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Formulation Development and Evaluation of liquisolid compacts of Epelerenone Hydrochloride

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ABSTRACT

Eplerenone hydrochloride is a poorly water soluble drug, which is an aldosterone receptor antagonist used in the management of chronic heart failure. The rate of its oral absorption is often controlled by dissolution rate in the gastro intestinal tract. The aim of the present research work was to improve the solubility and dissolution properties of insoluble drug, eplerenone hydrochloride by liquisolid technique. Liquisolid compacts of eplerenone hydrochloride were formulated by dispersing the drug in various non volatile liquid vehicles. Several formulations were prepared using a new mathematical model to calculate the appropriate powder and liquid ingredients required to produce acceptably flowing and compressible mixtures. Avicel PH 102, Lactose monohydrate and Syloid

244 FP were used as carrier materials and Aerosil was used as coating material. The effect of different concentrations of drug on the dissolution rate was studied and it was observed that the liquisolid compacts containing 25%w/w of drug in solvent with lactose monohydrate and Aerosil in the ratio of 10:1 gave the maximum dissolution rate when compared with other formulations. Optimized formulation was compressed into tablets after addition of sodium starch glycolate as a disintegrant in a concentration of 5% of the total weight of tablet and evaluated. Enhanced drug release rates were observed when compared to pure drug and conventional tablet. This is due to increased wetting properties and surface of drug available for dissolution. It was further confirmed from the ex vivo studies that the liquisolid formulation has shown improved rate of permeation than the pure drug and conventional tablet. The crystalline state of eplerenone drug state was changed to amorphous state due to liquisolid formation and was confirmed by X-ray diffraction study. Fourier transform infrared spectroscopy results revealed that there was no interaction between drug and excipients.

Keywords: Liquisolid compacts, eplerenone hydrochloride, Avicel PH 102, Lactose monohydrate and Syloid 244 FP, XRD, FTIR.

INTRODUCTION

One of the major challenges of current pharmaceutical research is to enhance the dissolution profile, absorption efficiency and bioavailability of water insoluble drugs. Therapeutic effectiveness of a drug depends upon the bioavailability which in turn dependent on the solubility and dissolution rate of drug molecules. The dissolution rate is often the rate determining step in the absorption of lipophilic or water insoluble drugs which belongs to Biopharmaceutical Classification System (BCS) class II drugs (low solubility, high permeability)[1].

Strategies to Increase the Drug dissolution at the absorption site [2]

Various formulation approaches have been established to increase aqueous solubility of poorly soluble drugs such as:

- **Particle size reduction:** Micronization or nanonisation is one of the approaches to improve the bioavailability of lipophilic drugs by an increase in surface area by means of reduction of the particle size to sub-micron level.
- **Use of surfactants:** Surfactants enhance the dissolution rate by promoting wetting and penetration of dissolution fluid into solid drug particles.
- **Use of salt forms:** Salts have improved solubility and dissolution characteristics in comparison to original drug. e.g. salt of basic drug like atropine is more soluble than parent drug.
- **Solid dispersions:** It was defined as the dispersion of one or more active ingredients in an inert carrier matrix in solid-state prepared by fusion, solvent or melting-solvent method.
- **Co-solvency:** The solubility enhancement by the strategy of co solvent solubilization can often be accomplished by a combination of water and co solvent (reduced polarity). The normally used co solvents include propylene glycol, ethanol, glycerol, polyethylene glycol 400 and dimethyl acetamide.
- **Cyclodextrin complexation:** The beta and gamma cyclodextrins are unique in having the ability to form molecular inclusion with hydrophobic drugs having poor aqueous solubility.
- Thus the molecularly encapsulated drug has greatly improved aqueous solubility and dissolution rate.

The technique of "liquisolid compacts" is the most promising technique which is of low cost, simple formulation technique and capability of industrial production serve to be advantages of this technique.

A more recent technique, entitled **"powder solution technology"** or **"liquisolid technology"** has been applied to prepare water-insoluble drugs into rapid release solid dosage forms. Powdered solutions contain liquid medications in powdered form, thereby possessing mechanisms of drug delivery similar to those of soft gelatin capsule preparations which contains liquids.

The concept of powdered solutions enables one to convert drug solutions or liquid drugs into acceptably free flowing powders, readily compressible and apparently dry powders by a simple admixture with selected powder excipients (e.g., cellulose and silica). The liquid portion which can be a liquid drug, drug suspension, or a drug solution in suitable non-volatile liquid vehicles is incorporated into the porous carrier material. This method does not involve drying or evaporation[3]. It is well established that better bioavailability of a relatively water insoluble drug is achieved when the drug is in solution form. Therefore, soft gelatin capsules of such drugs demonstrate higher bioavailability compared to the conventional oral solid dosage forms[4]. The same principle governs powdered solutions and it is responsible for their improved dissolution profiles. In this instance, even though the drug is in a tableted form or encapsulated dosage form, it is held in solution thus enhancing its release.

Liquid lipophilic drugs (e.g. chlorpheniramine and clofibrate) or solid drugs (e.g. prednisolone, hydrocortisone, theophylline, polythiazide, carbamazepine and naproxen) are dissolved in nonvolatile, high boiling point solvent systems (e.g. polyethylene glycols & propylene glycols, glycerin, N,N-dimethyl acetamide, various oils) have been formulated in powdered solutions by admixture with various carriers (e.g. cellulose) and coating materials (e.g. silica).This technique has been reported to produce improved dissolution profiles as compared to the commercially available products [5].

The mechanism involved in enhancement of solubility by liquisolid technique includes;

- Increased surface area of drug available for release
- Increased aqueous solubility of the drug
- Increased wettability of the drug particles

Classification of Liquisolid Systems

Based on the type of liquid medication contained therein, liquisolid systems may be classified into four sub-groups:

- Powdered drug solutions
- Powdered drug suspensions
- Powdered liquid drugs
- Powdered drug emulsions

Powdered drug solutions and suspensions may be produced from the conversion of drug solutions or drug suspensions into liquisolid systems and powdered liquid drugs are produced from the formulation of liquid drugs into liquisolid systems (e.g. clofibrate, liquid vitamins).

Based on the formulation technique used, liquisolid systems may be classified into:

- Liquisolid compacts
- Liquisolid Microsystems

Preformulation studies

Saturation solubility studies

Saturation solubility studies of pure drug were performed in various solvents such as polyethylene glycol 400 (PEG400), propylene glycol, tween 80, glycerin, distilled water, 0.1 N HCL and 7.4 pH phosphate buffer. These studies were carried out for the selection of best solvent.

Flow properties

Angle of repose is used to characterize flow properties of solids. By using fixed funnel method angle of repose of pure drug was determined. Accurately weighed pure drug was taken in a funnel. The height of funnel was adjusted such that tip of funnel just touches the apex of heap of the powder. From the funnel, the powder was allowed to flow onto surface. The height and diameter of powder cone was measured and angle of repose was calculated by using following equation.

$\tan(\theta) = h/r$

Where, h is the height in cm and r is the radius in cm

Formulation studies of eplerenone hydrochloride liquisolid compacts

Selection of solvent

Selection of solvent was done based on results obtained in saturation solubility studies. The solubility in which the drug was having more solubility has been selected as non volatile liquid for the formulation.

Selection of carrier and coating material

In the current study, lactose monohydrate, avicel PH 102, syloid FP 244 were selected as carrier materials and aerosil as coating material.

Determination of liquid loading factor (L_f)

Liquid loading factor was calculated for different carrier materials in propylene glycol solvent by using formula Lf = W/Q.

Preparation of eplerenone hydrochloride liquisolid formulations

Calculated quantities of eplerenone hydrochloride and propylene glycol were accurately weighed in a 20-mL glass beaker and then mixed well. The resulting medication was incorporated into calculated quantities of carrier and coating materials. The mixing process was carried out in three steps. In the first, the system was blended at an approximately one minute in order to evenly distribute liquid medication in the powder. In the second, the liquid/powder admixture was evenly spread as a uniform layer on the surface of a mortar and left standing for approximately 5 min to allow the drug solution to be absorbed inside powder particles. In the third, the powder was scraped off the mortar surface using an aluminum spatula**.** Then Carrier: Coating material was added to this mixture and blended in a mortar. Then the formulations are evaluated for flow properties and for drug content and dissolution. Formulation of liquisolid compacts with lactose monohydrate, avicel PH 102, syloid 244 FP as carriers were shown in Table No. 1, 2 & 3 respectively.

Evaluation of precompression parameters of liquisolid formulations

Micromeritic properties

Flow properties such as angle of repose, carr's index, hausner's ratio were conducted for the

liquisolid formulations as shown in previous sections.

Content uniformity

An accurately weighed amount of each preparation was dissolved in small volume of methanol and further diluted in phosphate buffer with pH of 7.4. The content of eplerenone hydrochloride was determined spectrophotometrically at 243 nm using UV visible spectrophotometer.

In vitro drug release studies

In vitro drug release studies were conducted for all the liquisolid formulations. From the results of evaluations, one formulation was selected as optimum formulation. The final optimized formulation blend was compressed into tablets using a 12mm punch tablet compression machine after the addition of 5% sodium starch glycolate as disintegrating agent.

Data Treatment of Dissolution Studies

Dissolution Efficiency (DE_T)

A model independent parameter, the dissolution efficiency (DE_T) was employed to compare dissolution profiles of different samples. DE_T was calculated according to the following equation.[6]

$$DE_T = \frac{\int_0^T y_t . dt}{y_{100} . T}$$

Where y_t is % of drug dissolved at any time t, y_{100} denotes 100% dissolution, the integral represents the area under dissolution curve between time zero and T.

Mean Dissolution Time (MDT)

Mean dissolution time was employed to compare dissolution profiles of different samples. MDT was calculated according to the following equation.

$$MDT = \sum_{j=1}^{n} * tj * \delta Mj / \sum_{j=1}^{n} * \delta Mj$$

Here j=sample number; n= no. of dissolution times: tj = time at midpoint between tj and tj-1, δMj= additional amount of drug release between tj and tj-1.[7]

Relative Dissolution Rate (RDR)

It was used to calculate the relative drug release in 30 minutes between optimized formulation and directly compressed tablet formulation.

Preparation of conventional directly compressed tablet of eplerenone hydrochloride

Tablet containing eplerenone hydrochloride was prepared by mixing 25 mg of drug with lactose, starch, sodium starch glycolate (5%) as disintegrant and mixed for 10 min. Glidant and lubricant are added and then compressed by tablet punching machine.

Evaluation of optimized eplerenone hydrochloride liquisolid tablets

Thickness

The thickness of liquisolid tablets was determined by using Digital micrometer.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2.

Weight variation test

The test was performed as per USP. The average weight and standard deviation of three batches were calculated. It passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown. It was calculated on an electronic weighing balance.

% Deviation = (Individual weight- Average weight/ Average weight) x 100

Friability Test

The test was performed using a Roche Friabilator. Percentage friability was calculated by using following formula:

% Friability = $[w_0 - w] / w_0) \times 100$

Where, W = final weight of tablets after 100 revolutions. W_0 = original weight of tablets at time zero before revolution.

Assay

The drug content was performed by taking six randomly selected liquisolid tablets of the formulation. They were grinded in a mortar to get powder. This powder was dissolved in methanol, kept aside for 30min and filtered through filter paper. The drug content was analyzed by UV spectrophotometer at 243nm.

Disintegration test

Liquisolid tablets are selected randomly from each batch and the test was conducted in disintegration apparatus baskets.

Dissolution studies of eplerenone hydrochloride tablets

Drug release from eplerenone hydrochloride liquisolid compacts was determined by using dissolution test apparatus United States Pharmacopoeia (USP) type II (paddle).

Dissolution medium with a pH of 7.4	:	phosphate buffer
Volume	:	900ml
Speed/rpm	:	50
Temperature	:	37± 0.5^{0}C.

5 ml of aliquots of dissolution media were withdrawn at specified time intervals (5, 10, 15, 20, 25, 30, 45, 60, 90, 120, 150 minutes) and replaced with fresh medium to maintain sink conditions and constant volume. The samples were filtered and analyzed using UV visible spectrophotometer.

Ex vivo permeation studies

Ex vivo permeation studies were conducted for optimized liquisolid formulation, pure drug, and conventionally prepared directly compressed tablet. For this permeation studies, fresh intestinal membranes were carefully removed from the intestine of goat which were obtained from the local slaughterhouse.

Tissue samples were inserted in open tube cell displaying a permeation area of 3.14 cm^2. Phosphate buffer (pH 7.4) was added to the acceptor chamber. The temperature was maintained at 37^{0}C. Formulation equivalent to 25 mg of liquisolid tablet, directly compressible tablet and pure drug was placed in the donor chamber in the form of suspension. At predetermined time points, 1-mL samples were withdrawn from the acceptor compartment, replacing the sampled volume with phosphate buffer (pH 7.4) after each sampling, for a period of five hours. The samples withdrawn were filtered and used for analysis. The amount of permeated drug was determined using a UV-visible spectrophotometer at 243 nm. Comparison was done between pure drug, directly compressed tablet and optimized formulation.

Drug and excipients compatibility studies

X-Ray Powder Diffraction studies (XRD)

X-Ray powder diffraction studies were performed on drug, excipients, and formulations for characterization of the different polymorphic forms of solvated and unsolvated forms of compounds using Phillips PW 3719, Netherlands. These samples were exposed to Cu-K_α radiation at a scan rate of 2^0/ min over the 2θ range of 3-40^{0}C.

Fourier transform infrared (FTIR)

FTIR studies were performed on drug, and the optimized formulation using V5300 FT-IR (Tokyo, Japan). The samples were analyzed by pressed pellet KBR technique between wave numbers of 4000 and 400 cm^{-1}.

RESULTS AND DISCUSSION

Saturation solubility studies

Solubility of eplerenone hydrochloride was high in propylene glycol compared with other solvents. Thus among the non volatile solvents tested, propylene glycol could be the better choice.

Formulation studies of eplerenone hydrochloride liquisolid compacts

Selection of non volatile solvent

Selection of non volatile solvent was done based on the saturation solubility studies. Thus

propylene glycol was selected as liquid vehicle for the eplerenone hydrochloride liquisolid formulations.

Selection of carrier and coating materials

In the current study, lactose monohydrate, avicel PH 102, syloid FP 244 were selected as carrier materials and aerosil was selected as a coating material.

Determination of liquid loading factor

Liquid loading factor was determined for different carrier materials in propylene glycol solvent and the results are shown in Table No.4.

Precompression evaluation studies for eplerenone hydrochloride liquisolid formulations

All the liquisolid formulations of eplerenone hydrochloride prepared by using various carrier materials were evaluated for flow properties and the results confirmed that the flow ability of eplerenone hydrochloride liquisolid formulations was enhanced when compared with pure drug.

Drug content of liquisolid compacts

Drug content was estimated for all the formulations of eplerenone hydrochloride. It was found that all the formulations were passed for content uniformity test as the results obtained were within the acceptable limits i.e. 98-102%.

Invitro dissolution studies of liquisolid formulations

Invitro dissolution studies were conducted for all the eplerenone hydrochloride liquisolid formulations prepared withvarious carrier materials such as avicel PH 102, lactose, syloid 244 FPand coating material as aerosil in different ratios of carrier to coating material. Propylene glycol used as liquid vehicle in all the formulations.

In vitro drug release studies were carried out for all the prepared formulations. Percentage drug release values and dissolution efficiency values were calculated at various time intervals and results obtained were shown in Figure 1-3 respectively for different carriers.

It was observed that all the liquisolid formulations prepared with 25% w/w of liquid medication (F4, F5, F6, F10, F11, F12, F16, F17, F18) has shown higher drug release. This might be probably due to the higher amount of propylene glycol which might have contributed to the increase in the saturation solubility of the drug when compared with 50% w/w of liquid medication (F1, F2, F3, F7, F8, F9, F13, F14, F15).Moreover, the liquisolid formulations prepared with lactose as carrier has shown higher drug release within less time compared to other carriers and it was also observed that when the ratio of carrier to coating material increased the dissolution rate was decreased. Hence it can be concluded that F4, F10, F16 showing high amount of drug release of all the formulations i.e. 96.73%, 64.97%, 85% respectively. Among the three formulations F4 was selected as optimized formulation as it is showing higher drug release within 30 minutes of all the liquisolid formulations. This formulation contains 25%w/w of liquid medication with lactose as carrier and aerosil as coating material in 10:1 ratio. Hence this has been compressed into tabletsby the addition of 5% of sodium starch glycolate as disintegrant and subjected to further studies.

Evaluation of optimized liquisolid formulation

Post Compression Parameters

The mean hardness of optimized formulation was determined and proved that it had acceptable hardness. Eplerenone hydrochloride liquisolid tablets had acceptable friability as none of the tablet had percentage loss in tablets weights that exceed 1% also, no tablet was cracked, split or broken. Since the prepared formulae met the standard friability criteria, they are expected to show acceptable durability and withstand abrasion in handling, packaging and shipment. The optimized formulation was showing percentage drug release of 96.73% within 30min.

Comparison of dissolution profiles of optimized formulation with pure drug and conventional tablet.

Comparative dissolution profiles of optimized formulation, pure drug and conventional tablet were shown in Figure 4

Data Treatment of Dissolution Studies

Figure 4, optimized formulation F4 was showing highest dissolution rate when compared with directly compressible tablet and pure drug. The amount of drug release in thirty minutes (Q30) of the optimized formulation (F4) and directly

compressible formulation (F19) was 97.66% and 68.15% respectively.

The dissolution efficiency of the optimized formulation (F4) and for the directly compressed tablet was found to be 74.45% was 65.76%. The relative dissolution rate of the optimized formulation (F4) was found to be 1.93.

The dissolution performance of eplerenone hydrochloride was improved with liquisolid formulation technique compared to conventional tablet as described by the dissolution parameters. The drug is not in the native form and adsorbed onto a carrier in suspended form, the enhanced effective surface area and change in the physical state might have led to the improved dissolution characteristics for liquisolid system.

Exvivo permeation studies

Results of *ex vivo* permeation studies were shown in Figure 5. From the results of *ex vivo*studies it was observed that the liquisolid formulation prepared with lactose as carrier showed enhanced permeation when compared with directly compressed tablet and pure drug.

Drug and excipient compatibility

X-Ray Diffraction (X-RD)

Figures 6-12 shows the X-ray diffractograms of eplerenone hydrochloride, lactose, avicel, syloid 244 FP, aerosil, physical mixture and optimized liquisolid formulation respectively. Eplerenone hydrochloride showed sharp peaks at 8.28, 10.35, 15.02, 17.99, 16.05 2-Theta confirms that it is in the crystalline state. The X-Ray diffraction of optimized formulation shown in Figure 12 and the peaks are at 13.09, 17, 20.58, 21.81, 23.38 2-Theta indicates the absence of eplerenone hydrochloride constructive peaks and points out that eplerenone hydrochloride converted to amphorous state due to its solubilisation in the liquid vehicle which was absorbed into the carrier such as lactose monohydrate and adsorbed on the coating material such as aerosil.

Fourier Transform Infrared Spectroscopy (FT-IR)

Samples of pure drug, liquisolid formulation (F4) were subjected to FT-IR spectroscopic analysis, and their spectra at 4000 and 400 cm^{-1} are shown in figures 13-14.

Peaks were not disappeared at the same wave numbers for drug and liquisolid formulations. It indicates that there was no interference of drug with excipients.

Table No.1: Formulation of liquisolid compacts with lactose monohydrate as carrier

Formulation	Eplerenone hydrochloride conc. in PG (%w/w)	R	Lf	lactose monohydrate (mg)	aerosil(mg)	Total weight of compacts (mg)
F1	50	10	0.37	132.7	13.2	246
F2	50	20	0.37	169	16.9	286
F3	50	30	0.37	172.7	17.2	290
F4	25	10	0.46	133.6	13.3	247
F5	25	20	0.46	232.7	23.2	356
F6	25	30	0.46	204.5	20.4	325

Table No.2: Formulation of liquisolid compacts with avicel PH 102 as carrier.

Formulation	Eplerenone hydrochloride conc. in PG (%w/w)	R	Lf	avicel PH 102(mg)	aerosil(mg)	Total weight of compacts (mg)
F7	50	10	0.26	15.4	1.5	117
F8	50	20	0.26	45	4.5	150
F9	50	30	0.26	50	5	156
F10	25	10	0.34	260	26	296
F11	25	20	0.34	203.6	20.3	324
F12	25	30	0.34	173.6	17.3	291

Table No.3: Formulation of liquisolid compacts with syloid 244 FP as carrier

Formulation	Eplerenone hydrochloride conc. in PG (%w/w)	R	Lf	syloid 244 FP 102(mg)	aerosil(mg)	Total weight of compacts (mg)
F13	50	10	0.32	207.2	20.7	328
F14	50	20	0.32	118	11.8	230
F15	50	30	0.32	265.4	26.5	292
F16	25	10	0.37	327.2	32.7	460
F17	25	20	0.37	240.9	24	365
F18	25	30	0.37	345.4	34.5	480

Table No.4: Determination of liquid loading factor

Carrier material	Loading factor (L_f)
Lactose	0.37
Microcrystalline cellulose	0.26
Syloid FP 244	0.32

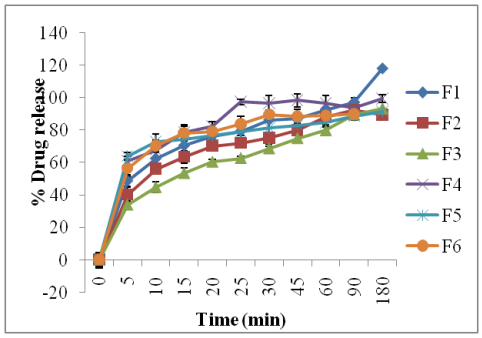

Fig 1: Dissolution profiles of eplerenone hydrochloride liquisolid formulations with lactose monohydrate as carrier.

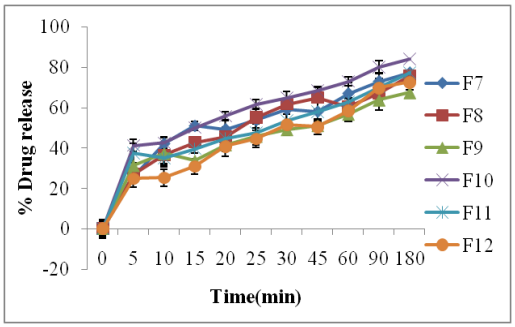

Fig 2 : Dissolution profiles of eplerenone hydrochloride liquisolid compacts with avicel PH 102 as carrier

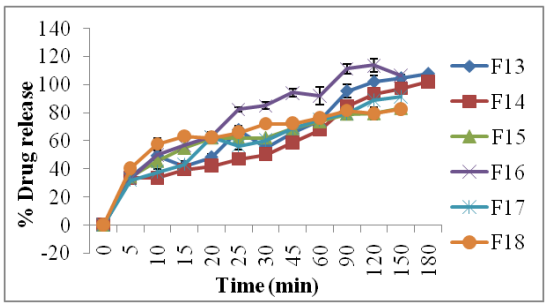

Fig 3 : Dissolution profiles of eplerenone hydrochloride liquisolid compacts with syloid244 FP as carrier.

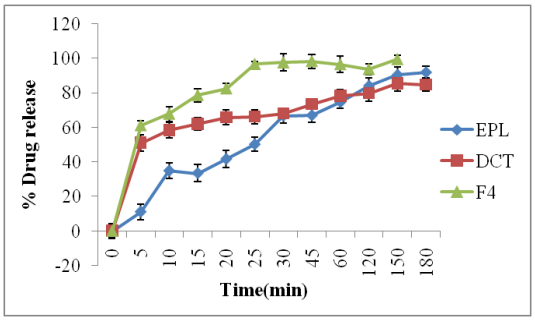

Figure 4: Comparative*in vitro* dissolution profiles of optimized formulation with pure drug and directly compressible tablet (DCT)

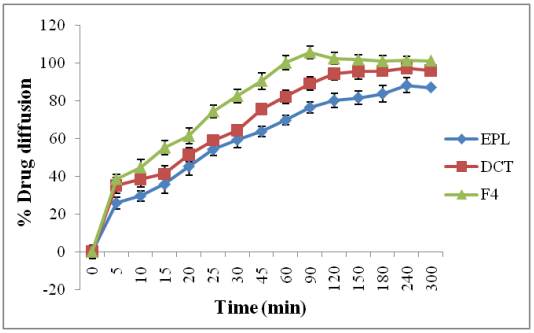

Fig 5: Comparative diffusion profiles of pure drug, conventional tablet and liquisolid formulation

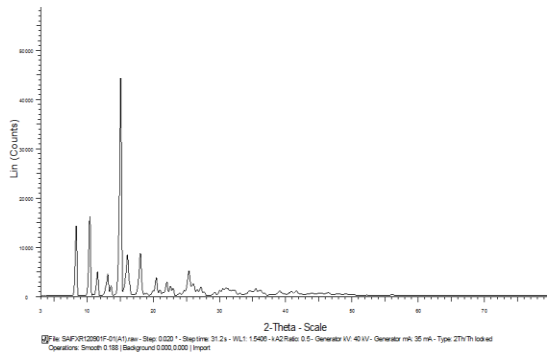

Figure 6: X-ray powder diffraction of eplerenone hydrochloride

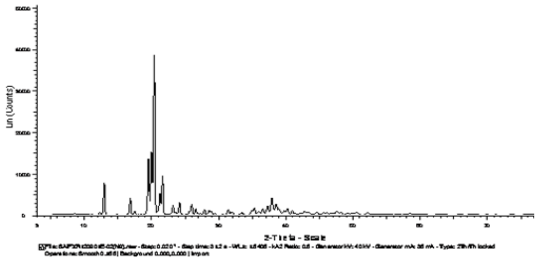

Figure 7: X-ray powder diffraction of lactose

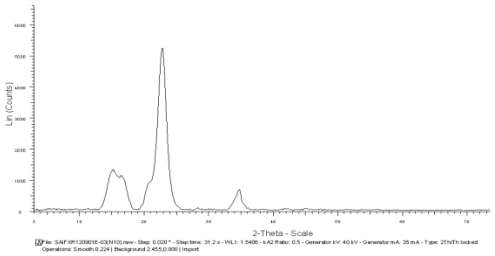

Figure 8: X-ray powder diffraction of avicel

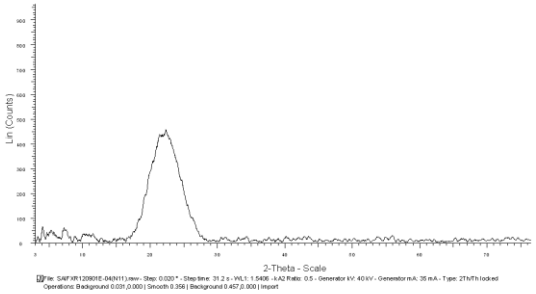

Figure 9 : X-ray powder diffraction of syloid FP 244.

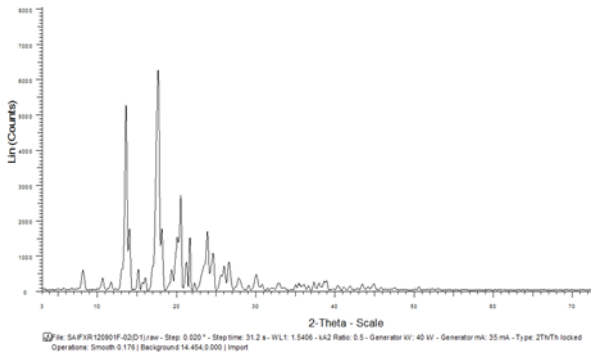

Figure 10: X-ray powder diffraction of aerosil

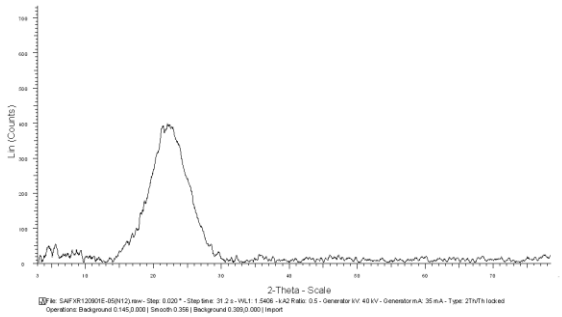

Figure 11.X-ray powder diffraction of physical mixture

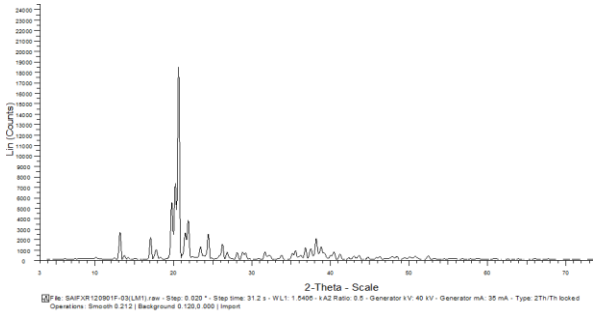

Figure 12: X-ray powder diffraction of optimized eplerenone hydrochloride liquisolid formulations

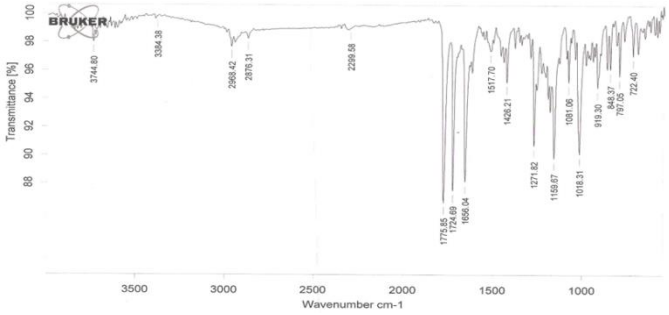

Fig 13: FT-IR spectra of eplerenone hydrochloride

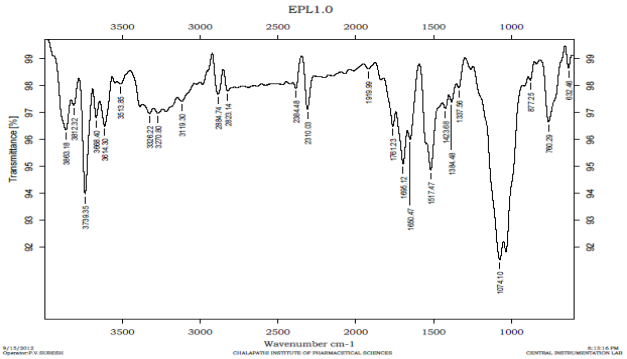

Fig 14: FT-IR spectra of optimized liquisolid powder formulation

CONCLUSION

This study shown that liquisolid technique could be a promising strategy in improving dissolution of poorly water soluble drugs and formulating immediate release solid dosage forms. The liquisolid formulations prepared with propylene glycol at drug concentration of 25% w/w with lactose monohydrate and aerosil in the ratio of 10:1 is the best formulation among all the formulations in terms of faster dissolution profiles. Liquisolid technique changes the properties of eplerenone hydrochloride particles by simply dispersing the particles in a non volatile liquid vehicle, which in turn increase the wetting property and surface area of drug particles. The optimized formulation of eplerenone hydrochloride tablet showed highest dissolution rate compared with pure drug and conventional tablet. Hence the solubility and dissolution rate of eplerenone hydrochloride has been enhanced by this liquisolid technique.

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