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Research Article

Enhancement of Dissolution Rate of Gliclazide by Liquisolid Technique

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Abstract: The purpose of the present research was to investigate the in vitro dissolution properties of poorly water soluble gliclazide by utilizing liquisolid technique. Avicel PH 102 and Neusilin were employed as carrier material; Aerosil 200 as coating material and crosspovidone as disintegrant respectively for preparing liquisolid compacts. Liquisolid compacts were prepared and evaluated for their tabletting properties. The tabletting properties of the liquisolid compacts were within the acceptable limits and drug release rates of all prepared LS compacts were distinctly higher as compared to directly compressed tablets, and marketed tablets. The results showed that liquisolid compacts demonstrated significantly higher drug release rates than those of conventionally prepared directly compressible tablets. This was due to an increase in wetting properties and surface of drug available for dissolution. From this study it concludes that the LS technique is an effective approach to enhance the dissolution rate of gliclazide.
Keywords: Liquisolid compacts (LS), Gliclazide, Dissolution rate, Liquid load factor.

INTRODUCTION

Solubility behaviour of a drug is one of the key determinants of its oral bioavailability. In recent years, the number of poorly soluble drug candidates has increased tremendously. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists [1]. The active pharmaceutical ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. For hydrophobic drugs, the dissolution process acts as the rate-controlling step and, which determines the rate and degree of absorption[2-3]. There are certain methods available which are as follows[4-5]. Pharmaceutical approach: Pharmacokinetic approach:. Biologic approach: Liquisolid compact is one of the most promising techniques. Low cost, simple formulation technique and capability of industrial production serve to be advantages of this technique. Several researchers have shown that the liquisolid technique is the most promising method for promoting dissolution rate of poorly water-soluble drugs[6-7]. Liquisolid system is novel technique developed by Spireas et al [8-9] liquisolid systems involves conversion of liquid lipophilic drugs or water insoluble solid drugs dissolved in non-volatile solvent and this liquid medication can be converted into free-flowing, non adherent, dry looking, and readily compressible powders with the use of carrier and coating materials. Gliclazide 1-(3-Azabicyclo (3, 3, 0)-oct-3-yl)-3-(p-tolyl sulfonyl) urea is an oral potent hypoglycemic second generation sulfonyl urea drug which is used for a long term treatment of non-insulin dependent diabetes mellitus (NIDDM)[10]. Gliclazide is insoluble in water which leads to poor dissolution rate and subsequent decrease in its gastrointestinal absorption [11]. The formation of amorphous forms to increase drug solubility and the reduction of particle size to expand surface area for dissolution and decrease the interfacial tension with the aid of water soluble carrier among the possible mechanisms for increasing dissolution rates thereby improving bioavailability of poor water soluble drugs[12].

MATERIALS AND METHODS

Materials

Gliclazide was obtained as a gift sample from Torrent Pharmaceuticals Limited, Ahmadabad, Gujarat. All other excipients were used of analytical grade.

Solubility study[13]

Solubility of the drug was measured in: Distilled Water, 0.1N HCl and pH 7.4 phosphate buffer. The solubility of drug was determined by adding an excess amount of drug to snap-cap Eppendorf tube containing 1 mL of solvent. The resulting mixture was thoroughly vortexed and then placed in a 37°C incubator for two days. Aliquots were centrifuged at 1000 rpm for 10 min. The supernatant layer was carefully removed and then diluted with a solution. The concentration of drug was then measured using UV/Visible

spectrophotometer by comparison with a standard calibration curve.

***Flow Properties of Drug*[14]**

All the flow properties were studied of the drug such as bulk density, tapped density, Carr's Index, Hausner's Ratio and angle of repose.

***Saturation solubility studies* [15]**

The solubility of gliclazide in different non-volatile liquid vehicles that are commonly used for the formulation of liquisolid compacts, namely, propylene glycol (PG), polyethylene glycol 200 (PEG 200) PEG 400 , Tween 80 and acrysol EL 135 was determined by preparation of saturated solutions of the drug in these solvents and measuring their drug concentration. Excess Gliclazide was stirred in the above mentioned solvents for 48 h at 25˚C. Accurately weighed quantities of the filtered supernatants were further diluted with methanol and analyzed spectrophotometrically at 226 nm for their drug content. From these results, the solubility of gliclazide in the respective liquid vehicle was calculated. Each experiment was carried out in triplicate.

***Preparation of Liquisolid compacts* [16]**

Briefly, calculated quantities of Drug and Solvent were accurately weighed in a glass beaker. The resulting medication was incorporated into calculated quantities of carrier and coating materials at a fixed ratio. The appropriate amounts of the carrier and coating materials used in the liquisolid formulation were derived from their Ø-value and liquid load factors (Lf). This mixture was mixed for 10 minutes in mortar. Finally, crosspovidone was mixed for a period 10 minutes and then magnesium stearate was added before compression as a lubricant. This had yield a final formulation of liquisolid tablets. The liquisolid formulations thus prepared were compressed with a tablet compression machine. All formulations contain Gliclazide 80mg, 5% Crosspovidone as superdisintegrant, 5% Magnesium oxide, 2% talc and 1% magnesium stearate.

Table-1: Composition of Liquisolid tablets

Formulation	Amount of liquid in (mg)	Ratio of carrier to coating material (R)	Liquid load factor (Lf)	Amount of Avicel PH 102 (mg) (Q = W/Lf)	Amount of Neusilin (mg) (Q = W/Lf)	Aerosil 200 (mg) (q= Q/R)	MgO (mg)	Crosspovidone (mg)	Tablet Weight (mg)
F1	50	5	0.48	104.16	-	20.83	12.74	13.38	281.11
F2	50	10	0.32	156.25	-	15.63	15.09	15.84	332.8
F3	50	15	0.266	192.30	-	12.82	16.75	17.59	333.46
F4	100	5	0.48	208.33	-	41.66	21.49	22.57	474.05
F5	100	10	0.32	312.5	-	31.25	26.18	27.49	577.42
F6	100	15	0.266	384.61	-	25.64	29.51	30.98	650.74
F7	50	5	0.54	-	92.59	18.51	12.05	12.65	265.8
F8	50	10	0.38	-	131.57	13.15	13.73	14.42	302.87
F9	50	15	0.32	-	156.25	10.41	14.83	15.57	327.06
F10	100	5	0.54	-	185.18	37.03	20.11	21.11	443.43
F11	100	10	0.38	-	263.15	26.31	23.47	24.64	517.57
F12	100	15	0.32	-	312.5	20.83	25.66	26.94	565.57
DCT*	-	-	-	181		--	-	15.00	300

***DCT= Direct Compressible Tablet**

Pre-Compression Study

***Flow Properties* [17]**

All the flow properties were studied of the liquisolid compacts such as bulk density, tapped density, Carr's Index, Hausner's Ratio and angle of repose.

***Post-Compression* [16, 18-22]**

Hardness Test

Hardness was measured using Monsanto hardness tester in terms of kg/cm^2. Average hardness of three tablets was taken to study the reproducibility.

Friability Test

Six tablets from each batch were exposed to Roche friability test apparatus for 100 rotations and percentage loss in weight was measured against initial weight.

$$\%\text{Friability (F)} = \{1-(W/W0)\} \times 100$$

Where,

W0=Initial Weight of tablet

W=Weight of tablets after the test

Uniformity of Weight

Twenty tablets were selected at random from each formulated batch to check the uniformity of weight

using electronic balance. Average weight and maximum percent deviation (positive and negative) were determined.

% Drug content of Gliclazide liquisolid Tablets

Drug content uniformity was determined by dissolving the tablets in methanol and filtering with Whattman filter paper (0.45 µm). Then by suitable dilution, drug concentration was analyzed at 226 nm using a UV spectrophotometer (UV-1700, shimadzu Inc. Japan). The experiments were performed in triplicate, and average values were reported.

Disintegration Test

The disintegration test was carried out using disintegration test apparatus USP (Hicon, India) using distilled water as disintegration medium. One tablet was introduced into each tube and a disc was added to each tube. Assembly was suspended in the beaker containing 900 ml distilled water. Time for disintegration of all six tablets was noted down.

In-Vitro Drug Release Study

The test was performed on the prepared gliclazide liquisolid tablets using the USP dissolution apparatus II. Six individual tablets from each formula were tested. Test was performed in 900ml of two different dissolution medium (0.1 N HCl, 7.4 pH phosphate buffer). In all studies, the temperature of the dissolution medium was maintained at 37± 0.5 °C. The aliquots of 5ml were withdrawn at regular time intervals 10, 20, 30, 40, 50 and 60 minutes, filtered, and analyzed spectrophotometrically at 226 nm.

***Comparison of dissolution profile by similarity factor* [23]**

The dissolution profile of optimized liquisolid formulation was compared with marketed formulation of gliclazide (Dianorm Micro Lab) using similarity factor.

$$f_2 = 50 \text{ x } \log\{[1 + (\frac{1}{n})\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5}\text{x}100\}$$

Where, n =No. of time points, R_t = The reference profile at the time point t, T_t = The test profile at the same point.

RESULTS AND DISCUSSION

Solubility Study

Solubility of the drug was measured in three different solvents and the drug showed maximum solubility in phosphate buffer pH 7.4. Results of solubility studies are as shown in table 2.

Table 2: Solubility of drug in different mediums

Medium	Solubility (g/ml)
Water	0.081±0.005
0.1N HCl	0.029±0.003
Phosphate buffer pH 7.4	0.097±0.02

Flow Properties

All the flow properties were studied and drug showed poor flow property. Results of flow property are as shown in table 3.

Table-3: Flow properties of drug

Parameters	Observations
Bulk density (g/ml)	0.18
Tapped density (g/ml)	0.253
Angle of repose (ɵ)	41.19
Hausner's ratio	1.40
Carr's index (%)	28.85%

Saturation solubility studies

The solubility of gliclazide in different non-volatile liquid vehicles namely, propylene glycol (PG), polyethylene glycol 200 (PEG 200) PEG 400 , Tween 80 and acrysol EL 135 was determined by preparation of saturated solutions of the drug in these solvents and measuring their drug concentration and results are as shown in table 4.

Table 4: Saturation solubility studies in different non volatile solvents

Solvents	Solubility (mg/ml)
Propylene glycol	5.22± 0.88
Tween 80	29.1± 1.4
PEG 400	7.5±0.23
PEG 200	3.4±0.62
Acrysol EL 135	102.3±2.31

Evaluation parameters

Flow Properties of Liquisolid Compacts

The flow property of the liquisolid compacts were studied and was observed that the flow properties were enhanced as compared to that of the drug as shown in table 5.

Post-compression

All the parameters of the liquisolid tablets were performed and the results are as shown in table 6.

Table 5: Precompression Studies of liqisolid compacts

Formulation	Bulk density (n = 3)	Tapped density (n = 3)	Carr's index (%)	Hausner's Ratio	Angle of repose (ɵ)
F1	0.130 ±0.02	0.178±0.002	19.53 ± 0.37	1.12 ± 0.01	26.50 ± 0.07
F2	0.152±0.11	0.199±0.012	17.87 ± 0.57	1.20 ± 0.11	27.25 ± 0.23
F3	0.161±0.05	0.216±0.01	15.27 ± 0.04	1.11 ± 0.01	23.82 ± 0.49
F4	0.210±0.02	0.254±0.06	16.35 ± 0.37	1.21 ± 0.42	24.11 ± 0.02
F5	0.225±0.10	0.263±0.12	15.61 ± 0.50	1.17 ± 0.01	29.35 ± 0.33
F6	0.197±0.002	0.228±0.07	14.07 ± 0.52	1.16 ± 0.01	29.02 ± 0.27
F7	0.228±0.05	0.260±0.08	17.46 ± 0.49	1.14 ± 0.26	28.86 ± 0.63
F8	0.206±0.023	0.232±0.004	16.49 ± 0.37	1.13 ± 0.33	22.31 ± 0.01
F9	0.177±0.021	0.233±0.03	20.64 ± 0.49	1.15 ± 0.03	36.38 ± 0.92
F10	0.143±0.12	0.165±0.08	12.61±0.54	1.10±0.34	22.17±0.31
F11	0.265±0.06	0.332±0.005	12.17±0.24	1.05±0.032	20.54±0.05
F12	0.149±0.32	0.174±0.06	13.92±0.008	1.13±0.06	21.45±0.08
DCT	0.126±0.045	0.185±0.15	31.89±0.023	1.46±0.071	40.57±0.05

***DCT= Direct Compressible Tablet**

Table 6: Post compression results of formulation F1-F12

Formulation	Hardness (kg/cm^2) (n =3)	Friability (n = 6)	Disintegration (sec) (n = 6)	Weight variation (n =20)	% drug content
F1	4.8 ± 0.4	0.78	120.4±3.2	Pass	97.32±1.53
F2	4.7 ± 0.12	0.81	115±3.1	Pass	96.45 ± 0.65
F3	4.4 ± 0.2	0.88	95.6±4.7	Pass	98.43±2.22
F4	4.6 ± 0.3	0.83	88±2.0	Pass	97.58 ± 1.18
F5	4.5 ± 0.2	0.71	69.7±1.2	Pass	98.86 ± 2.18
F6	3.7± 0.4	0.65	72±3.0	Pass	97.33 ± 0.71
F7	4.3 ± 0.07	0.79	110±5.0	Pass	98.28±1.92
F8	4.4 ± 0.031	0.68	50.7±5.6	Pass	101.11±1.61
F9	3.8 ± 0.22	0.91	72.2±6.1	Pass	97.46 ± 0.47
F10	4.6±0.045	0.59	58.1±4.3	Pass	96.54±0.87
F11	4.5±0.012	0.22	42±2.0	Pass	101.43±1.34
F12	4.7±0.003	0.74	78.4±3.1	Pass	99.71±1.71
DCT	3.1±0.02	0.80	93±4.2	Pass	98.57±0.63

***DCT= Direct Compressible Tablets**

In-Vitro Drug Release Study

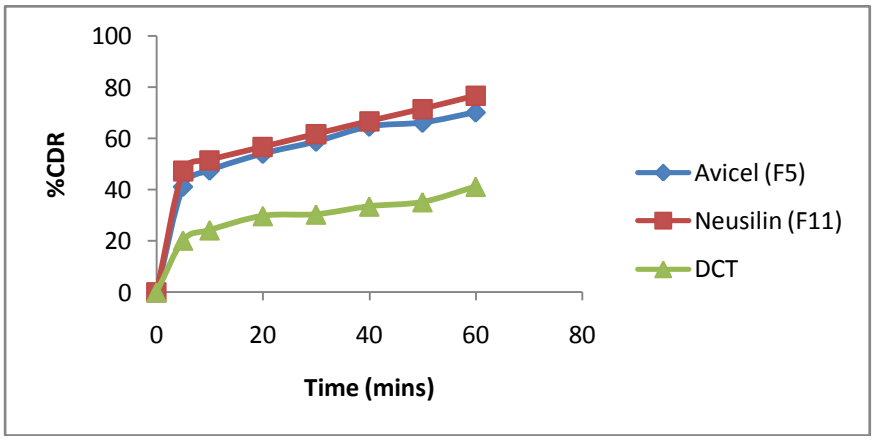

Fig-1: Iv-vitro release study of F5, F11 and DCT in 0.1N HCl

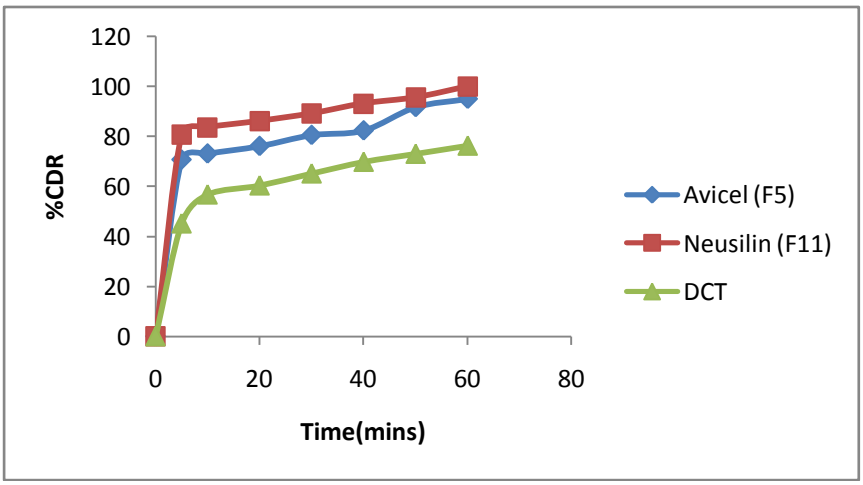

Fig-2: Iv-vitro release study of F5, F11 and DCT in pH buffer 7.4

Comparison of dissolution profile by similarity factor

Prepared gliclazide liquisolid tablet was compared with marketed formulation of gliclazide and DCT by using similarity factor and it was found that liquisolid formulation showed dissimilarity with marketed formulation and DCT. The results were recorded as in table 7 and as shown in figure 3.

Table 7: Comparison of dissolution profile by similarity factor

Type of Formulation	f_2 values	
	0.1N HCl	pH 7.4
DCT and F11	26	30
F11 and Marketed	44	32

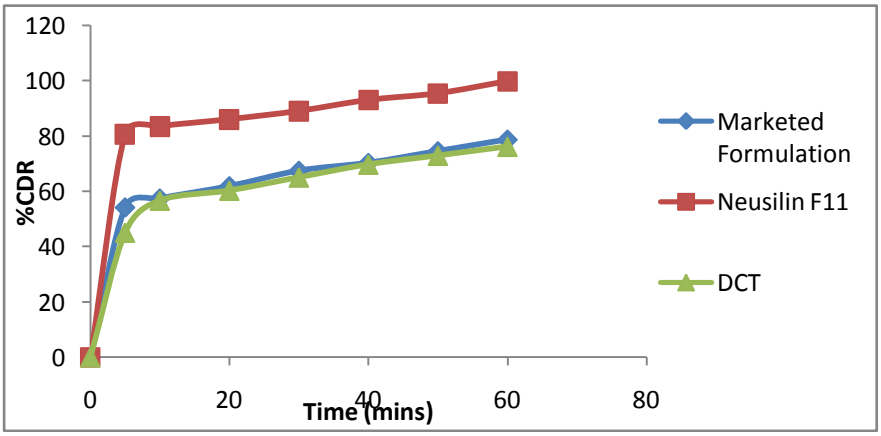

Fig- 3: Comparison of dissolution profile of F11 and marketed formulation

CONCLUSION

In conclusion, this study showed that liquisolid technique could be a promising strategy in improving dissolution of poorly water soluble drugs and formulating them in to immediate release solid dosage forms. The optimized formulations F5 and F11 showed better drug release as compared to the other formulations. The formulation F5 and F11 were considered better among other formulations to produce fast release of the gliclazide. The improvement in the dissolution characteristics of a Liquisolid technique changes the properties of gliclazide particles by simply dispersed the drug particles in a non volatile liquid vehicle, which in turn increase the wetting properties and surface area of drug particles, and hence improve the dissolution profiles and might be oral bioavailability of the drug.

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