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DEVELOPMENT AND EVALUATION OF LIQUISOLID COMPACTS OF FINASTERIDE

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ABSTRACT

The aim of the present study was to improve the solubility of a poorly water soluble drug, Finasteride under BCS class II drug. Finasteride (FNS) is an antiandrogen which acts by inhibiting 5-alpha reductase, the enzyme that converts testosterone to dihydrotestosterone. It is used in benign prostatic hyperplasia (BPH) in low doses and in prostate cancer in higher doses. The term 'liquisolid systems' (LS) is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water-insoluble solid drug in suitable non-volatile solvent systems into dry looking, nonadherent, free-flowing and readily compressible powdered mixtures by blending with selected carrier and coating materials. From non-volatile solvents such as PEG 400, 600, tween 80, glycerine, propylene glycol etc., Tween 80 is optimised and carrier materials such as starch, lactose, micro crystalline cellulose etc were used to formulate the liquisolid tablets in different ratios. The percentage release of the drug was increased by using tween 80 as non volatile solvent with carrier materials MCC Avicel 101, Avicel 102 and Aerosil 200 as a coating material. The ratio of (20:1) of both Avicel 101 and Avicel 102 formulation was found to be releasing 99% and 98% of the drug in 60 mins which is optimized with dissolution media as distilled water using USP II apparatus at 50 rpm and absorbance were seen at 254 nm respectively. The Liquisolid tablets of Avicel 101 and Avicel 102 with (20:1) i.e carrier:coating ratio showed higher dissolution rate (98.75±0.21) and (99.25±0.35) when compare to marketed (43.49±0.26) and pure drug(17.77±0.22).

Hence Tween 80 and Avicel 101, Avicel 102 were optimised non volatile solvent and carrier material in enhancing the dissolution rate of finasteride drug. FTIR and XRD studies showed no evidence of drug excipients interaction. Accelerated stability studies for 1 month indicated the tablets were stable.

KEYWORDS: Finasteride, Liquisolid tablets, Tween 80, Avicel, Aerosil 200.

INTRODUCTION

Tablets are the most primitive and cheapest route of drug administration in the modern era of formulation development, but it has many draw backs still to be solved like solubility, stability, dissolution, disintegration and patient acceptability. For formulating the drug in the convenient way and to enhance the acceptability of the dosage form, the biggest hurdle is to enhance the drug solubility in the solvent used for its formulation and then its dissolution in the *in-vivo* conditions that is necessary for the drug to show its action.[1] By using the modern techniques the solubility of the drug is either enhanced or decreased to control the drug release that is convenient for the treatment. Further techniques are employed for conveying the solid dosage form through different routes.[2]

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

The term “liquisolid compacts” refers to immediate or sustained release tablets or capsules prepared, combined with the inclusion of appropriate adjuvants required for tabletting or encapsulation, such as lubricants, and for rapid or sustained release action, such as disintegrants or binders, respectively.[3]

Liquid lipophilic drugs (e.g., chlorpheniramine and clofibrate) or solid drugs (e.g., prednisone, prednisolone, hydrocortisone, theophylline, polythiazide and spiranolactone) dissolved in nonvolatile, high-boiling point solvent systems (e.g., polyethylene & polypropylene glycols, glycerin, N,N-dimethylacetamide, 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.[4]

Spireas[5] proposed mathematical expressions for the calculation of the amount of excipients needed for powdered solution formulations. The major drawback of this approach was that the final product exhibited poor and erratic flowability due to the inadequacy of the proposed model to calculate the appropriate amount of excipients required to produce powder admixtures of acceptable and consistent flow properties. Mathematical model expressions based on powder properties and the fundamentals principles and mechanisms of powdered solutions are derived.

However, the industrial application of this technique has been hampered by the poor and erratic flowability and compressibility of the produced liquid/powder admixtures. Flow problems of such systems were addressed by the introduction of a new theoretical model for the principles underlying the formation of powdered solutions.

MATERIALS AND METHODS

Materials

Finasteride was obtained from RA Chem Pharma Ltd. as a gift sample. Tween 80, Starch, Lactose, Microcrystalline cellulose, Avicel 101 and 102, Aerosil 200, were purchased from SD fine chemicals. All the other materials used were of analytical grade.

Preparation of Liquisolid Tablets

Desired quantities of previously weighed solid drug and the liquid vehicle were taken in a beaker and heated to 80-90^{o} C with constant stirring, until a homogenous drug solution was obtained. The mixing procedure was conducted in three stages.

In the first stage, weighed quantity of carrier material was blended with liquid medication in order to evenly distribute the liquid medication into the powder. In the second mixing stage, calculated quantities of coating material (Aerosil 200) was added to the system and blended for 2 min. The liquid powder admixture was left undisturbed for approximately 5 min to allow the drug solution to be absorbed into the interior of the powder particles.

The blend was compressed into tablet, at a hardness of 2.5-2.9 kg/cm^2 on a rotary tablet punching machine with punch size of 11.9 mm, batch size of 10 tablets were prepared each time.

Preparation of LS Formulations

From the solubility studies, tween 80 was considered as a suitable nonvolatile solvent. Thus according to the mathematical model calculations, the required amount of excipients was calculated. The LS formulations were prepared and evaluated for further studies.[6]

Formulation of tablets was embedded from LS1 to LS14 respectively. Based on the solubility of the drug, quantity of solvent is selected to which a carrier material is added as an adsorbent to it. Different carrier materials such as starch, lactose, MCC, Avicel 101 and 102 were used. To this admixture depending upon the ratios selected amount of coating material is added to form a free flow of the contents. Load factor (L_f) of a formulation can be determined as weight of the solvent by weight of the carrier material. Excipients ratio (R) can be calculated as weight of the carrier material to the weight of the coating material. From which they are directly compressed into tablets using 11.9 mm tablet punch. The details are tabulated in table 1.

It was observed that the formulations from LS1 to LS4 has load factor (0.162) with 10, 15 as excipient ratios. From LS5 to LS7 the load factor of the formulations were (0.270) with carrier:coating material as 10, 15 and 20. And the formulations from LS8 to LS14 the load factor was (0.324) with 10, 15, 20, 25 as carrier:coating material respectively.[7]

Table 1: Formulation of LS compacts of finasteride

Formlation code	Drug(mg)	Solvent (mg)	Excipients						Load factor (Lf)	Excipient ratio (R)	Total tablet wt (mg)
			Starch	lactose	MCC	Avicel 101	Avicel 102	Aerosil 200			
LS1	5	81	500	---	---	---	---	50	0.162	10	636
LS2	5	81	500	---	---	---	---	33	0.162	15	619
LS3	5	81	---	500	---	---	---	50	0.162	10	636
LS4	5	81	---	500	---	---	---	33	0.162	15	619
LS5	5	81	---	---	300	---	---	30	0.270	10	416
LS6	5	81	---	---	300	---	---	20	0.270	15	406
LS7	5	81	---	---	300	---	---	15	0.270	20	401
LS8	5	81	---	---	---	250	---	25	0.324	10	361
LS9	5	81	---	---	---	250	---	16	0.324	15	352
LS10	5	81	---	---	---	250	---	12	0.324	20	348
LS11	5	81	---	---	---	---	250	25	0.324	10	361
LS12	5	81	---	---	---	---	250	16	0.324	15	352
LS13	5	81	---	---	---	---	250	12	0.324	20	348
LS14	5	81	---	---	---	---	250	10	0.324	25	346

EVALUATION

Flow Behaviour

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to reduce high dose variations. Angle of repose, Carr's index and Hausner's ratio were used in order to ensure the flow properties of the liquisolid system.

Pre-compression Studies of the Prepared Liquisolid Powder Systems

In order to ensure the suitability of the selected excipients, Fourier Transform Infra Red Spectroscopy, Differential scanning Calorimetry, X-ray Diffraction and Scanning Electron Microscope studies are to be performed. In addition, flowability studies are also to be carried out to select the optimal formulae for compression, prior to the compression of the powders into the dosage forms such as into tablets and capsules.

Evaluation of Prepared Liquisolid Tablets

Weight Variation

Twenty tablets were randomly selected and average weight was determined. Then individual tablets were weighed and percent deviation from the average was calculated.[8]

Hardness

The strength of tablet is expressed as tensile strength (Kg/cm^2). The tablet crushing load, which is the force required to break a tablet into pieces by compression. It was measured using a tablet hardness tester (Monsanto hardness tester). Three tablets from each formulation batch were tested randomly and the average reading noted.[8]

Thickness

Control of physical dimensions of the tablets such as size and thickness is essential for consumer acceptance and tablet-tablet uniformity. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. The thickness of tablet is measured by screw gauge. The thickness of the tablet is related to the tablet hardness. Tablet thickness should be controlled within a ± 5% variation of a standard value. In addition, thickness must be controlled to facilitate packaging. The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using screw gauge. The average thickness and standard deviation were reported.[8]

Friability

Friability of the tablets was determined using Roche Friabilator (Electrolab, India). This device consists of a plastic chamber that is set to revolve around 100 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. Pre weighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed.[8] The friability (F %) is given by the formula

$$F\ \% = (1 - W_0 / W) \times 100$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablets after test

Disintegration Time

Disintegration times of tablets were determined in a tablet disintegration test apparatus, using distilled water 1000ml at 37 ± 2^0C as disintegration medium.[3]

In Vitro Dissolution Studies

The dissolution studies were performed in dissolution apparatus using paddle method (USP II). Dissolution studies were carried out using 900 ml of distilled water at 37 ± 0.5^oC at 50 rpm. Finasteride 5 mg or its equivalent amount of tablet was added to distilled water. The volume of dissolution medium was adjusted to 900 ml by replacing with 5 ml of fresh distilled water. Solutions were immediately filtered and analyzed spectrophotometrically at 254 nm. The dissolution profile was constructed by plotting percentage cumulative drug release versus time. Similarly dissolution studies were performed for pure drug and directly compressible tablets.

***In vitro* dissolution study of the Pure Drug**

The standard dose of finasteride 5 mg was accurately weighed. These samples were analyzed for the drug release in the same manner as the physical mixture by powder dispersion technique. The release rate of the pure drug from the samples was compared to the release rate of the drug of prepared physical mixtures.

Accelerated stability studies

The optimized formulation was subjected to stability studies at 40°C $\pm$ 2°C / 75% $\pm$ 2% RH for period of one month. Each tablet was individually wrapped in aluminum foil and packed in ambered colour bottle and put at above specified condition in a heating humidity chamber

for one month. The tablets were analyzed for the hardness, disintegration time and drug content and in-vitro drug release.

RESULT AND DISCUSSION

Evaluation of flow properties for LS formulations

The LS8 formulation has least flow property (31.21±0.29) when compared to the other formulations and LS3 has the highest flow property (36.18±0.44) when compared to the other formulations. Hausners ratio was observed as least (1.11±0.28) which is LS2 formulation and highest was observed as LS13 i.e. (1.16±0.33). Carr's index was found to be least for LS8 formulation (11.2±0.16) and highest was found to be (15.7±0.21) which is LS14 formulation when compared to other formulations respectively. The details are tabulated in Table 2.

Table 2: Flow property evaluation studies

Formulation	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Compressibility index (%)
LS1	35.19±0.34	0.35±0.37	0.41±0.35	1.12±0.32	14.6±0.26
LS2	34.21±0.29	0.35±0.12	0.39±0.29	1.11±0.28	11.4±0.19
LS3	36.18±0.44	0.32±0.25	0.36±0.37	1.12±0.27	12.5±0.34
LS4	35.31±0.53	0.31±0.28	0.35±0.35	1.12±0.31	12.9±0.21
LS5	34.29±0.51	0.31±0.10	0.35±0.25	1.12±0.21	12.9±0.34
LS6	33.22±0.59	0.30±0.14	0.34±0.37	1.13±0.34	13.3±0.29
LS7	32.18±0.32	0.29±0.29	0.35±0.33	1.13±0.38	15.6±0.26
LS8	31.21±0.29	0.35±0.12	0.38±0.36	1.12±0.24	11.2±0.16
LS9	33.19±0.34	0.34±0.27	0.41±0.25	1.13±0.30	13.6±0.24
LS10	34.31±0.38	0.29±0.10	0.37±0.16	1.14±0.27	13.3±0.34
LS11	33.17±0.38	0.36±0.36	0.43±0.10	1.15±0.28	14.4±0.33
LS12	34.22±0.22	0.38±0.10	0.46±0.39	1.15±0.39	15.0±0.28
LS13	34.18±0.29	0.41±0.29	0.48±0.22	1.16±0.33	14.0±0.18
LS14	35.21±0.36	0.45±0.25	0.53±0.15	1.15±0.26	15.7±0.21

Values are expressed as Mean ±SD, n=3.

The prepared tablets were subjected to various evaluation parameters like weight variation, hardness, thickness, disintegration time etc. It was found that there is not much difference in the weight variation of the formulations. It was observed that the formulation LS10 has the highest hardness (3.0) and lowest was (2.7) for LS1, LS2, LS3, LS8 and LS11. Thickness was found to be highest with LS4 formulation (5.82 ± 0.26) and lowest was LS13 (3.42 ± 0.39). Disintegration time for LS4 was found to be highest (3.07 ± 0.45) and lowest was found to be LS11 (2.29±0.39) when compared to the other formulations respectively. The details are tabulated in Table 3.

Table 3: Evaluation parameter

Formulation code	Weight variation (mg)	Hardness (Kg/cm^2)	Thickness (mm)	Disintegration time (min)
LS1	635.89±1.33	2.7±0.33	5.45±0.35	2.46±0.44
LS2	618.84±1.27	2.7±0.38	5.63±0.46	2.38±0.37
LS3	635.74±1.14	2.7±0.34	5.63±0.38	3.03±0.37
LS4	618.93±1.18	2.8±0.19	5.82±0.26	3.07±0.45
LS5	415.79±1.38	2.8±0.23	4.54±0.25	2.39±0.42
LS6	405.97±1.23	2.9±0.21	4.53±0.44	2.48±0.49
LS7	400.82±1.11	2.8±0.24	4.52±0.33	2.55±0.45
LS8	360.88±1.14	2.7±0.22	3.44±0.34	2.57±0.36
LS9	351.92±1.32	2.8±0.36	3.57±0.28	2.49±0.42
LS10	347.94±1.24	3.0±0.29	3.52±0.39	2.56±0.38
LS11	360.91±1.43	2.7±0.31	3.54±0.28	2.29±0.39
LS12	351.73±1.36	2.8±0.25	3.54±0.33	2.38±0.34
LS13	347.79±1.24	2.8±0.29	3.42±0.39	2.46±0.31
LS14	345.81±1.43	2.9±0.41	3.53±0.17	2.41±0.29

Values are expressed as Mean ±SD, n=3.

The LS tablet was subjected to various evaluation parameters such as friability, drug content and content uniformity. The details are tabulated in Table 4. All the parameters were found to be within the specification limits.

Table 4: Evaluation parameter

Formulation code	Friability (%)	Drug content (%)	Content uniformity (%)
LS1	0.645±0.001	97.78±0.65	97.5±0.35
LS2	0.724±0.003	96.66±0.86	95.8±0.24
LS3	0.657±0.002	98.72±0.58	97.4±0.26
LS4	0.835±0.002	95.69±0.60	96.2±0.19
LS5	0.768±0.002	96.54±0.58	100.2±0.37
LS6	0.868±0.003	98.84±0.39	99.4±0.32
LS7	0.783±0.001	97.56±0.48	98.7±0.16
LS8	0.875±0.003	97.47±0.73	98.2±0.18
LS9	1.125±0.002	98.56±0.63	96.4±0.21
LS10	0.956±0.004	98.88±0.55	98.7±0.24
LS11	0.962±0.002	96.56±0.57	97.4±0.26
LS12	0.857±0.003	98.54±0.67	96.5±0.31
LS13	0.967±0.002	98.59±0.75	99.5±0.28
LS14	0.889±0.001	98.58±0.84	95.6±0.22

Values are expressed as Mean ±SD, n=3.

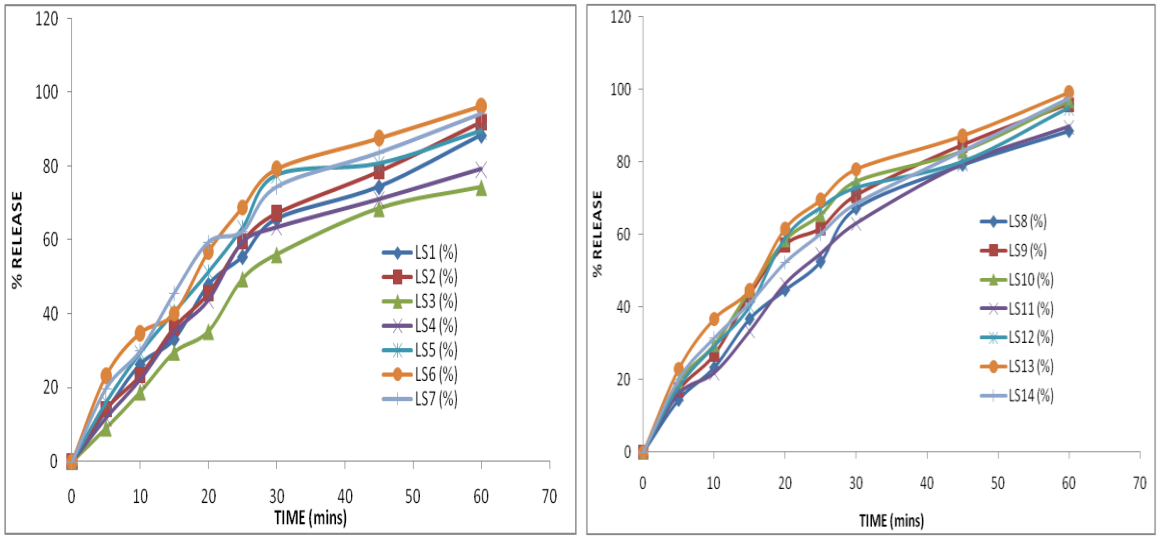
In vitro dissolution studies[7,9] [43,44]

All the formulations were subjected to in vitro dissolution studies in distilled water. The dissolution studies of pure drug and LS compacts were performed and compared.[6,9] Dissolution rate of pure finasteride was less because of hydrophobic nature of drug as it falls in to BCS class II. The reported solubility of finasteride was 66.66 mg/ml in tween 80 solvent.

The figure 1 and 2 shows the drug release profiles of LS formulations from LS1 to LS7 and LS8 to LS14 respectively which are subjected to in-vitro dissolution studies in distilled water. The dissolutions were carried out by standard USP method.

From the drug release profiles in above figure the LS6 formulation was found to be better compare to other formulations. These might be due to the surface area of drug exposed to dissolution media.

In comparison with all the LS formulations, LS10 (98.75±0.21) and LS13 (99.25±0.35) showed the maximum drug release than all the other formulations. These might be due to increased wetability property and increased surface area.



(1) **(2)**

Figure 1 & 2: Dissolution Profile of Liqusolid Compacts LS1 to LS7

The comparative dissolution release of pure drug, marketed, LS10, LS13 are shown in figure 3, thus the increased dissolution rate was found to be for the LS compacts prepared with tween 80 in (20:1) excipient ratio are LS10 and LS13 when compared to all other formulations, pure drug released was (17.77±0.22) and marketed drug release was

(43.49±0.26). This might be due to the higher solubility of finasteride drug in tween 80 solvent, and also the increased wettability of the drug molecules, and also may be due to the absorption and adsorption of the carrier, coating materials on to the liquid medication with the excipients ratio of (20:1). Thus LS10 and LS13showed the higher dissolution rates of all the formulations.

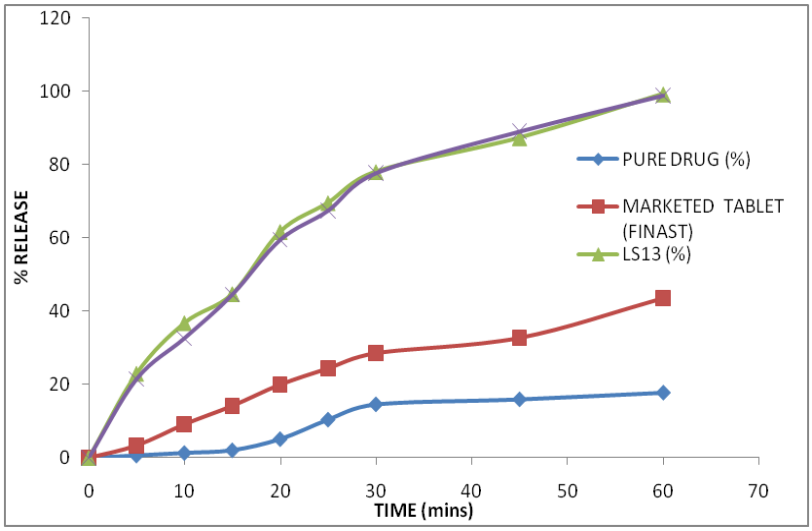


Figure 3: Comparison of Optimised Liqusolid Compacts with Marketed and Pure Drug

Compatibility studies by XRD

The crystallinity of the prepared liquisolid formulations of finasteride is studied by XRD. The change in degree of crystallinity was studied. The pure drug and optimized formulations were also analyzed by XRD in same manner and the peak intensity and presence of new peaks were noted.

The X-ray diffraction pattern of finasteride exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug as shown in figure 4. Optimized Formulations (LS13), (LS10) revealed a reduction in peak intensity when compared with XRD of plain drug as shown in figure 5 and 6 respectively. The characteristic peaks identified in the drug XRD was not detected in formulation. Decrease in the intensities and less number of peaks was probably due to change in crystal habit or conversion to an amorphous form. Reduced crystalline properties when compared to pure drug could account for increased dissolution.

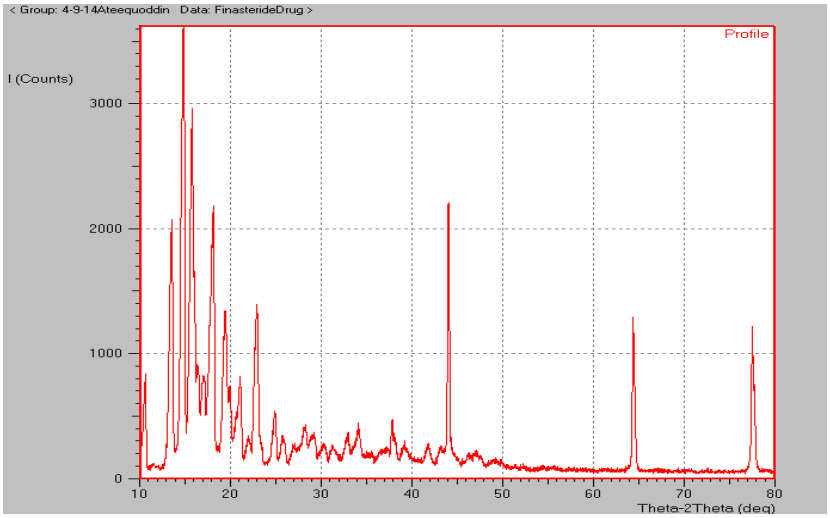


Figure 4: XRD studies: Pure Drug

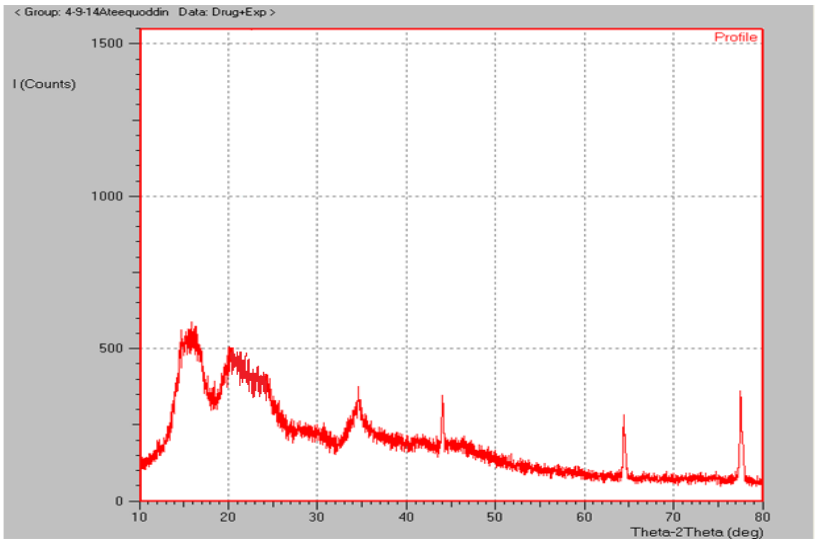


Figure 5: XRD graph of physical mixture (LS13)

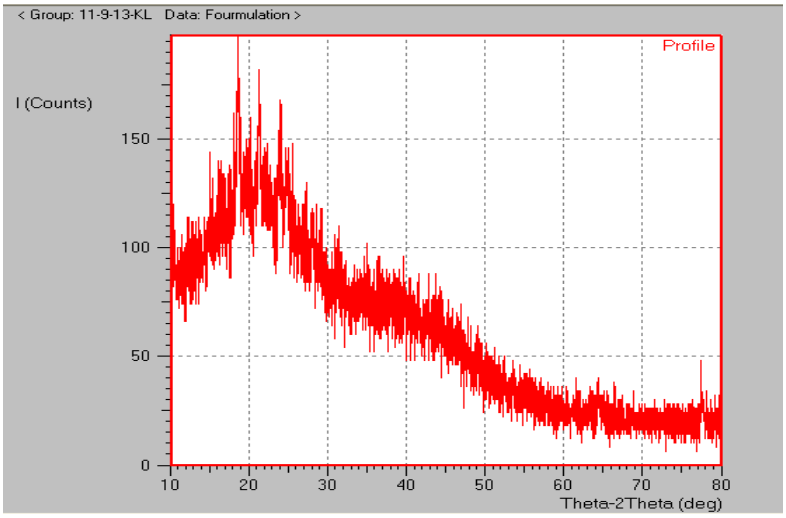


Figure 6: XRD graph of physical mixture (LS10)

Drug - excipient compatibility study by FT-IR

Finasteride compatibility with excipients was studied by FTIR. The FTIR spectra of formulations with excipients reveal no interaction between drug and excipients; both the drug and excipients peaks were identified and interpreted in the spectra. The FTIR studies from the spectra confirmed the absence of any chemical interaction between the drug and excipients. The FT-IR spectra of drug and formulation are shown in figure 7.

DSC of the pure drug showed a sharp peak at 257.9ºC. DSC of LS13 showed peak characteristic of the drug with no additional peaks. The thermogram of the optimized formulation (LS13) was superimposed with the plain drug to compare the results.

From DSC, it can be concluded that the drug and carrier showed no interaction. Thermograms are shown in figure 8 and 9.

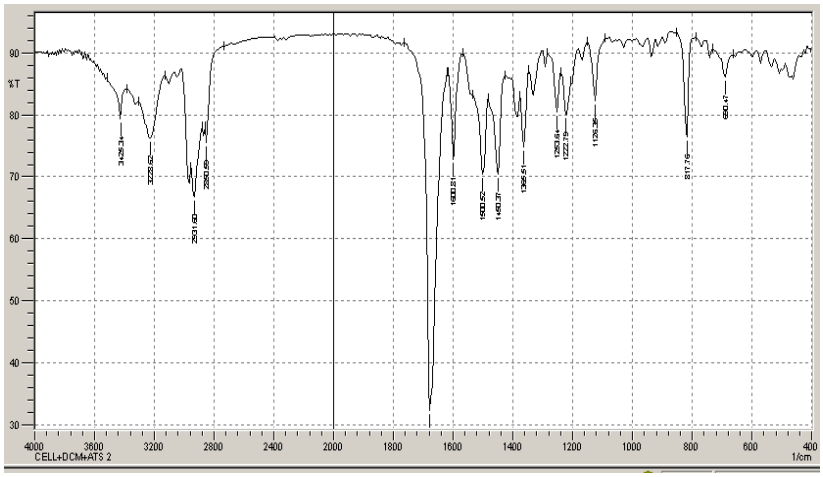


Figure 7: Thermal Analysis by DSC

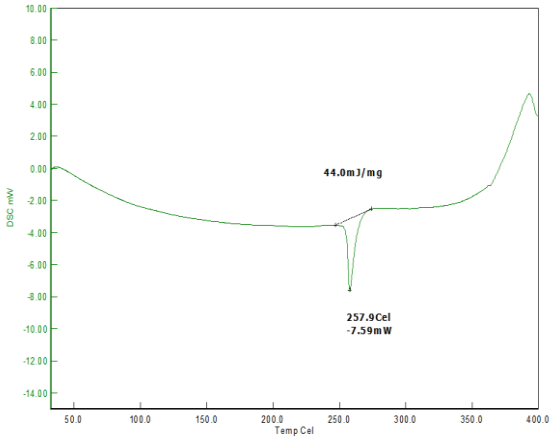


Fig 8

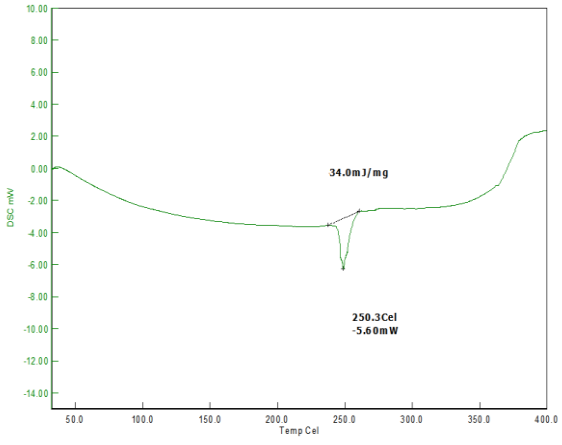


Fig 9

Figure 8 & 9: DSC graph of pure drug and optimized formulation (LS13) respectively

The optimized LS formulations were subjected to various quality control parameters like appearance, drug content, hardness and disintegration time .The evaluation study results were given in Table 5. All the results of optimized formulation were found to be complied with official specifications.

Table 5: Stability study of optimized formulation (LS13)

Time in weeks				
Parameters	**0 (Initial)**	**1st week**	**2nd week**	**1 month**
Appearance	No change	No change	No change	No change
Drug content (%)	99.25±0.35	99.01±1.20	98.85±1.24	98.68±1.76
Hardness (Kg/cm^2)	2.8±0.29	2.8±0.17	2.8±0.13	2.8±0.06
Disintegration time (mins)	2.46±0.31	2.46±0.23	2.46±0.26	2.46±0.14

Values are expressed as Mean ±SD, n=3.

CONCLUSION

The present study was to improve the dissolution rate of finasteride utilizing the approach of liquisolid compacts technology using various carriers. It was envisaged that these technique would improve the solubility of finasteride, since it is poorly soluble drug (BCS class II).

Various non volatile solvents and different excipients were used in the preparation of LS formulations. Liquisolid tablets were prepared using tween 80 as non volatile solvent for preparation of drug solution and varios carrier materials like starch, lactose, MCC, Avicel P^{H}101, Avicel PH102 and Aerosil 200 as the coating material respectively.

Carrier to coating (20:1) ratio LS formulation of both Avicel PH 101 and Avicel PH 102 had shown higher dissolution profiles than marketed and pure drug. The optimized formulation was evaluated for various parameters. In LS formulations of excipient ratio (20:1) with tween 80 showed marked increase in dissolution profiles.

The optimized formulation of finasteride was characterized by X-ray diffraction, FTIR, assay and *in-vitro* dissolution studies. No interaction was observed. XRD data revealed that all the optimized formulations of all techniques showed reduced crystallinity when compared to pure drug.

In conclusion it can be stated that the objective of the study was achieved in improving the solubility of the finasteride using liquisolid compact technology.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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