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Enahancement of Dissolution Properties of Glibenclamide by using Liquisolid Compact Technique

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ABSTRACT

Glibenclamide, a sulfonylurea derivative is widely used as hypoglycaemic agent. Glibenclamide is a highly permeable class II drug. Hence, rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal (GI)tract. Therefore, the Liquisolid compact of Glibenclamide has been prepared for the enhancement of dissolution of Glibenclamide. Neusilin US2 was selected as carrier material and Aerosil 200 was selected as coating material. A Central composite factorial design was applied to optimize the drug release profile systematically. The amounts of drug (%) in PEG 400 (X_1) and Excipient ratio, R (X_2) were selected as independent variables. Angle of repose (Y_1), Hardness (Y_2) and CPR at 10 min (Y_3) were seleced as dependent variables. All the batches of Liquisolid compacts showed significance improvement in dissolution of Glibenclamide. Various dissolution parameters like DP_{10min}, $\%DE_{10min}$ and MDT of optimized batch and direct conventional tablet were compared. DSC and XRD analysis of pure Glibenclamide, physical mixture and final formulation indicated that the drug was solubilized in non-volatile vehicle and solubilization of Glibenclamide was the main cause of enhancement of solubility of Glibenclamide. Storage of the prepared formulations at 45°C for one month showed no any chemical incompatibility. It was concluded that, Liquisolid compact technique can be a simple and effective to enhance the dissolution of poorly water soluble drug.

Introduction

Over the years, various techniques have been employed to enhance the dissolution profile and, in turn, the absorption efficiency and bioavailability of water insoluble drugs and/or liquid lipophilic medications. The use of water-soluble salts and polymorphic forms, the formation of water-soluble molecular complexes, drug micronization, solid dispersion, co-precipitation, lyophilization, microencapsulation, and the inclusion of drug solutions or liquid drugs into soft gelatin capsules are some of the major formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs, however, among them, the technique of ‘‘liquisolid compacts” is one of the most promising techniques(1-3).

From the historical point of view, liquisolid compacts were evolved from ‘Powdered Solutions’ which depended on preparing a true solution of the drug in a high boiling point, water-miscible solvent, which was carried out on the extensive surface of an inert carrier. Also have a acceptably flowing and compressible powdered forms of liquid medications (that implies liquid lipophilic (oily) drugs, or water-insoluble solid drugs dissolved in suitable water-miscible nonvolatile solvent systems) (4-6).

A formulation mathematical model by Spireas (7) of liquisolid systems enabled calculation of the appropriate amounts of both the carrier and the coating material to be added to produce acceptable flow and compressibility. This model of liquisolid systems is based on the Flowable (U-value) and the Compressible (W-number) Liquid Retention Potentials of the constituent powders. The Flowable Liquid Retention Potential of a powder is defined as the maximum amount of a given non-volatile liquid that can be retained inside its bulk (w/w) while maintaining acceptable flowability. This U-value is determined by recording powder flow(8).

The Compressible Liquid Retention Potential of a powder is the maximum amount of liquid, the powder can retain inside its bulk (w/w) while maintaining acceptable compactability, to produce compacts of suitable hardness, and friability, with no liquid squeezing out phenomenon during the compression process. The W-number of powders can be determined by using pacticity theories (9).

The excipient ratio R of the powder substrate is defined in the following equation 1 as:

R ¼ Q=q ð1Þ equ.1

where R is the fraction of the weights of carrier Q and coating q materials present in the formulation. The amounts of excipients used to prepare the tablets are related to the amount of liquid medication W through the ‘Liquid Load Factor’ (Lf) as shown in the following equation 2:

Lf ¼ W =Q ð2Þ equ.2

For a given excipient ratio R, there exists a specific Flowable Lf factor denoted as ULf, as well as a specific compressible Lf factor denoted as wLf.

The optimum liquid load factor Lo that produces acceptable flow and compression characters is equal to either ULf, or wLf, whichever possesses the lower value.

Glibenclamide, a sulfonylurea derivative, widely used as hypoglycaemic agent. Chemically it is 1-[[p- [2-(5-chloro-o-anisamido)-ethyl] phenyl]-sulfonyl]-3- cyclohexylurea. For poorly soluble, highly permeable (class II) drugs (like

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Glibenclamide), the rate of oral absorption is often controlled by the dissolution rate in the gastrointestinal (GI) tract. Therefore, together with permeability, the solubility and dissolution behaviour of a drug are key determinants of its oral bioavailability. This undesired property, may also increase the amount of GI damage, due to long contact of drug with the mucous of GI. Many studies were done in trial to improve the bioavailability and permeability as well as reduce mucosal toxicity of Glibenclamide. The liquisolid technique was adopted in an attempt to improve the dissolution properties, and hence, the bioavailability of Glibenclamide.

In present work, improve dissolution of Glibenclamide is done using Liquisolid compact in which various carrier materials like Neusilin US2, Avicel PH 101, lactose and magnesium aluminium silicate, various coating materials like Aerosil 200, silica and talc and various non-volatile vehicle like PEG 400, glycerin, tween 80, PEG 200 and propylene glycol were utilized in order to achieve the goal. The flowability and compressibility of liquisolid compacts were addressed simultaneously in the ‘‘new formulation mathematical model of liquisolid systems”, which was used to calculate the appropriate quantities of the excipients (carrier and coating materials) required to produce acceptably flowing and compressible powders based on new fundamental powder properties called the flowable liquid retention potential (U-value) and compressible liquid retention potential (w-number) of the constituent powders.as well suitable ratio of carrier and coating material can be fixed by using suitable statistical design. Final liquisolid formulation can be compare with directly compressed Glibenclamide tablet.

Experimental

Material

Glibenclamide and Neusilin US2 procure gift sample by Prudence Pharma Camp, Ankleshwar. Potassium dihydrogen orthophosphate obtained from Sisco Research laboratories Pvt. Ltd. Mumbai, India. Cross povidone procure sample from Yarrow Chem. Products, Mumbai, India. Potassium bromide powder(IR grade) as a purchage from Merck Specialities Pvt. Ltd. Mumbai, India. Polyethylene Glycol 400, Sodium Hydroxide, Silicon dioxide all reagent are used analytical grade

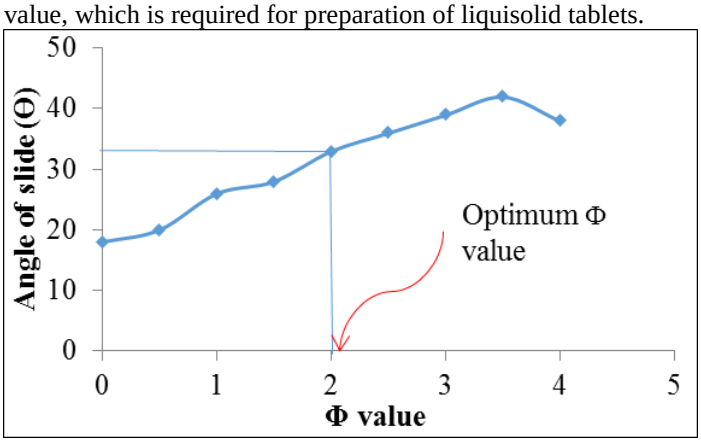
Methodology

Selection of non-volatile vehicle (10)

Selection of non-volatile vehicle for formulation of liquisolid compact was done based on solubility of drug in various non-volatile liquid. Solubility study of Glibenclamide was carried out in PEG 400, Glycerine, Propylene Glycol, PEG 200,Tween 80, Distilled water, Phosphate buffer 7.4 and 0.1 N HCl. excess amount of drug added to prepare saturated solution in respective vehicles and shaking on the rotary shaker bath for 48 h at 25° C under constant vibration at 100 RPM. Filtered samples (1 ml) were diluted appropriately with phosphate buffer pH 7.4 and Glibenclamide was determined spectro photometrically at 230 nm. The average value of three trials was taken. A non-volatile liquid which was able to solubilised highest amount of drug, selected as a non-volatile vehicle for liquisolid compact.

Selection of carrier material (10)

Carrier material was selected based on its optimum Φ-value. Optimum Φ-value of carrier material can be calculated by measuring angle of slide of several uniform liquid vehicle-powder mixture which contain constant amount of powder material with increasing amount of liquid vehicle. The Φ-values of mixture were plotted against the corresponding θ. An angle of slide (for measurement Ten grams of carrier were weighed accurately and placed at one end of a metal plate with a polished surface. This end was raised gradually until the plate made an angle with the horizontal at which the powder was about to slide. This angle h represented the angle of slide.) It was taken as a measure for the flow characters of powders. An angle of slide corresponding to 33^0corresponded to optimal flow properties of a powder admixture represented the optimum Φ-value, which is required for preparation of liquisolid tablets.



The carrier material which show highest optimum ϕ-value with selected liquid vehicle was selected as carrier material.

Selection of coating material (10)

Selection of coating material done same as the carrier material based on its optimum ϕ-value of coating material. The coating material which show highest optimum ϕ-value with selected liquid vehicle was selected as coating material.

Method of preparation of liquisolid compact

The desired quantities previously weighed of the drug (Glibenclamide) and the liquid vehicle (PEG 400) were mixed and heated with constant stirring, the solution was then sonicated for 15 min, to obtain homogenous drug solution . Next, the calculated weights (W) of the resulting hot liquid medications were incorporated into the calculated quantities of the carrier material(Q), after mixing, the resulting wet mixture was then blended with the calculated amount of the coating material(q) using a standard mixing process to form simple admixture. Later on, each selected liquisolid formula was blended with 5% of the disintegrant Explotab (cross providone) and the prepared liquisolid systems that have acceptable flowability and compressibility were compressed into cylindrical tablets of desired weight using a single punch tablet press machine.

Method of preparation of conventional direct compressible tablet and capsule of Glibenclamide

For preparation of conventional direct compressible tablet (DCT), Glibenclamide was mixed with calculated amount of carrier and coating material. To the above mixture superdisintegrant was added and mixed for a period of 10 to 20 min in a mortar. The final mixture was compressed using a single punch tablet press machine to achieve desire tablet hardness. For capsule above calculated amount of final mixture was packed in hard gelatin capsule shell.

Central composite design

A Central composite design was perform to study the combine effect of both independent variables on the dependent variable as well as effect of dependent variable on independent variable. In this design, two factors were evaluated.

In the present investigation, Amount of drug (% w/w) in PEG 400 and Excipient (carrier : coating) ratio were selected as independent variables. The experimental design and actual value for coded value was shown in table 1 & 2 respectively.

Angle of repose of powder (Y_1), CPR at 10 min (Y_2) and Hardness of tablet (Y_3) were selected as dependent variables.
Data were further analyzed by Microsoft Excel ®2007 for regression analysis. Analysis of variance (ANOVA) was implemented to assure that there was no significant difference between the developed full model and reduced model. Response surface plots were plotted to study response variations against two independent variables using Design Expert® Version 8 software.

Evaluation of liquisolid compact

Precompression studies of the prepared liquisolid powder systems (11)

compression of the formulations into tablets, to ensure the suitability of the selected excipients with drug(Glibenclamide), various studies were performed including differential scanning calorimetry (DSC), X-ray diffraction (XRD), and scanning electron microscope (SEM). In addition, so as to select the optimal formula for compression, flowability studies were also carried out.

Differential scanning calorimetry (DSC):

DSC was performed using Shimadzu differential scanning calorimeter, DSC-60 (Shimadzu, Kyoto, Japan), in order to assess the thermotropic properties and the thermal behaviors of the drug (Glibenclamide), Neusilin US2, Aerosil 200, as well as the liquisolid system prepared. Samples of 3–4 mg of the pure famotidine or the above-mentioned samples were sealed in a 50µl aluminum pans at a constant heating rate of 5ºC/min. in the scanning temperature range of 35 to 250ºC. Empty aluminum pans were used as references and the whole thermal behaviors were studied under a nitrogen purge.

Fourier transforms IR spectroscopy

Drug and excipients were analysed by IR spectral studies by taking FT-IR (Thermo scientific, Japan) of powder in the range of 400-4000cm^{-1}. Spectra were recorded for pure drug, excipients, physical mixture and final formulation.

Powder XRD analysis

The physical state of Glibenclamide in the Liquisolid formulations and physical mixture were evaluated by X-ray powder diffraction (XRPD). Diffraction patterns of pure Glibenclamide, physical mixture and Liqisolid formulation were analysed with a X-ray Diffractometer where the tube anode was Cu with K_= 15,405 A. The pattern was collected with a tube voltage of 30 kV and a tube current of 15 mA of in step scan mode (4°/min). The samples were analysed at a 2° angle range of 0 to 60°.

The flowability of a powder is of critical importance in the production of pharmaceutical dosage forms in order to get a uniform feed as well as reproducible filling of powder material in cavity of dies, otherwise, high dose variations will occur. In order to ensure the flow properties of the liquisolid systems that will be selected to be compressed into tablets and further evaluated, angle of repose measurements, Carr's index and Hausner's ratios were adopted. In the angle of repose method, the fixed height cone method was adopted ($\tan\theta = h/r$ Where, h = height of heap r = radius of heap).The procedure was done in triplicate and the average angle of repose was calculated for each powder. In the bulk density measurements, fixed weight of each of the liquisolid powder formula prepared were placed in a graduated cylinder and the volume occupied was measured and the initial bulk density DBmin was calculated. The cylindrical graduate was then tapped at a constant velocity till a constant volume is obtained when the powder is considered to reach the most stable arrangement, the volume of the powder was then recorded as the final bulk volume, then the final bulk density DBmax was calculated. Carr's compressibility index was then calculated according to the equation 3.

$$Carr's\ index\ \% = \frac{DB\ max - DB\ min}{DBmax} \times 100 \qquad equ.3.$$

in addition, Hausner's ratio was calculated from the equation 4.

$$Hausner\ ratio = \frac{DB\ max}{DBmin} \times 100 \qquad equ.4.$$

The experiments and calculations were done in triplicate and Carr's compressibility index and Hausner's ratio with the corresponding standard deviations for each of the prepared formula were then calculated.

Evaluation of Glibenclamide liquisolid tables and direct compressible tablet (11)

To each of the selected formulae, 5% filler material added and then, the tablets were compressed using a rotary tablet press machine with 12 mm punch and die (Karnavati Engineering, Ahmedabad, India). The prepared Glibenclamide liquisolid tablets of the selected formula were further evaluated. Glibenclamide content in different liquisolid tablet formulations was determined by accurately weighing 10 tablets of each formula individually. Each tablet was then crushed and dissolved in 00 ml phosphate buffer pH7.4 , then, the solution was filtered, properly diluted, and then measured spectrophotometrically using Spectrophotometer UV-1700 (Shimadzu, Kyoto, Japan) at λmax of Glibenclamide (230 nm), thereafter, the Glibenclamide formula was measured using Digital tablet friability tester (Electro lab – EF 2, USP, Mumbai, India.), and the percentage loss in weights were calculated and taken as a measure of friability. The hardness of the liquisolid tablets prepared was evaluated using monsanto hardness tester, the mean hardness of each formula was determined. The disintegration time was performed using USP disintegration tester, VTD-3 (Progressive Incorp., Bombay, India) and following its procedure. Finally, the in vitro dissolution studies were carried out and the dissolution rate of Glibenclamide from liquisolid tablets was determined using USP Dissolution Test Apparatus II (Electro lab TDT 060P, USP, Mumbai,India) containing 900 ml of phosphate buffer pH7.4 at 37 ± 0.5 ºC. This was done by placing a tablet of each formula, containing an equivalent of 20 mg Glibenclamide in the basket fitted with stainless steel screen of pore size 100 lm. to prevent fine particles from emerging. The basket was then rotated at 50 rpm, then, 1ml aliquots from the dissolution medium were withdrawn at predetermined time intervals, the aliquots withdrawn were filtered through 0.45 µm Millipore membrane filter diluted and analyzed spectrophotometrically for their famotidine content at λmax 230 nm against a blank of phosphate buffer pH7.4. The experiments were done in triplicates for each of the selected liquisolid formula and for conventional directly-compressed Glibenclamide tablets containing also an equivalent of 20 mg Glibenclam ide for comparison.

The dissolution data was analyzed by model independent parameters calculated at different time intervals, such as dissolution percent (DP), dissolution efficiency (%DE) and Mean dissolution time (MDT). DP at different time interval and can be obtained from present dissolution vs time profile data.
The concept of dissolution efficiency (%DE) was proposed by Khan and Rhodes in 1975. Dissolution efficiency is a parameter for the evaluation of in vitro dissolution data. Dissolution efficiency is defined as the area under curve (AUC) up to certain time(t) expressed as percentage of the area of the rectangle described by 100% dissolution in the same line equation 5. Explain dissolution efficiency.

$$\%DE = \frac{\int_0^t y \times dt}{y100 \times t} \times 100 \qquad equ.5.$$

Here, y is the drug percent dissolved at time t

MDT reflects the time for the drug to dissolve and is the first statistical moment for the cumulative dissolution process that provides an accurate drug release rate. It is accurate expression for drug release rate. A higher MDT value indicate greater drug retarding ability. In order to understand difference in dissolution rate of DCT and Liquisolid tablet, obtained dissolution data were fitted into following equation 6.

$$MDT = \frac{\sum_j^n tj\Delta Qj}{\sum_{j=1}^n \Delta Qj} \qquad equ.6.$$

Here, j is the sample number, n the number of time increments considered, t^j is the time at midpoint between tj and tj−1, and ΔQj the additional amount of drug dissolved in the period of time tj and tj−1.

Result and discussion

Selection of non-volatile vehicle

Solubility of Glibeclamide in various non volatile solvent shown in fig.1 from the solubility studies it was found that Glibenclamide showed highest solubility in PEG 400 (15.11 mg/ml). Hence, PEG 400 was selected as non-volatile vehicle for Liquisolid compact system.

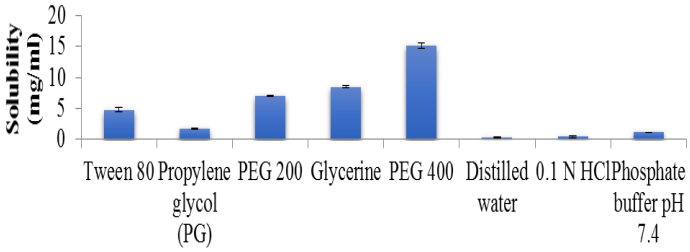


Figure 1. solubility of Glibeclamide in various non-volatile solvent

Selection of carrier material

Carrier material can be selected based on there Φ value from the primary studies it was found that Neusilin US2 shows the highest Φ value (0.3). Hence, Neusilin US2 was selected as carrier material. Φ value of various carrier material with nonvolatile solvent can be shown in table.3 and in figure 2.

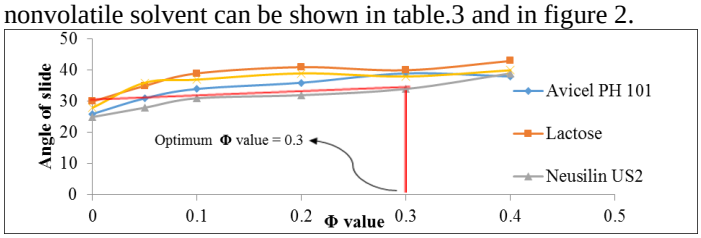


Fig 2. Graph of Angle of slide v/s Φ value of carrier material

Selection of coating material

Coating material can be selected based on there Φ value from the primary studies it was found that Aerosil 200 shows the highest Φ value (0.3). Hence, Aerosil 200 was selected as coating material. Φ value of various coating material with nonvolatile solvent can be shown in table.4 and in figure 3.

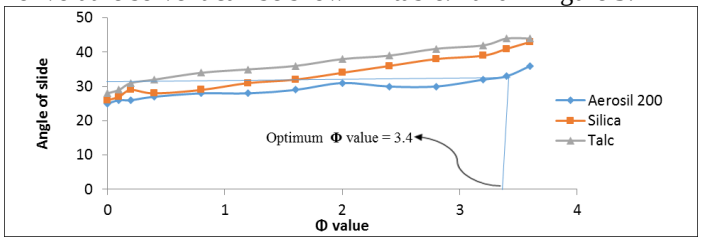


Fig 3. Graph of Angle of slide v/s Φ value of coating material

Selection of level of independent variables

Here, in central composite design, amount of drug (% w/w) in PEG 400 (X_1) and excipients ratio (X_2) were selected as independent variables. Solubility of Glibenclamide in PEG 400 is 15.1 mg/ml and dose of Glibenclamide is 5 mg. Hence, 296 mg of PEG 400 is sufficient to dissolve whole amount of drug. So, as a -1 (minimum) level of amount of drug (% w/w) (X_1) was selected 1.5%, in which amount of PEG 400 is 333 mg. 2% and 2.5% was selected as mean and maximum level of X_1. Based on literature review for excipients ratio, R (X_2), 5, 10 and 15 were selected as minimum, mean and maximum level.

Formulation of liquisolid compact

Final formula for factorial Liquisolid tablet batches

Formulation for factorial batches with suitable concentration shown in table.5.

Regression analysis of result of factorial batches

A stepwise multivariate linear regression was performed to evaluate the observations. The statistical evaluation of the results was carried out by analysis of variance (ANOVA) using Microsoft Excel® Version 2007.

The equation representing the quantitative effect of the formulation variables on the measured responses are shown below:

1. Angle of repose (Y_1)

$Y_1 = 30.74 - 2.74\ X_1 + 1.48\ X_2 - 0.28\ X_1X_2 + 0.71\ X_1^2 - 0.83\ X_2^2$

2. Hardness (Y_2)

$Y_2 = 4.79 + 1.14\ X_1 + 0.12\ X_2 + 0.032\ X_1X_2 + 0.0018\ X_1^2 - 0.048\ X_2^2$

3. CPR at 10 min (Y_3)

$Y_3 = 86.59 - 5.49\ X_1 - 1.15\ X_2 + 0.29\ X_1X_2 - 0.75\ X_1^2 - 0.52\ X_2^2$

Coefficients with one factor (X_1 or X_2) represent the effect of that particular factor, while coefficients with more than one factor (X_1X_2) and these with second order terms (X_1^2 or X_2^2) represent the interaction between these factor and the quadratic nature of the phenomena, respectively. A positive sign in front of the terms indicates a positive effect, while a negative sign indicates a negative effect of the factor.

The fitted polynomial equations (Full and Reduced model) relating the responses to the transformed factors are shown in the following Table 7 The polynomial equations could be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carried, i.e. positive or negative. The significant factors in the equations were selected using a stepwise forward and backward elimination for the calculation of regression analysis. The term of full model having non-significant p value (>0.05) showed negligible contribution in obtaining dependent variables and thus are neglected.

Above Table 8, shows the result of analysis of variance (ANOVA), performed to identify insignificant factors. It was concluded that the interaction terms where P>0.05, did not contribute significantly to the prediction of desired responses and hence could be omitted from the full model. From the Table 8, it was concluded that Fcal < Ftab, which was an indication of validation of reduced model.

The change in responses as a function of X_1 and X_2 is depicted in the form of contour and response surface plot based on full factorial design. The data of all the 12 batches of factorial design were used for generating interpolated values using Design Expert® Software 8.0.5.2 Trial program (Stat-Ease, inc., Minneapolis, MN). High level of X_1 and low level of X_2 were found to be favorable conditions for obtaining good flow property whereas, High level of X_1 was favorable for getting

higher hardness while X_2 was not much effective in hardness of tablet because of smaller coefficient of X_2 (0.12). For CPR at 10 min X_1 was much effective than X_2. Here, for CPR at 10 min low level of X_1 and X_2 were favorable for obtaining highest drug release.in figure 4. Shown contour and response surface plot.

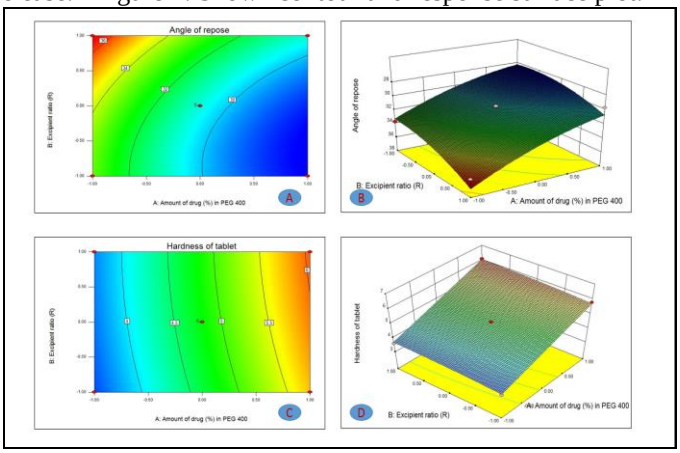


Fig 4. A. Effect of dependent variable on angle of repose B. Counter plot for angle of repose of powder mixture. C. Effect of dependent variable on hardness D. Counter plot for hardness

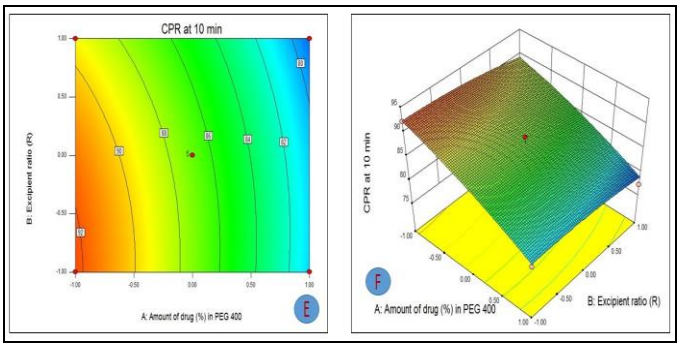


Fig 4 E. Effect of dependent variable on CPR at 10min. F. Counter plot for CPR at 10min

From Fig.4 A&B concluded that, by increasing amount of drug (%w/w) resulted into decrease in angle of repose, this might be because, as the amount of drug (%w/w) increases, amount of PEG 400 decreases, so powder became less cohesive and posses good flow property. While by increasing the excipient ratio (R), the angle of repose increases, this is due to, as the excipient ratio increases, amount of Aerosil 200 decreases, so flow property of powder decrease.

From Fig.4.C&D concluded that, when the amount of drug (%w/w) was at higher level, hardness of tablet was higher. This might be because of least amount of PEG 400, as the amount of PEG 400 in formulation increased, the compressibility of powder material decreased. As the excipient ratio (R) increased, hardness of tablet was also increased, this was because as the excipient ratio (R) increased, amount of Neusilin US2 also increased which have good compressibility property.

From Fig.4 E&F concluded that, as the amount of drug (% w/w) increased, CPR decreased. This is might be because of as the amount of drug (% w/w) increased, amount of PEG 400 decreased. Higher amount of PEG 400 resulted in more amount of drug got solubilized in it. Moreover, PEG 400 also increased wetting property of drug and effect of co-solvency too. So, higher amount of PEG 400 enhanced the dissolution of drug. As the excipients ratio increased resulted into higher CPR due to the higher amount of Neusilin US2 but its effect was less significant than amount of drug (% w/w) in PEG 400.

Precompression studies of the prepared liquisolid powder systems

Differential scanning calorimetry (DSC)

One of the most classic applications of DSC analysis is the determination of the possible interactions between a drug entity and the excipients in its formulation; it is very important to establish the existence of any incompatibilities during the preformulation stage to ensure the success of the subsequent stability studies. Fig. 5 reveals the thermal behaviors of the pure components together with the thermal behavior of the final liquisolid system prepared. Glibeclamide peaks are clear in its DSC thermogram (Fig. 5a) demonstrating a sharp characteristic endothermic peak at 175.96 °C corresponding to its melting temperature (Tm); such sharp endothermic peak signifies that Glibeclamide used was in pure crystalline state. The thermograms in fig 5b displayed complete disappearance of characteristic peaks of Glibeclamide; a fact that agrees with the formation of drug solution in the liquisolid powdered system, i.e., the drug was molecularly dispersed within the liquisolid matrix. That was accompanied by the formation of a new endothermic peak that might correspond to the melting and decomposition of the whole liquisolid system. Such disappearance of the drug peaks upon formulation of the liquisolid system who declared that the complete suppression of all drug thermal features, undoubtedly indicate the formation of an amorphous solid solution.

Fourier transform infrared (FTIR) spectroscopy

The FTIR spectra of the pure drug, excipients and physical mixture were recorded in between 400-4000 cm^{-1}. The Glibenclamide spectrum is shown in Fig.6. All the characteristic peaks of Glibenclamide at 3367.5, 3315.19 due to amide group. 1617.82 due to urea carbonyl stretching and at 1521.91 due to urea N-H stretching, 1341.57 & 1158.99 peak due to SO2 stretching vibration.. FTIR spectrums of various excipients and physical mixture are shown in Fig.6.A. All the principal peaks of Glibenclamide are found in the spectra of physical mixture. There is no disappearance of any characteristic peaks of pure drug in the physical mixture spectrum, which confirms the absence of chemical interaction between drug and polymer.

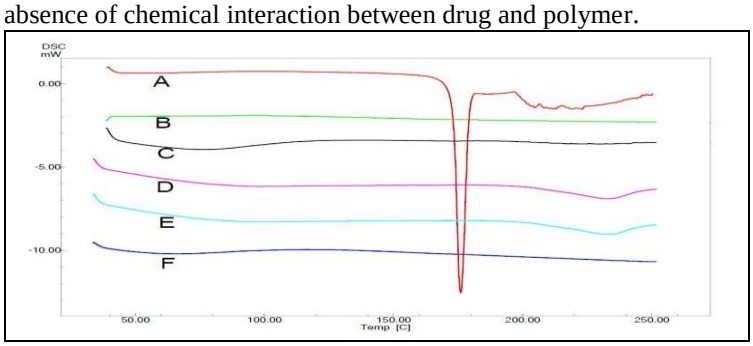


Fig 5. DSC thermogram of (A) Glibenclamide, (B) Final formulation, (C) Physical mixture, (D) Neusilin US2, (E) Crosspovidone and (F) Aerosil 200

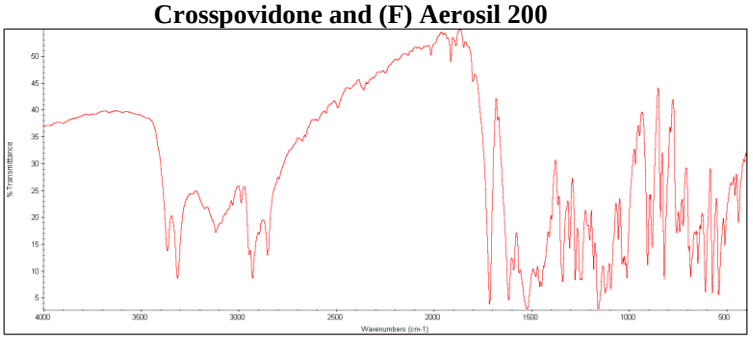


Fig 6. FTIR spectra of Glibeclamide

Table 1. Experiment design batches

Batch code	X1	X2	Batch code	X1	X2	Batch code	X1	X2
F1	-1	-1	F5	0	0	F9	0	-1.414
F2	+1	-1	F6	0	0	F10	0	+1.414
F3	-1	+1	F7	-1.414	0	F11	0	0
F4	+1	+1	F8	+1.414	0	F12	0	0

Table 2. Actual value for coaded value X_1 and X_2

Level	-1.414	-1	0	+1	+1.414
Value of X1 (%)	1.293	1.5	2	2.5	2.707
Value of X2	2.93	5	10	15	17.07

Where X1:amount of drug in PEG400(%), X2: carrier to coating ration

Table 3. Value of Angle of slide and Φ value of various carrier material

Φ value	0	0.05	0.1	0.2	0.3	0.4
Avicel pH101	26	31	34	36	39	38
Lactose	30	35	39	41	40	43
Neusilin US2	25	28	31	32	34	39
Mg. aluminium silicate	28	36	37	39	38	40

Table 4. Value of Angle of slide and Φ value of various coating material

Φ value	0	0.1	0.2	0.4	0.8	1.2	1.6	2.0	2.4	2.8	3.2	3.4	3.6
Aerosil 200	25	26	26	27	28	28	29	31	30	30	32	33	36
Silica	26	27	29	28	29	31	32	34	36	38	39	41	43
Talc	28	29	31	32	34	35	36	38	39	41	42	44	44

Table 5. Final formulation for factorial batches

Batch code	Drug (mg)	PEG 400	Neusilin US2	Aerosil 200	Cross povidone
F1	5	333.33	336.73	67.34	36.95
F2	5	200	204.08	40.81	22.49
F3	5	333.33	626.66	41.77	50.17
F4	5	200	379.79	25.31	30.50
F5	5	250	390.62	39.06	34.23
F6	5	250	390.62	39.06	34.23
F7	5	386.7	878.86	87.88	67.92
F8	5	184.7	419.78	41.97	32.57
F9	5	250	198.41	67.71	26.05
F10	5	250	836.12	48.98	57.00
F11	5	250	390.62	39.06	34.23
F12	5	250	390.62	39.06	34.23

Table 6. Result of dependant variables

Batch code	Independent variable		Response		
	X1	X2	Y1	Y2	Y3
F1	-1	-1	33.69 ± 1.22	3.45 ± 0.02	92.19 ± 1.95
F2	+1	-1	29.05 ± 1.98	5.82 ± 0.11	80.12 ± 1.59
F3	-1	+1	35.53 ± 2.03	3.6 ± 0.02	88.14 ± 2.08
F4	+1	+1	29.74 ± 1.41	6.1 ± 0.10	77.23 ± 1.85
F5	0	0	30.46 ± 2.02	4.8 ± 0.08	85.19 ± 1.41
F6	0	0	31.21 ± 2.32	4.78 ± 0.09	86.25 ± 1.85
F7	-1.414	0	36.52 ± 2.74	3.3 ± 0.03	93.42 ± 1.51
F8	+1.414	0	28.39 ± 1.74	6.32 ± 0.15	78.56 ± 2.33
F9	0	-1.414	29.39 ± 1.29	4.5 ± 0.08	87.25 ± 2.30
F10	0	+1.414	36.02 ± 1.85	4.92 ± 0.11	85.65 ± 1.86
F11	0	0	30.83 ± 1.44	4.82 ± 0.09	86.69 ± 2.09
F12	0	0	30.46 ± 1.82	4.79 ± 0.08	88.23 ± 2.11

Table 7. Result of regression analysis of factorial batches of Glibenclamide liquisolid tablet

Model	b_0	b_1	b_2	b_{12}	b_1^1	b_2^2	R^2
Angle of repose (Y_1)							
FM	30.74	-2.74	1.48	-0.28	0.71	-0.83	0.923
RM	31.77	-2.74	1.48	---	---	---	0.848
Hardness (Y_2)							
FM	4.79	1.14	0.12	0.032	0.0018	-0.048	0.995
RM	4.76	1.12	0.12	---	---	---	0.993
CPR at 10 min (Y_3)							
FM	86.59	-5.49	-1.15	0.29	-0.75	-0.52	0.946
RM	85.74	-5.49	-1.15	---	---	---	0.889

Table 8. Result of ANOVA

Angle of repose						
Regression	D.F.	SS	MS	F	R^2	
FM	5	84.63	16.92	14.39	0.9230	F_{cal}= 1.9282
RM	2	77.82	38.91	25.25	0.8487	F_{tab}= 4.75
Error						D.F= (3,6)
FM	6	7.057	1.176	Fcal < Ftab, Hence model is validated.		
RM	9	13.86	1.540			
Hardness						
Regression	D.F.	SS	MS	F	R^2	
FM	5	10.59	2.12	256.30	0.9953	F_{cal}= 0.8034
RM	2	10.57	5.28	684.37	0.9934	F_{tab}= 4.75
Error						D.F=(3,6)
FM	6	0.04960	0.008268	Fcal < Ftab, Hence model is validated.		
RM	9	0.06953	0.007727			
CPR at 10 min						
Regression	D.F.	SS	MS	F	R^2	
FM	5	257.38	51.47	21.35	0.9467	F_{cal}=1.14
RM	1	241.95	241.95	80.90	0.889	F_{tab}=9.276
Error						D.F=(3,3)
FM	6	14.46	2.411	Fcal < Ftab, Hence model is validated		
RM	10	29.90	2.990			

Table 9. Pre compression flowability parameter of Liquisolid powder blend

Batch	Angle of repose*	Carr's index*	Hausner's ratio*
F1	33.69 ± 1.22	20.83 ± 0.89	1.26 ± 0.03
F2	29.05 ± 1.98	15 ± 0.72	1.17 ± 0.12
F3	35.53 ± 2.03	17.39 ± 1.12	1.21 ± 0.08
F4	29.74 ± 1.41	19.04 ± 1.35	1.23 ± 0.05
F5	30.46 ± 2.02	21.73 ± 1.69	1.27 ± 0.09
F6	31.21 ± 2.32	18.18 ± 1.23	1.22 ± 0.11
F7	36.52 ± 2.74	22.22 ± 2.03	1.28 ± 0.07
F8	28.39 ± 1.74	15 ± 1.52	1.17 ± 0.05
F9	29.39 ± 1.29	14.28 ± 1.63	1.16 ± 0.05
F10	36.02 ± 1.85	22.22 ± 2.03	1.28 ± 0.04
F11	30.83 ± 1.44	21.73 ± 1.58	1.27 ± 0.09
F12	30.46 ± 1.82	17.39 ± 1.56	1.21 ± 0.06

Table 10. Post compression parameters of Liquisolid tablet

Batch	% Drug content*	Thickness in mm*	%Friability*	Hardness* (Kg/cm^2)	Average weight# (mg)
F1	98.74 ± 0.57	6.74 ± 0.01	0.85	3.45 ± 0.02	776.2 ± 3.52
F2	99.27 ± 1.25	4.8 ± 0.0	0.70	5.82 ± 0.11	473.32 ± 2.03
F3	97.37 ± 0.65	5.11 ± 0.04	0.61	3.6 ± 0.02	1053.4 ± 7.74
F4	98.41 ± 1.03	5.43 ± 0.03	0.52	6.1 ± 0.10	640.98 ± 2.68
F5	99.24 ±1.49	6.3 ± 0.0	0.69	4.8 ± 0.08	721.04 ± 2.22
F6	96.04 ± 0.74	6.29 ± 0.04	0.58	4.78 ± 0.09	719.16 ± 2.95
F7	99.07 ± 1.10	6.74 ± 0.03	0.65	3.3 ± 0.03	1426.28 ± 8.6
F8	98.91 ± 3.47	5.85 ± 0.01	0.73	6.32 ± 0.15	684.14 ± 3.66
F9	98.44 ± 0.57	5.35 ± 0.02	0.60	4.5 ± 0.08	45.86 ± 2.081
F10	100.8 ± 1.12	5.98 ± 0.04	0.63	4.92 ± 0.11	1197.83 ± 7.1
F11	98.42 ± 1.18	6.29 ± 0.02	0.55	4.82 ± 0.09	719.81 ± 4.67
F12	99.06 ± 1.69	6.29 ± 0.03	0.69	4.79 ± 0.08	718.88 ± 2.95

Table 11. Values of $\%DE_{10\ min}$, $DP_{10\ min}$ and MDT for F7 batch and DCT

Sample	$\%DE_{10\ min}$	$DP_{10\ min}$	MDT
F7 batch	62.22 %	93.42 %	5.28
DCT	10.53 %	15.11 %	14.50

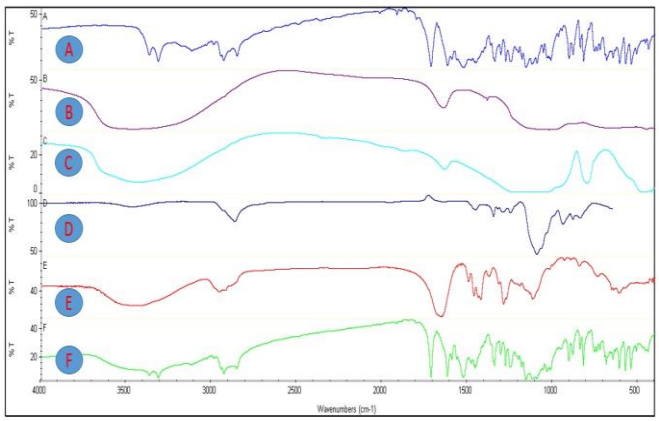


Fig 6.A. FTIR spectra of (A) Glibenclamide, (B) Neusilin US2, (C) Aerosil 200, (D) Cross povidone, (E) PEG 400 and (F) Physical mixture

X-ray powder diffraction analysis

The powder X-ray diffraction patterns of pure Glibenclamide, physical mixture and liquisolid formulation are shown in Fig.7. The diffraction pattern of the pure Glibenclamide showed a highly crystalline nature, indicated by numerous distinctive peaks at various 2Ɵ values like 10.97°, 11.77°, 14.87°, 16.31°, 20.5°, 21.05°, 23.25°, 27.79°, 29.33°, 31.83° and 32.33° throughout the scanning range. The diffraction patterns of the liquisolid formulation showed disappearance of sharp distinctive peaks which evidenced that the drug had got solubilized in the liquid vehicle (PEG 400) used in formulating the liquisolid compacts. The solubilization of Glibenclamide in the liquid vehicle was the main cause for the dissolution enhancement. This was also supported by the DSC thermograms of pure Glibenclamide, physical mixture and the liquisolid formulation.

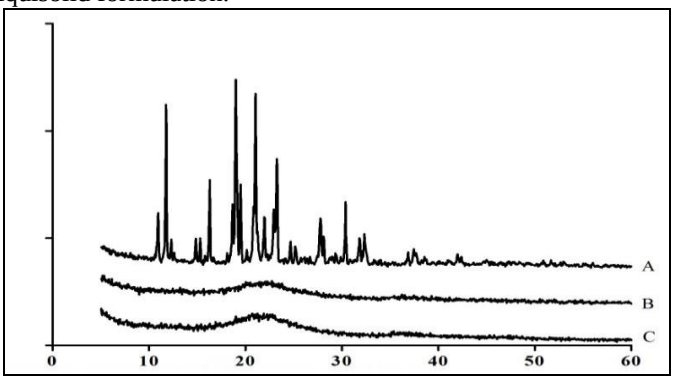


Fig 7. X-ray diffractograms of pure Glibenclamide (A), Liquisolid formulation (B) and physical mixture (C)

Flowability parameter of liquisolid powder composition

As the angle of repose (h) is a characteristic of the internalfriction or cohesion of the particles, the value of theangle of repose will be high if the powder is cohesive andlow if the powder is non-cohesive. As presented in Table9, F1, F3,F7 and F10 showed (h) values of 33.69,35.53,36.52 and 36.02, respectively, were chosen as liquisolid systems with acceptable flowability according to the angle of repose measurements, while those having higher angles of repose were considered as non-acceptable. Powders showing Carr's index (Ci) up to 21 are considered of acceptable flow properties. In addition to Carr's index, Hausner found that the ratio DBmax/DBmin was related to the inter particle friction, so, he showed that powders with low interparticle friction, had ratios of approximately 1.25 indicating good flow. Therefore, formulae F1, F3,F6,F8 and F12 were selected as acceptably flowing property.

Post compression parameter for Glibeclamide liquisolid tablets.

Liquisolid tablet were characterized for weight variation, thickness, hardness, friability and *in vitro* drug release. Results are shown in the Tab.10.

Deviation in weight in all the batches below 2.5 % indicated that there was no significant weight variation in the Liquisolid tablets. Hence, all the tablet formulations passed the weight variation test.

Thickness of tablet was found to be in the range from 4.8 ± 0.0 to 6.74 ± 0.03 mm.

Hardness of all formulation prepared by direct compression was found to be 3.3 ± 0.03 to 6.32 ± 0.15 kg/cm^2 as shown in Table 4.9. Out of all the batches, F8 batch showed maximum hardness (6.32) due to least amount of PEG while F7 batch showed minimum hardness (3.3) due to highest amount of PEG. The % Friability was less than 1% in all the formulations, indicated that the friability was within the prescribed limits. The results of friability indicated that the tablets possesed good mechanical strength.

% drug content in the tablets were found to be in the range of 96.04 ± 0.74 to 100.8 ±1.12. As per IP 2010, Glibenclamide Tablets contained not less than 90.0 percent and not more than 110.0 percent of the stated amount of Glibenclamide. So, Percent drug content were found within the acceptable limit as per IP.

The dissolution of Liquisolid tablets were carried out in phosphate buffer pH 7.4 medium using USP dissolution apparatus II and data are given in Fig.8..Here, all the liquisolid formulation showed significant improvement in dissolution of Glibenclamide compared to DCT. Among them, F7 formulation showed highest CPR at 10 min (93.42 %) due to high amount of PEG 400. This enhancement in dissolution of Glibenclamide was due to solubilization of drug in PEG 400.

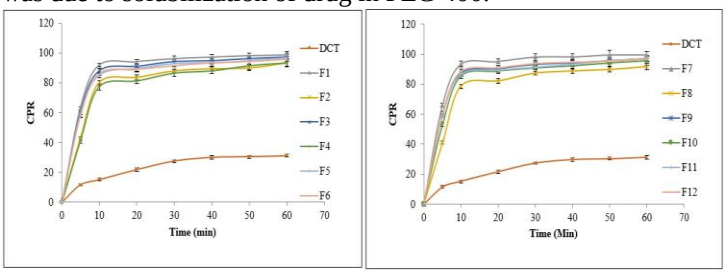


Fig 8. In vitro drug release of factorial batches compare with directely compressed tablets

Dissolution profile for batch F7 calculated that can be shown in tab.11. from that results shows that, high DP $_{10\ min}$, %DE $_{10\ min}$ and low MDT was given by F7 batch. Hence, there was a significant improvement in dissolution of Glibenclamide prepare in Liquisolid formulation.

Conclusion

The present investigation was concerned with the enhancement of dissolution of Glibenclamide. In this study PEG 400 selected as non-volatile vehicle, Neusilin US2 as carrier material and Aerosil 200 as coating material for formulation of Liquisolid compact of Glibenclamide. A Central composite factorial design was applied to optimize the drug release profile systematically. Prepared Liquisolid tablets possessed required physicochemical properties and shows significance improvement of dissolution of drug. Based of dissolution profile batch F7 selected as optimized batch and this optimized batch F7 passes desire dissolution profile as compare to Directly compressible tablets.

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