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ENHANCEMENT OF SOLUBILITY & DISSOLUTION RATE OF POORLY SOLUBLE DRUG OF NATEGLINIDE BY LIQUISOLID TECHNIQUE.

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ABSTRACT

The main aim of the present investigation is to enhance the dissolution rate of poorly water soluble drug such as Nateglinide. In this technique liquisolid system refers to formulation prepared by water insoluble drug mix with non-volatile solvent which is further converted into free flowing, non adherent powder form and which is directly compressed into tablets. In that the propylene glycol is used as non-volatile solvent in which drug having high solubility. Formulations F1,F2,F3were prepared by using microcrystalline cellulose and aerosil (silica),F4,F5,F6 were prepared by using lactose and cab-o-silica & F7 to F9 were prepared by using lactose and Syliod 244FP as carrier and coating material in the ratio of 10:1 and 20:1 respectively. Sodium starch glycolate acts as superdisintegrant and magnesium stearate as glidant in liquisolid system. The prepared liquisolid system were evaluated to their flowing properties such as bulk density, tap density, Hausner's ratio, Carr's index, and angle of repose. Fourier Transform Infrared spectroscopy (FTIR) and X Ray Diffraction (XRD) study shows no interaction between the drug and excipients. Further tablets were evaluated for hardness, diameter, thickness, weight variation, friability, disintegration test, uniformity of contents and *in-vitro* release study the studies shows liquisolid compact exhibited higher percentage of drug release than conventional and marketed tablets because of due to increase in wetting properties and surface availability for dissolution.

KEYWORDS: Nateglinide-Liquisolid Compacts, Direct Compression, *In-vitro* Dissolution Study.

INTRODUCTION

During the last four decades the pharmaceutical industry invested the time and money in study of tablet compaction. The reason behind it the oral dosage forms are self administered by patient, they more profitable to manufacture than parenteral dosage forms. Also their low cost of manufacture, package, shipment, increased stability and tamper resistance. There are many types of tablet formulations that provide for release of drug to be delayed or control the rate of drugs availability. And some tablets are the fast disintegrating or fast dissolving tablets are present to give the quick effect of drug.[1,2] The poor dissolution rates of water insoluble drugs are still a substantial problem confronting the pharmaceutical industry. Various solid dosage formulation techniques, to enhance the dissolution of poorly soluble substances, have been introduced with different degrees of success. Drug dissolution is the single most important factor in the absorption of it, especially from the most widely used conventional solid dosage forms, tablets and capsules.[3-5] Diabetes is the metabolic disorder characterized by hyperglycemia, glycosuria, hyperlipaemia, negative nitrogen balance and ketonemia. Type II diabetes (also known as non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes) is one of the most serious medical conditions affecting our nation today. The number of people who have it has been rising widely. For this the fast delivery of drug is required to the diabetic patient.[6] Nateglinide (NTG) is an amino-acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. This action is dependent upon functioning beta-cells in the pancreatic islets. Nateglinide interacts with the ATP-sensitive potassium (K+ATP) channel on pancreatic beta-cells. The subsequent depolarization of the beta cell opens the calcium channel, producing calcium influx and insulin secretion. The extent of insulin release is glucose dependent and diminishes at low glucose levels. The tablets have to be taken 10-20 minutes before meal.[7] The main objective of this work is to develop and explore a new formulation to enhance the bioavailability of a highly permeable and a poorly soluble antidiabetic drug Nateglinide by following liquisolid compacts. And to compare the in vitro drug release profile of formulated liquisolid tablets with marketed and conventional tablet.

MATERIALS AND METHODS

Materials: NTG was a gift sample from Divis laboratories Ltd(Hyderabad).India as a gift sample. Propylene glycol, tween-80, and glycerol were purchased by Merck Specialities Pvt. Ltd., Mumbai, India. Microcrystalline cellulose and silica were purchased from Labindia, sodium starch glycolate obtained from Labindia, Mumbai, India. Magnesium stearate was

obtained from merki, Mumbai, India. All the other chemicals and reagents were of analytical grade.

METHODS

Determination of Solubility of Nateglinide

The solubility determination of Nateglinide was carried out in distilled water, 0.1 N HCl, propylene glycol, glycerol, and tween-80. The excess drug was added gradually to 10 ml of each solvent contained in 100 ml beaker. The beaker was place on magnetic stirrer for 24 hr until solubility equilibrium was reached The solutions were filtered through Whatmann filter paper. Aliquots of the filtrate were suitably diluted and the dilutions were analyzed spectrophotometrically at 212 nm. (javadzadeh 2005 at el…).

Determination of liquid load factor (Lf)

It is defined as the ratio of liquid medication (w) to weight of coating material (q). It is determined by dissolving or dispersing the drug in non volatile solvent and to this carrier-coating material admixture is added and blended. The amount of carrier-coating admixture is used to convert free flow powder and is determined by using the following formula.

Lf = W/Q

Where, W= Weight of liquid medication

Q= weight of carrier material The Φ value is for calculating excipients quantities. Equation is Lf = Φ + Φ (1⁄R) Where, Φ and Φ are values of carrier and coating material.[14] It is used to calculate amount of carrier and coating material in each formulation. The excipients ratio R of powders is defined as the ratio of carrier and coating material present in the formulation. R is suitably selected for successful formulation. R=Q/q Where, Q= weight of carrier Q= coating material.

Determination of holding capacity of the excipients

The capacity of each excipient to hold liquid and behave like dry powder (holding capacity) was determined using the following simple technique: Different weights of Propylene glycol were transferred to a mortar. The constant weight of powder excipient was added gradually and the mixture was triturated after each addition to help distributing the liquid throughout the powder particles. The addition of powder and the trituration was continued until mortar contents start to look like dry powder.**(**Bhavani.G et al. 2014).

Formulation of Nateglinide Tablets by liquisolid technique

Preparation liquisolid compacts

Weigh accurately 60 mg Nateglinide in each batch and place in the mortar and add the propylene glycol as non-volatile solvent to form dispersion mix well. Add the small amount of the binary mixture of carrier and coating material (microcrystalline cellulose and silica) in it and mix. Depending upon the type of carrier in formulation, different liquid loading factors were employed in liquisolid preparations. Finally, 5% (w/w) of sodium starch glycolate as disintegrant and 1% magnesium stearate were mixed with mixture for 5 minutes. Final mixture was compressed on 13 mm punch and die, using the manual hydraulic press at constant pressure. The batch design is reported in table. (k.rajesh 2011 at el…).

Table 1: formulation of liquisolid compacts.

Formulations	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Non volatile oil	310	310	310	310	310	310	310	310	310
MCC	500	500	500	-	-	-	-	-	-
Aerosiol 200	35	25	30	-	-	-	-	-	-
Lactose	-	-	-	500	500	500	500	500	500
Cab-o-silica	-	-	-	35	25	30	-	-	-
Syliod 244fp	-	-	-	-	-	--	35	25	30
R value	14	20	16	14	20	16	14	20	16
Lf value	8.8	12.4	10.3	8.8	12.4	10.3	8.8	12.4	10.3
SSG	3	3	3	3	3	3	3	3	3
Mg **stearate**	1	1	1	1	1	1	1	1	1
Total wt	**870**	**870**	**870**	**870**	**870**	**870**	**870**	**870**	**870**

Evaluations: (Mark gibson 1992 at el…).

Flow Properties: Flow properties of liquisolid formulation were studied by angle of repose, Carr's index, and Hausner's ratio. Each analysis was carried out in triplicate. Bulk density measurements were carried by placing a fixed weight of powder in a graduated cylinder, and the volume occupied was measured and the initial bulk density was calculated. The cylinder was then tapped at a constant velocity until a constant volume was obtained. The tapped density was then calculated. The angle of repose was calculated by the fixed-height cone method. All studies were done in triplicate. Then after the Carr's index, and Hausner's ratio was calculated from bulk and tapped density.

FTIR Spectra Analysis: In the preparation of liquisolid Tablets, NTG and excipients may interact as they are in close contact with each other, which could lead to the instability of

drug to overcome this problem, FTIR Spectroscopy was employed to ascertain the compatibility between NTG and excipients.

Evaluation of Liquisolid Tablets

Hardness: The hardness of liquisolid tablets was determined using Monsanto hardness tester. The mean hardness of each was determined.

Diameter and Thickness: The diameter and thickness of tablets were calculated by Vernier calliper.

Weight variation

Weight variation was measured by weighing 20 tablets and average weight was found of the individual tablet should fall within specified limits.

Friability: The friability of the tablets was determined by laboratory friability tester known as Roche Friabilator, the percentage loss in tablet weight before and after 100 revolutions of 10 tablets were calculated and taken as percentage friability.

Disintegration Test: One tablet in to each tube was introduced and disc was added. The assembly was suspended in a beaker containing 1000mL of water and the apparatus was operated for 30 minutes. The time taken for complete disintegration of each tablet was noted. The tablets pass the test if all of them have disintegrated within the time (30 min).

FTIR spectra analysis: In the preparation of liquisolid Tablets, NTG and excipients may interact as they are in close contact with each other, which could lead to the instability of drug. FTIR Spectroscopy was employed to ascertain the compatibility between NTG and excipients.

X-Ray diffraction study: For further characterization of the crystalline state, the X-ray diffraction (XRD) patterns were determined for Nateglinide powder and Liquisolid formulation were are analysed by powder X-Ray Diffractometer (D8 ADVANCE, Bruker, Germany) with Cu Kα radiation (1.540 Å), in the range of 2θ=20-60o at slow angle scan of 0.020/step. The results were then obtained as peak height (intensity) versus 2θ.

In-Vitro* Release Study:** The ***in vitro dissolution studies were carried out by using USP Type II (Paddle type) (Electrolab TDT 06) dissolution test apparatus. All batches of liquisolid

tablets were evaluated by using 1000 ml of 0.01N HCl with 0.5% sodium lauryl sulphate. Following parameters were used during release study. Speed of paddle 50 rpm, temperature 37±2°C Sampling time 5,10,15,20,30,45,60 minutes, filtered using (Millipore Millex-HN), and analyzed spectrophotometrically at 212nm. The spectrophotometric readings were converted into cumulative percent of drug release using the standard calibration curve of Nateglinide.[20]

RESULTS AND DISCUSSION

Results

Drug solubility

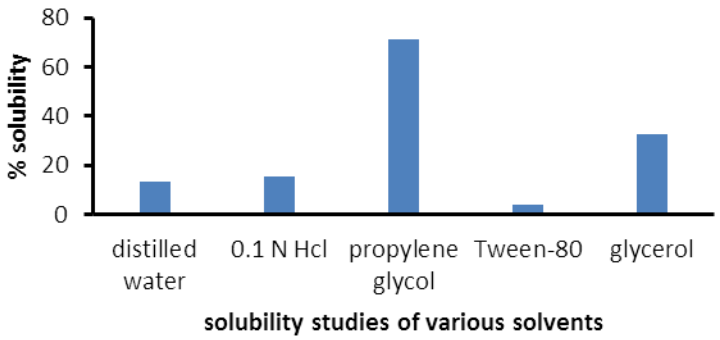

Fig 1: solubility studies of various solvents.

Table 2: Flow properties of Liquisolid compressible powder.

Batch	Bulk Density (gm/ml)	Tap Density (gm/ml)	Hausner's Ratio	Carr's Index	Angle of Repose (º)
F1	0.5066±0.005	0.45±0.14	26.67±0.03	1.36±3.8	46.04±3.65
F2	0.5000±0.002	0.31±0.11	25.00±0.08	1.33±1.4	42.6±2.8
F3	0.5263±0.003	0.53±0.17	10.52±0.17	1.11±0.5	32.61±2.9
F4	0.5308±0.004	0.61±0.19	33.33±0.28	1.50±0.8	46.16±0.56
F5	0.4960±0.002	0.39±0.13	26.66±0.01	1.36±0.6	45.00±2.6
F6	0.4595±0.002	0.43±0.13	23.81±0.10	1.31±0.1	42.87±4.2
F7	0.5184±0.002	0.46±0.14	30.76±0.01	1.44±0.5	44.1±063
F8	0.4876±0.006	0.6908±0.18	29.41±0.10	1.41±0.3	42.70±2.5
F9	0.4434±0.009	0.6000±0.16	26.10±0.06	1.35±0.9	41.98±2.1

Table 3: Post-compression evaluation of liquisolid compacts.

Batch	Diameter (mm)	Thickness (mm)	Uniformity of contents (%)	Hardness (Kg/cm2)	Weight Variation (mg)	DT (sec.)	Friability (%)
F1	13.14±0.01	2.97±0.18	95.77±0.21	3.7±0.08	870.85±0.02	151±0.69	0.77±0.077
F 2	13.17±0.04	4.44±0.02	100.97±0.13	3.6±0.08	871.4±0.04	154±0.01	0.16±0.04
F 3	13.51±0.8	2.77±0.07	94.95±0.45	4.1±0.09	880.75±0.05	186±0.02	0.2±0.08
F 4	13.13±0.01	3.94±0.1	97.07±0.37	3.8±0.04	870.9±0.01	152±0.05	0.13±0.04
F 5	13.16±0.03	2.16±0.1	89.44±0.67	4.1±0.14	870.75±0.03	256±0.04	0.1±1.3
F 6	13.14±0.02	1.89±0.05	98.05±0.12	4.1±0.16	871.6±0.6	204±0.01	0.16±0.04
F 7	13.15±0.02	2.82±0.07	99.35±0.31	4.1±0.24	872.85±0.2	381±0.05	0.43±0.04
F8	13.61±0.8	2.27±0.1	100.97±0.13	4.1±0.19	870.75±0.05	152±0.09	0.14±0.09
F9	13.19±0.04	2.95±0.07	89.49±0.67	3.8±0.07	871.6±0.9	209±0.01	0.19±0.04

IR Spectra of pure Nateglinide

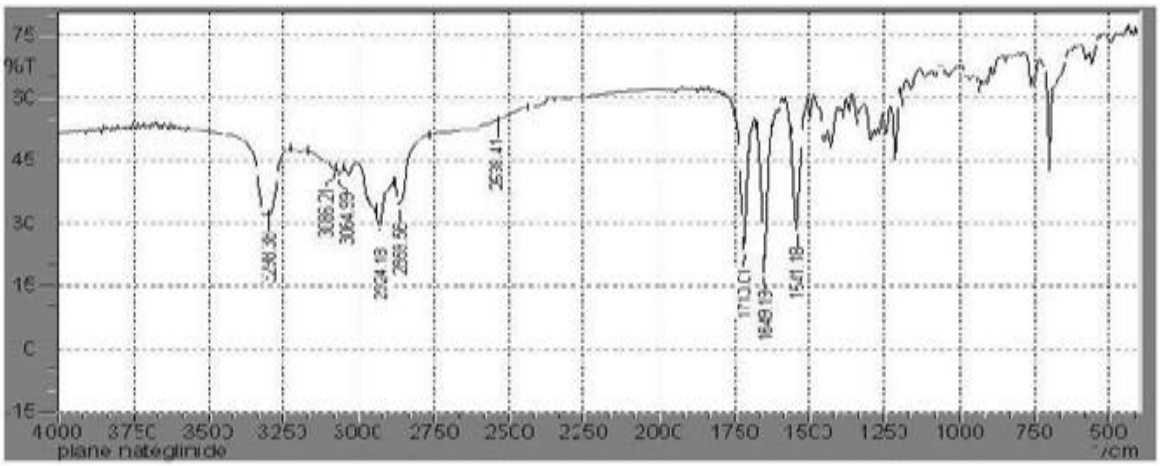

Fig: 2 IR Spectra of pure Nateglinide.

IR Spectra of optimized formulation

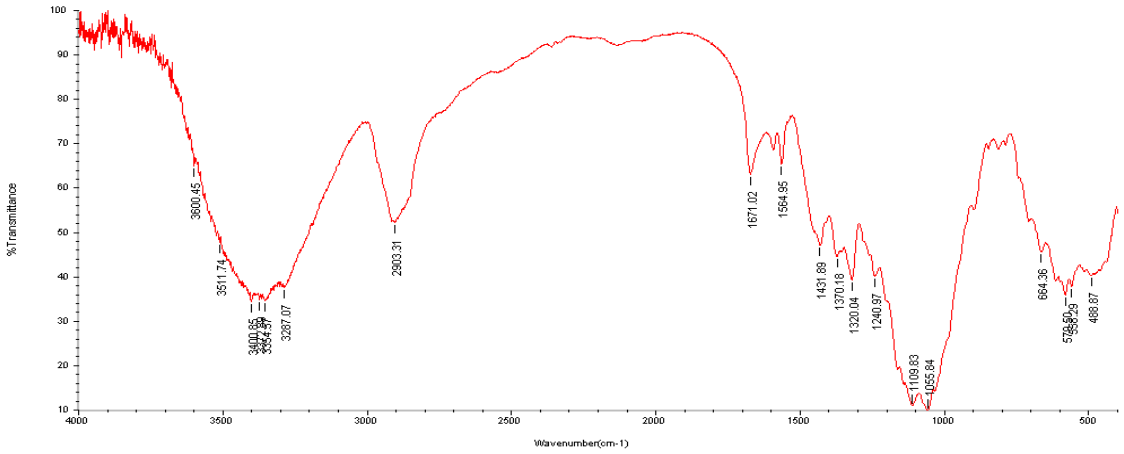

Fig: 3 IR Spectra of optimized formulation.

X-Ray Diffraction study

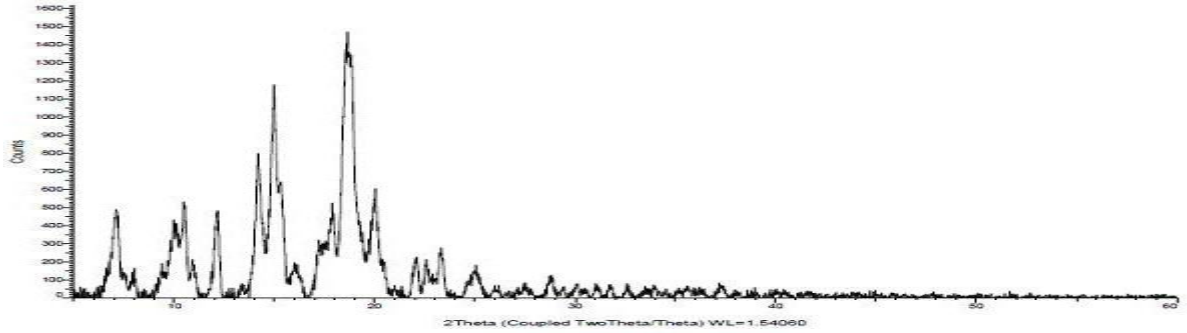

Fig 4: X-Ray Diffraction study of nateglinde pure drug.

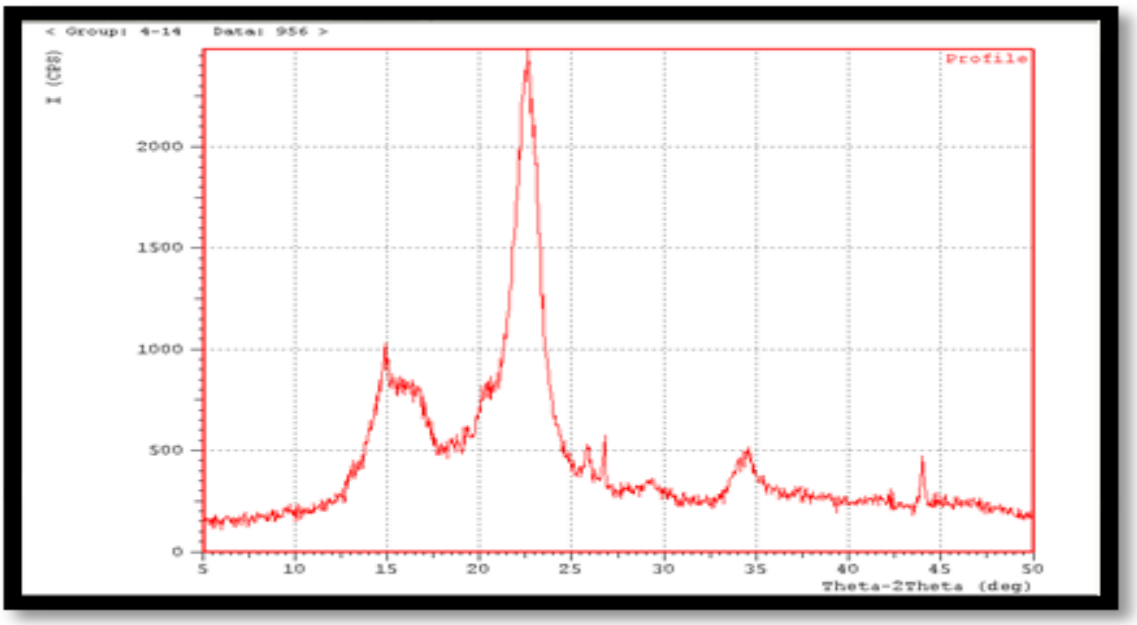

Fig 5: X-Ray Diffraction study of optimized formulation.

Table 4: formulae % cumulative drug release.

TIME(MIN)	PURE	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0	0
5	12.75	30.52	26.72	15.75	21.69	15.89	18.68	24.93	9.72	29.14
10	16.39	34.65	37.92	36.78	31.46	22.16	25.50	36.22	14.52	41.66
20	18.67	47.35	57.46	49.23	43.54	26.52	39.49	59.41	37.45	55.64
30	23.24	61.48	70.67	63.68	62.39	40.58	48.53	72.90	52.88	65.04
45	23.83	82.46	81.42	79.45	75.09	66.80	66.35	87.80	70.56	77.91
60	27.66	96.78	92.46	94.59	92.31	86.03	90.12	98.59	92.45	95.96

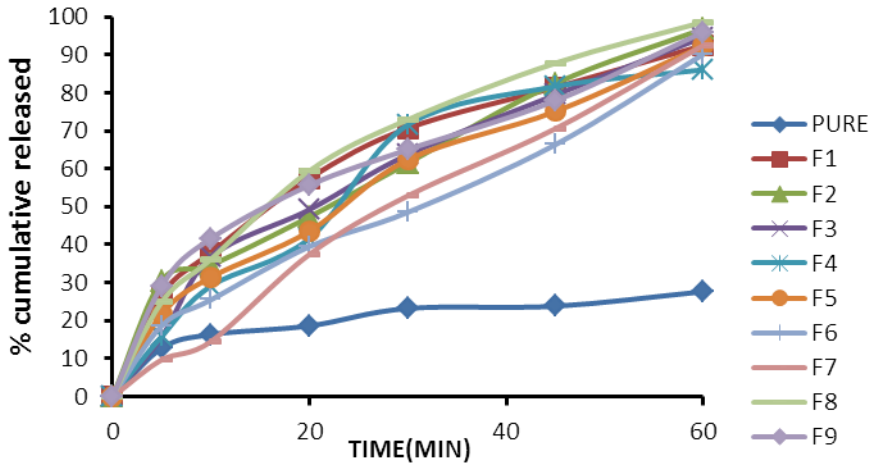

Fig 6: Comparative dissolution profiles of liquisolid compacts.

DISCUSSION

Determination of Solubility of Drug: The solubility studies were carried out in distilled water, 0.1 N HCl, propylene glycol, Glycerol and Tween 80. The drug showed low solubility in distilled water, 0.1N HCl, glycerol and showed significant solubility in Tween 80 and propylene glycol. Hence propylene glycol was selected as non -volatiles solvent. The results were showed in fig 1.

Flow Properties: The flow properties of liquisolid powders were analysed before compression to compact. By using bulk density, tap density, hausners ratio and Carr's index. The hausners ratio below 1.25 shows good flowability for direct compressible tablet. The Carr's index is between 12 to 21 shows good to fair flowability. The angle of repose between 31 to 40 shows good to fair flowability of powder. The Hausners ratio of batch F5 shows more than normal. The Carr's index of batch F4 and F5 shows more values. The angle of repose of the all batches shows acceptable results reported in table 2,3.

FTIR Interference Study The FTIR spectrum of pure Nateglinide showed an absorption band at 2924 cm-1 (aliphatic C-H stretching; asymmetric), 2859 cm-1 (aliphatic CH stretching; symmetric, 1713 cm-1 (C = O stretching for Ketone), 3064 cm-1 (aromatic C-H Stretching), 3086 cm-1 (aromatic C=H Stretching). The FTIR spectrum of physical mixture and pure Nateglinide show all the peaks for drug and other excipients, hence no interaction was observed between them. The results were shown in Fig.2, and 3.

X-Ray Diffraction study X-ray diffraction patterns in Fig.4 and 5 revealed that pure Nateglinide was clearly in crystalline state as it showed sharp distinct peaks notably at 2θ diffraction angles of 5θ, 10.5θ, 12θ, 15θ and 19θ. In the Fig.5 clearly show that the disappearance of 2θ angles in the liquisolid compact formulation is evident that crystalline pure drug is converted into amorphous state due to its molecular solubilization of the drug in the non-volatile solvent, which proves the enhancement of solubility by this technique.

Estimation of drug content

The percentage drug content for all the prepared dispersions were found to be in the range of 94.58±1.27 to 99.84±1.78 indicating uniform drug distribution. results showed in table Among all formulations uniform drug distribution.

Post-compression evaluation of liquisolid compacts

The diameter and thickness of the tablets were varied with all batches because of the all bathes having variable in their weight. The uniformity of contents of tablets is between 89.44 to 100.97% which is acceptable for further study. Hardness of tablet was determined by Monsanto hardness tester hence average hardness was found to be between 3.7 to 4.1 kg/cm2, The disintegration time test revealed that the all formulations disintegrated in less than 250 seconds, only the conventional tablet shows more time to disintegrate. All the Nateglinide liquisolid tablets had acceptable friability which had no exceed than the 1%, no tablet was crack or broken in all batches. Since all the prepared batches shows acceptable durability and withstand abrasion in handling, packaging and shipment.

***In-Vitro* Release Study**

Initially dissolution studies of pure NTG were carried out in 0.01 N Hcl with 0.5w/v SLS. The % release data was given in table and profile was shown in fig. The cumulative percent release of pure NTG at 60 min was found to be 27.87% indicating the slower dissolution rate of drug.

Among the liquidsolid compacts using Lactose as carrier and Aerosil 200 as coating material, F1 containing 35mg aerosil showed 96.78% release at the end of 60min indicating enhanced dissolution rate of NTG compared to 27.87% of pure NTG at the same time point. Formulations F2 and F3 containing 25 and 30 mg of Aerosil showed 92.46 and 94.59 % NTG release respectively at the end of 60min.From the results obtained it was found that formulations prepared by liquid solid technique showed an increased dissolution rate of NTG

compared to pure NTG. Among the formulations prepared by liquid solid technique F1 containing 35mg of Aerosil showed superior dissolution rate compared to formulations containing 30 and 25 mg of Aerosil indicating that increasing in coating material concentration increase the dissolution rate. The dissolution rate was in the order of F1>F3>F2.

Formulations F4 F5 and F6 prepared using Lactose as carrier and cab o silica as coating material showed 92.31, 86.03 and 91.12% release respectively at the end of 60 min. Formulations with cab o silica showed lower release rates compared to formulations with aerosil as coating material. This may be due to lesser porosity of cab o silica compared to aerosil.

Formulations F7, F8 and F9 prepared using Lactose as carrier and syloid 244FP as coating material showed 98.58, 92.45 and 95.46% release respectively at the end of 60 min. formulations with syloid showed superior dissolution rates compared to formulations prepared with arosil and cab o silica. Higher dissolution rates with syloid can be attributed to porous nature of syloid compared to aerosil and cab o silica resulting in improved flow properties and efficient release of NTG.

The improved dissolution rates obtained with liquid soild technique compared to pure drug can be attributed to significantly increased surface of the molecularly dispersed NTG in the liquisolidtablets. Liquisolid tablets contain a solution of the drug in suitable solvent (NTG in propylene glycol), the drug surface available for dissolution is tremendously increased. In essence, after tablet disintegration, the liquisolid primary particles suspended in the dissolving medium contain the drug in a state of molecular dispersion, whereas the directly compressed tablets are merely exposing micronized drug particles. In other words, in the case of liquisolid tablets, the surface of drug available for dissolution is related to its specific molecular surface which by any means, is much greater than that of the NTG particles delivered by the plain, directly compressed tablets.

Among the different carriers used syloid 244FP showed significantly improved dissolution properties which may be due to highly porous nature of syloid resulting in improved flow properties along with efficient release of drug from the dosage form. Among the liquisolid compacts increase in coating concentration resulted in increase in dissolution rates which may be due to increased wettability of drug with dissolution medium.

Over all NTG liquisolid compacts displayed significantly improved dissolution properties compared to pure NTG. Such enhanced drug dissolution rates may be mainly attributed to the fact that this practically water insoluble drug is already in solution in propylene glycol, while at the same time it is carried by the powder particles of the liquisolid system. Since the drug is molecularly dispersed within its water-miscible liquid vehicle, its release is accelerated due to its markedly increased wettability and surface availability to the dissolving medium. Such higher drug dissolution rates displayed by liquisolid compact may also imply enhanced oral bioavailability.

CONCLUSION

The research work done for the novel formulation of high permeable and low solubility antihyperglycemic drug NTG by liquisolid compact technology was successful. As the drug will be presented in a state of molecular dispersion, the formulation disintegrates in dissolution media. This will increase the effective surface area of the particles available for dissolution. Comparison to marketed formulation our optimized formulation showed better dissolution profile. Hence, the liquisolid compact is the promising tool for enhancement of solubility of water insoluble drug.

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