the liquisolid formulations (13). were employed in our liquisolid preparations. Then the disintegrating (10% w/w) and lubricating (1% w/w) agents were added to all formulations and mixed for a period of 10 min and 5 min, respectively. Finally the mixture was compressed using a

single punch tableting machine (Korsch, Germany).

Physical tests

The hardness of the produced tablets was determined through using a hardness tester (Erweka, TBH30MD, Germany). Ten tablets from each formulation were taken for this measurement. Mass determination was performed according to UPS 30. Friability of the prepared formulations was determined by using friability tester (Erweka, Germany) as follow: first ten tablets accurately weighted, then these tablets placed in the apparatus, after 4 min rotating at 25 rpm tablets were deducted and weighted again and finally the amount of friability was calculated according to the following equation (15):

$$\% \text{Friability} = (\text{loss of mass} / \text{initial mass}) \times 100$$

Solubility studies

Solubility measurements were performed by preparing saturated solutions and analyzing by UV/Visible spectrophotometer (Varian, Australia). To prepare saturated solutions, excessive amounts of drug were added to the vehicles (PEG 400, glycerin and distilled water) and shaken on the shaker (Mettler, Germany) for 48 h at 25 ± 0.5 °C under constant vibration. Before analyzing by UV spectrophotometer at a wavelength of 239.8 nm the solutions were filtered and diluted with alcohol 30°. The above process was carried out in triplicate in order to calculate the solubility of spironolactone in these vehicles.

Dissolution studies

The dissolution profile of the liquisolid and direct compact prepared

Table 1 The key formulation characteristics of the prepared formulated tablets

Liquisolid system	Liquid vehicle	Drug con. in liquid medication (%w/w) (Cd)	Liquid load factor (Lf)	Unit dose (mg)	Molecular fraction (FM)	f_2 (%)
LS-1	Glycerin	55	0.341	205.65	0.014	72.15
LS-2	Glycerin	50	0.307	245.085	0.015	54.69
LS-3	Glycerin	45	0.279	293.35	0.017	35.29
LS-4	Glycerin	40	0.256	353.75	0.019	30.41
LS-5	Glycerin	35	0.236	431.29	0.022	25.39
LS-6	Glycerin	30	0.219	534.28	0.025	25.13
LS-7	Glycerin	25	0.205	679.73	0.030	17.86
LS-8	PEG400	55	0.286	235.38	0.079	23.72
LS-9	PEG400	50	0.258	281.55	0.087	22.57
LS-10	PEG400	45	0.234	337.85	0.096	18.73
LS-11	PEG400	40	0.215	408.4	0.109	18.46
LS-12	PEG400	35	0.198	498.92	0.124	18.21
LS-13	PEG400	30	0.184	619.83	0.145	16.78
LS-14	PEG400	25	0.172	789.15	0.174	16.43
CDCT	-	-	-	202.7	0.000	100

formulations, were studied in the 900 ml of distilled water at the temperature of 37 ± 0.1 °C by using The USP paddle method (Erweka, TD80, Germany). The rate of stirring was 100 ± 2 rpm. At appropriate intervals (0.5, 1, 1.5, 2, 3, 4, 5, 6 h) 5 mL of the sample were taken then purified through the filter and analyzed by the UV/Visible spectrophotometer at 239.8 nm. The

dissolution media was then replaced by 5 mL of fresh dissolution fluid to maintain a constant volume. The mean of at least four determinations was used to calculate the drug release from each of the formulations.

For comparing the *in vitro* release profiles of liquisolid tablets and conventional tablets similarity factors,

f_2 , was used. This factor is defined by the following equation (23).

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t) \right]^{-0.5} \times 100 \right\}$$

N: number of time points at which %dissolved was determined

R_t: %dissolved of one formulation at a given time point

T_t: %dissolved of the formulation to be compared at the same time point

The similarity factor's values are in the range of 0-100. The values 100 for similarity factor indicate that, the test and reference profiles are identical and value 0 indicates the dissimilarity between them. So f_2 above 50 indicates that, the two profiles are similar.

Differential scanning calorimetry (DSC) studies

The enthalpy and melting point of different formulations (LS-5, LS-12 and pure drug) were measured by DSC-60 (Perkin Elmer, Netherlands). Samples (3-5 mg) were accurately weighed to 0.01 mg and placed in aluminum pans then the lids were crimped using a Perkin Elmer crimper. The scanning rate was 10 °C min⁻¹ and the range of the temperature was 30 -300 °C. The indium standard was used to calibrate the instrument.

FT-IR spectroscopy studies

The FT-IR spectrums of different formulations and liquid vehicles (LS-5, LS-12, pure drug, glycerin and PEG400) were recorded by using FTIR apparatus (Perkin Elmer, Spectrum one) as follow, powders of the sample were blend with the powders of KBr (1:100) and after 30 sec at the pressure of 3-6 tons, the mixture were made in to pellets by hydraulic compression

(Perkin Elmer). Then the samples were analyzed between wave numbers 400-4000 cm⁻¹.

Statistical analysis

All the data were statistically analyzed by analysis of variance (ANOVA) followed by Tukey's multiple comparison tests using SPSS Statistics 17 software. A linear regression analysis was used to test associations between two parameters. Results are quoted as significant where $p < 0.05$.

Results

The key formulation characteristics of the prepared formulated tablets are shown in table1 and the results of physical tests are shown in table 2. The hardness mean values for the prepared tablets were 38.75 ± 1.83 . All prepared tablets were acceptable by the BP friability test criteria. The solubility of spironolactone in different solvents was shown in the table 3 and as it is showed in this table spironolactone had highest solubility in PEG 400. the release profile of formulated tablets are shown in figures 1-3, the dissolution rate of liquisolid compacts were higher than conventional direct compress tablets and dissolution properties of glycerin liquisolid compacts was poorer than PEG 400 liquisolid compacts in addition liquisolid compacts with higher amount of drug had lower dissolution rate. Differential scanning calorimetry (DSC) and FT-IR spectroscopy studies are shown in figures 4-9, these results showed that no interactions between spironolactone and excipients have been occurred and enhancing drug dissolution might be due to the solubilization of spironolactone in the liquid vehicle.

Discussions

Physical studies

The results of physical tests are shown in table 2. The hardness mean values for the prepared tablets were 38.75 ± 1.83 . All prepared tablets have sufficient strength due to the result of the friability test, all of them passed the BP friability test (the loss of the tablet materials was less than 1%). From the data of mass determination test, it can be indicated that the mixing of the drug and excipients were uniformed. Hence all of the prepared tablets were practically within the limits, it can be derived that making drugs with satisfied physical properties by using liquisolid technique can be possible.

The data obtained by Elkordy *et al.* (13) and Syed *et al.* (16) on liquisolid technique showed similar results. In both studies, tablets prepared by liquisolid technique had sufficient and satisfied physical properties.

Solubility and dissolution studies

As shown in table 3, the solubility of the drug in PEG 400 and glycerin is much higher than distilled water. In the liquisolid systems, solubility of the drug in the liquid vehicle is the most important aspect, as can improve the dissolution rate by the fact that solubility of the drug makes molecular dispersion (15, 24).

Table 2 Physical properties of prepared spironolactone liquisolid compacts and direct compress tablet

Liquisolid system	Hardness (N) \pm SD	Friability (%)	Drug content (%) \pm SD
LS-1	39.94 ± 0.84	0.11	96 ± 2.14
LS-2	39.51 ± 2.75	0.1	96.75 ± 1.54
LS-3	39.58 ± 2.54	0.11	97.55 ± 1.82
LS-4	39.21 ± 2.32	0.11	98.5 ± 2.09
LS-5	38.46 ± 1.58	0.13	98.92 ± 1.73
LS-6	38.25 ± 2.73	0.15	99.33 ± 2.21
LS-7	37.94 ± 1.81	0.14	100 ± 2.07
LS-8	40.45 ± 1.46	0.1	96.03 ± 1.18
LS-9	39.94 ± 0.87	0.11	96.23 ± 1.86
LS-10	38.68 ± 1.26	0.11	98.55 ± 2.04
LS-11	38.34 ± 2.08	0.13	98.92 ± 1.38
LS-12	37.94 ± 0.87	0.14	98.64 ± 2.05
LS-13	37.45 ± 1.46	0.15	99.75 ± 1.65
LS-14	37.07 ± 2.21	0.15	100 ± 2.03
CDCT	38.45 ± 1.46	0.155	99.86 ± 2.55

Table 3 Solubility of spironolactone in different solvents.

Solvent	Solubility (% w/w) \pm SD
Distilled water	0.0028 \pm 0.0001
PEG 400	4.31 \pm 0.03
Glycerin	0.77 \pm 0.02

The Noyes-Whitney equation (25) in the following paragraph can be used to explain more.

$$dC/dt = DS(CS - C) / h$$

In this equation dC/dt is defined as dissolution rate. D indicates diffusion coefficient of the dissolved drugs and S is the surface available for the dissolution medium. Another parameter of this equation, h indicates the diffusion layer thickness which can be affected by agitation (15); C is defined as drug concentration in the dissolution medium. Last parameter C_s is used to define saturation solubility of the drug which may increase by using nonvolatile solvent as a liquid vehicle in this technique. But the small amounts of this liquid vehicle may not be sufficient to increase the overall saturation solubility of the drug in the dissolution medium. Nevertheless the stagnant layer (the interface between liquisolid individual primary particles and dissolution medium) is such a micro environment that, liquid vehicle can diffuse with drug particles away from the primary liquisolid particles with high possibility. So this small amount of liquid vehicle can act as cosolvent with dissolution medium and improve the solubility of drug particles sufficiently. By increasing in C_s , the concentration gradient ($C_s - C$) will be increased,

consequently increasing in dissolution rate according to Noyes-Whitney equation will occur. As it is shown in figure 1 the dissolution rate of liquisolid compacts are higher than conventional direct compress tablets (13, 22, 26, 27).

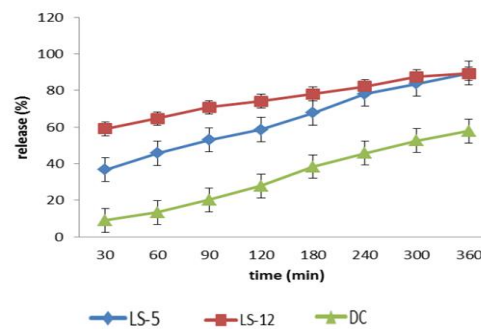


Figure 1 Percentages of drug released from the liquisolid tablets and conventional tablets in distilled water, error bars are standard error

Another explanation for this dissolution results may be due to the factor S of the Noyes-Whitney equation, means that by increasing in wettability and surface availability of drug particles in liquisolid compacts, increasing in dissolution rate will be observed. As the liquisolid compacts contained a solution of the drug in nonvolatile vehicle (4% w/w PEG 400, 0.77 % w/w glycerin) the available surface of drug particles would be increased (26). In other words, after disintegration particles suspended from liquisolid compacts to dissolution medium are in molecular state whereas in DC tablets, micronized drug particles are exposed to dissolution medium & it's clear that Specific molecular surface is greater than the surface of the drug particles. Other parameters of the Noyes-Whitney equation (D and h) were considered to be constant. Since the dissolving media

and rotational paddle speed was identical in all dissolution tests. Spereas *et al* showed similar results and inference in their study on enhancing the prednisolone dissolution properties by using liquisolid compacts (13, 15, 22, 26, 28). It seems that the kind of liquid vehicle used in preparing liquisolid compacts had some effects on drug dissolution properties (11). As shown in figure 1 different dissolution release profiles were observed by LS-5 and LS-12, which had identical, drug content (35%) with different kind of liquid vehicle. The poorer dissolution properties of glycerin liquisolid compacts can be attributed to the lower solubility of the Spironolactone in the glycerin that is shown in table 2. So the higher fraction of drug in PEG 400 is in the molecular state in comparison with glycerin, thereby improved dissolution properties presented (12,26). Results showed that the amount of liquid vehicle in the liquid medication seems to have effect on drug dissolution properties too. According to figure 2 the dissolution rate increased sequentially from LS1 to LS-7 and as it is mentioned previously the amount of drug in the liquisolid compacts was constant while the amounts of liquid vehicles were decreased sequentially from LS-1 to LS-7 these results may be justified by previously mentioned hypothesis of the effect of surface availability of the drug particles on dissolution rate. By increasing the amount of liquid vehicle in the liquid medication, molecular fraction increased. In other words the amounts of dissolved drug in LS-1 with higher amounts of liquid vehicle in the liquid medication would be more than LS-7 with lower amounts of liquid vehicle in the liquid medication subsequently the FM or molecular

fraction would be increased and higher dissolution rate would be expected. The amount of FM in table1 supported this hypothesis as it is seen the amounts of molecular fraction (FM) increased sequentially from LS-1 to LS-7. This result was also supported by further analysis of dissolution data using similarity factor (f_2) the f_2 for LS- 1 was 72.15% means that LS1 and DC had similar dissolution properties. In LS-2 the amount of this factor decreased to 54.69, but it was still above than 50% and showed similar dissolution properties. By further increase in the amount of glycerin in LS-3, f_2 decreased to 35.29 which was less than 50% and showed dissimilarity dissolution properties between DC & LS-3 (LS-3 had higher dissolution rate.) same results were seen for subsequent LS formulations (LS4-LS7), decreasing in amounts of f_2 were seen.

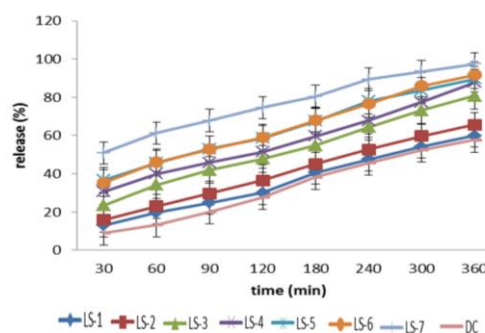


Figure 2 Percentages of drug released from the glycerin liquisolid tablets and conventional tablets, error bars are standard error

As it is shown in figure 3 the dissolution profile of LS8-LS9 that had PEG400 in their formulations were a little different. In this series except two formulations namely LS-8 and LS-9 that show slower dissolution rate in the initial 120 min of dissolution test, other formulations (10-

11-12-13-14) had similar dissolution properties. In this series the amount of PEG 400 increased from LS-8 to LS-14 but the amount of f2 changed negligibility. f2 was 23.72 for LS-8 and 22.57 for LS-9 that were so close. For liquisolids 10-11-12 f2 was 18 and for last two formulations LS-13 and LS14 it was 16. These results also showed that the dissolution rate of all PEG400 liquisolids was higher than DC (Fig. 3).

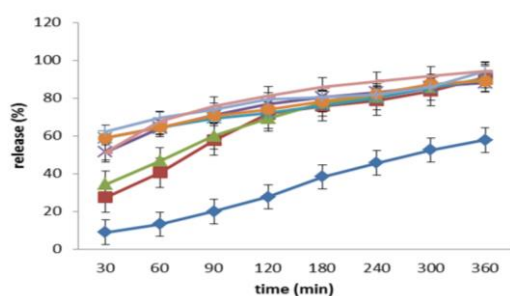


Figure 3 Percentages of drug released from the PEG 400 liquisolid tablets and conventional tablets, error bars are standard error

From these results it can be derived that, in addition of mentioned parameters other physicochemical characteristic of solvents like polarity, viscosity, molecular weight, chemical structure and hydrophylicity may also affect the dissolution properties (14,15, 26).

Differential scanning calorimetry (DSC) & FT-IR spectroscopy studies

Differential scanning calorimetry is one of the most common methods in order to analyze interactions between components in the formulation (14). DSC thermograms of pure Spironolactone, LS-5 containing glycerin and LS-12 containing PEG400 are shown in figure 4.

The thermogram of pure spironolactone showed a sharp endothermic peak at 212 °C that indicated the purity of spironolactone. This peak might also indicate melting of the drug. This sharp endothermic peak of spironolactone was disappeared in the thermograms of LS-5 and LS-12. This can be due to the solubilization of spironolactone in the liquid vehicle. Thermograms also showed that, no interactions between Spironolactone and excipients have been occurred. Furthermore it can be derived from this result that enhancing the dissolution rate of Spironolactone is due to the solubilization of the drug in the liquid vehicle. This result was supported by further analyzing using FT-IR spectroscopy.

The FT-IR spectra of spironolactone, glycerin, PEG400, LS-5 and LS-12 are depicted in figure 5.

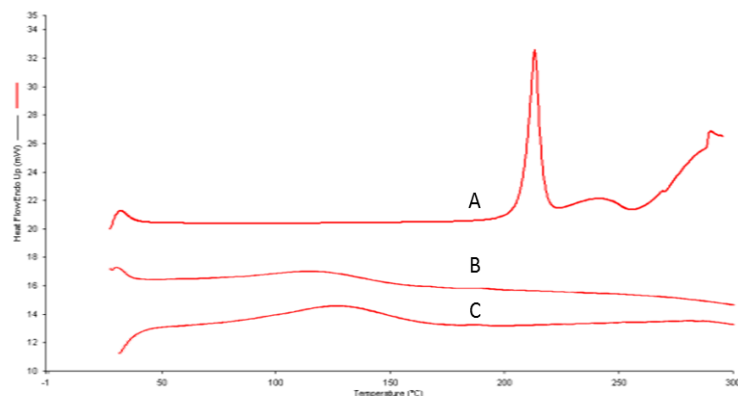


Figure 4 Differential scanning calorimeter of (A) spironolactone, (B) LS-5, (C) LS-12

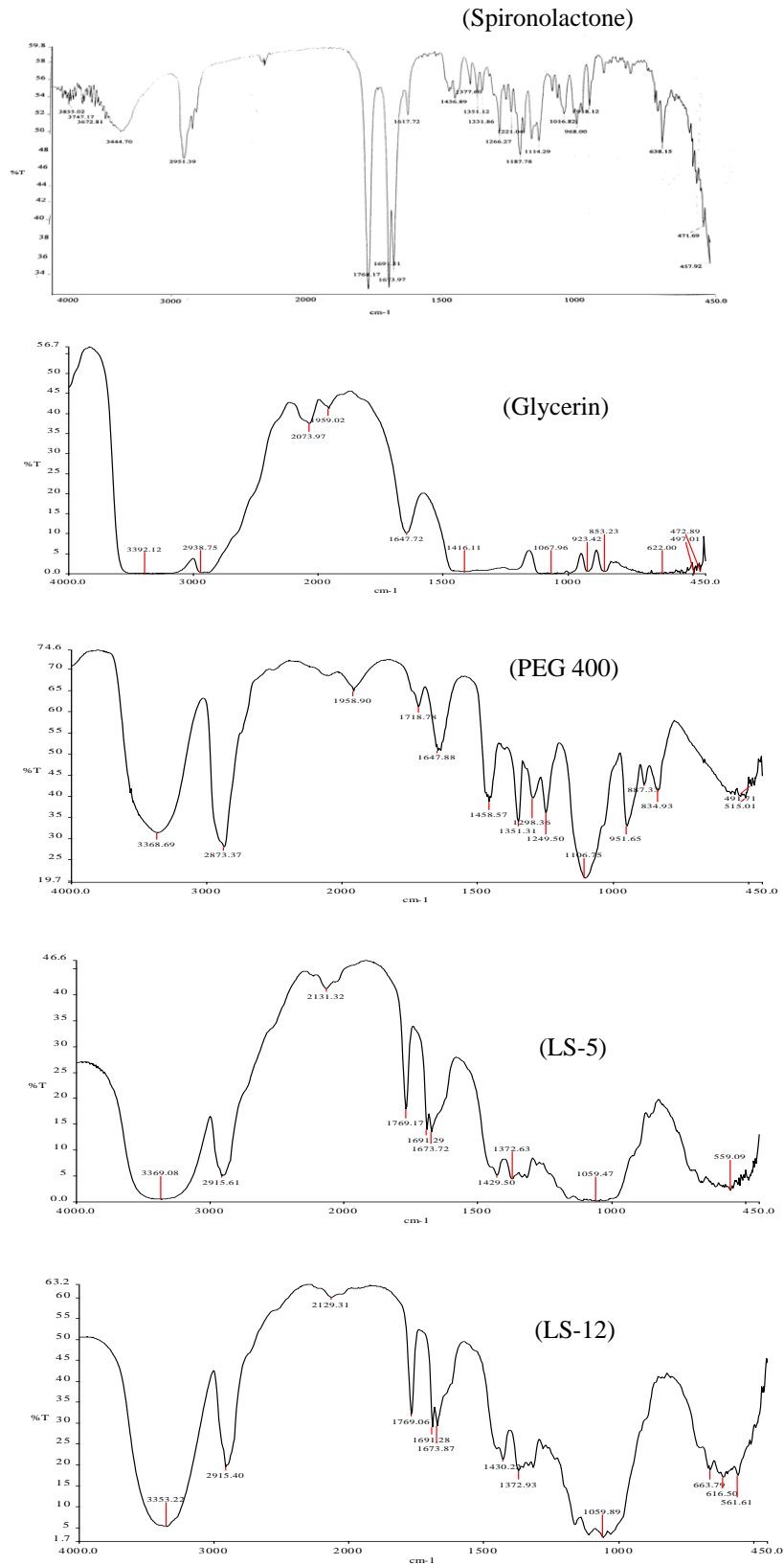


Figure 5 The FT-IR spectra of Spironolactone, Glycerin, PEG400, LS-5 and LS-12

The FT-IR spectrum of spironolactone showed stretching bond C-H between 2850-3000 cm^{-1} regions, carbonyl group of lactone (C=O) AT 1673 cm^{-1} , carbonyl stretching bond of thioacetyl at 1690 cm^{-1} , carbonyl stretching bond of the ring at 1673 cm^{-1} and stretching bond of C=C at 1617. These absorption bands were considered as specific markers to recognize spironolactone. These peaks were also seen in the study of Dong et al on Preparation and characterization of spironolactone nanoparticles by antisolvent precipitation (29). All liquisolid compacts' spectra showed this absorption bands with a reduction in intensity that might be due to hydrogen bonding interaction between Spironolactone and liquid vehicles. Therefore enhancing drug dissolution would be expected which is conformable to dissolution data as shown previously. Spectra also showed that no chemical interaction occurred between components. Specific absorption bands of Glycerin and PEG400 were seen in all liquisolid spectra too. The spectra of LS-5 and LS-12 were two examples of all spectra.

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Conclusion

The liquisolid technique can be a promising method in order to prepare rapid release tablets from water insoluble drugs such as Spironolactone. The main causes of drug dissolution enhancement may be solubilization of the drug in the liquid vehicle and increasing wettability and drug surface availability for dissolution. The DSC and FT-IR spectroscopy data confirmed this result, furthermore data showed that by increasing in the amount of the liquid vehicle the dissolution rate would be increased and the kind of liquid vehicle had effect on dissolution profile.

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Conflict of interest

The authors declared no potential conflict of interest with respect to the authorship, and/or publication of this study.

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