Original Article

Central Composite Design for the Development and Evaluation of Liquisolid Compacts of Glyburide

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ABSTRACT

Background: Glyburide is an oral antidiabetic agent with a shorter half-life and is practically insoluble in water. As a result, there is a need to enhance the drug solubility with a aim to improve drug absorption via the oral route. The goal of this study was to formulate, optimize and evaluate the liquisolid tablets of Glyburide using a suitable liquid vehicle in order to enhance the solubility, and bioavailability of the Glyburide. **Materials and Methods:** The liquisolid compacts of Glyburide were prepared by direct compression method using approved excipients. Using central composite design, the amount of Transcutol HP and carrier: coating ratio to be added in the formulations of Glyburide liquisolid compact has been theoretically generated by the software. The liquisolid tablets were evaluated for thickness and diameter, hardness, weight variation, friability, content uniformity, disintegration time, *in-vitro* dissolution study and compared with marketed product. **Results:** The prepared liquisolid system exhibited good flow-properties. The all-post compression parameters were well within the specified limits. The release profile of optimal formulation revealed higher drug release compared to marketed formulation. Increases in the concentration of liquid vehicle and carrier: coating material ratio resulted in an increase in the dissolution rate. **Conclusion:** The liquisolid compact method was discovered to be a potential method to enhance the dissolution profile, thereby enhancing the solubility of the Glyburide.

Key words: Liquisolid technique, Glyburide, Central composite design, Aerosil200, Transcutol HP, Avicel PH-102.

INTRODUCTION

The oral route has been one of the most favoured routes of drug delivery because of its greater patient compliance, ease of administration, low cost with flexible dosage forms design.[1] However, the poor bioavailability of oral dosage forms is the major challenge in their development. The oral bioavailability of drugs depends on various factors, but the most important and frequent cause includes aqueous solubility of the drug where dissolution may be the rate determining step for drug availability.[2,3] It has been reported that about 40% of the existing drug molecules are water insoluble; this makes the formulation a challenging task.[4] Drugs with poor solubility when administered orally, exhibit poor bioavailability due to poor wettability and slow rate of dissolution.[5]

The Liquisolid approach is a recent and potentially effective way for increasing the rate of dissolution of medications that are poorly water soluble. The rate limiting step in the oral absorption of poorly soluble medications is the dissolution rate. Liquisolid compacts have improved wettability and a larger surface area of the medication available for dissolution. As a result, they are projected to improve oral bioavailability and boost drug release patterns for weakly water-soluble medicines.[6] Combining liquid medications with suitable carrier and coating materials to form non-sticky, free-flowing, dry, and compressible powder admixtures is the Liquisolid technique. Liquid medication once been absorbed into the interior structure of carrier, a layer of liquid is produced on the carrier particles'

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surface, which is promptly adsorbed by the tiny coating materials. As a result, a powder mixture that looks to be dry, free-flowing, and compressible is produced.[7]

Glyburide (Glibenclamide) is an oral antidiabetic medication that is most commonly used to treat non-insulin-dependent diabetes mellitus (type II). Furthermore, its ability to deter cerebral ischemia and hemorrhagic stroke has recently been demonstrated,[8-10] and since 2015, it has been on the World Health Organization's model list of Essential Medicines.[11] Its biological half-life is 4-6hrs. Glyburide is practically insoluble in water and is a BCS class–II drug. Clinical studies have shown that Glyburide from different commercial tablets has variable *in vivo* bioavailability, *in vitro* dissolution, and a hypoglycemic effect.[12,13] These observations were related to Glyburides unsatisfactory and variable dissolution behavior, giving credence to previously reported issues with formulation-dependent oral absorption of the drug.[14]

To improve Glyburide solubility, a number of formulation techniques have been investigated. The micronization approach is the most often used method for improving drug solubility,[15] but micronized hydrophobic pharmaceuticals tend to agglomerate, making it less efficient in overcoming drug solubility issues, particularly in the form of tablets[16] Solid dispersion (SD) is another approach that has gained popularity for enhancing drug solubility profiles,[17-19] but it has poor storage stability due to a lack of solid-state structure recognition. Other techniques employed are gastro retentive multi-particulates system,[20] self-microemulsifying drug delivery system,[21-23] micellar solubilization, etc.[24]

The goal of this study was to formulate, optimise, and analyse Glyburide liquisolid tablets using a suitable liquid vehicle so as to improve the drug's solubility and its bioavailability. Also, the optimized liquisolid tablets were tested for their release profile with marketed formulation.

MATERIALS AND METHODS

Materials

Glyburide was purchased from Prudence pharmachem, Gujarat. Transcutol HP and Labrafil M2125CS were obtained from Gatteffosse, France. Avicel PH and 102 Aerosil 200, were purchased from Ozone International, Mumbai and Sisco Research Laboratories Pvt. Ltd., Mumbai respectively.

Methods

Solubility Studies

The optimum non-volatile solvent for dissolving Glyburide in liquid medication was determined through solubility tests. The solubility experiments were performed by creating saturated drug solutions by mixing excess medication with non-volatile solvents, stirring for 48 hr, and then sonicating for 1 hr at constant vibration. The supernatant was collected and analyzed spectrophotometrically at 231nm. The drug's saturation solubility was investigated in distinct non-volatile solvents: PEG 400, PEG 600, Transcutol HP, Labrafil M2125CS, water.[25]

Flowable Liquid-Retention Potential Calculation (Φ-value)

To make powder admixture, a motor pestle was used to combine an increasing amount of the liquid vehicle into 5g of Avicel-PH 102 or Aerosil 200. For each liquid vehicle concentration, the angle of repose was estimated. The flowable liquid-retention potential (Φ) was then calculated using equation.[26,27]

$$\Phi_{CA} = m_{max}/Q \qquad \Phi_{CO} = m_{max}/q$$

Where; Φ_{CA}- Flowable liquid-retention potential of carrier material, Φ_{CO}-Flowable liquid-retention potential of coating material, m_{max}- Maximum mass of non-volatile solvent, Q- Mass of carrier material and q- Mass of coating material.

The acquired Φ-values were plotted against the relevant angle of repose, which was estimated to be around 33˚.

Liquid Load Factor (L_f) Calculation

The success of a liquisolid system with good flow velocity and compressibility is determined by the liquid load factor (L_f) and excipient ratio (R). The L_f determines the maximum amount of liquid loads that can be carried on the carrier material.[28,29] It was calculated using equation;

$$L_f = \Phi_{CA} + \Phi_{CO}(1/R)$$

The required quantity of carrier as well as coating material was then calculated using the Lf factor:

$$L_f = W/Qq = Q/R$$

Where; W-weight of liquid medication, Q-quantity of carrier material, q-quantity of coating material and R-excipient ratio.

Design of Experiment

The ratio of carrier and coating material (X_1) and drug concentration in Transcutol HP (X_2) were used as formulation independent variables, while disintegration time in min (Y_1) and cumulative percentage drug release at 60 min (Y_2) were used as dependent variables for the optimization of Glyburide liquisolid compacts.

The formulation design or experimental runs were based on central composite design (Table 1). The response surface method was used to evaluate the response variables. The results were then analysed using multiple regression analysis to see if there was any correlation between the responses and the factors that were used.

Preparation of Liquisolid Tablets

Glyburide was suspended in Transcutol HP, a liquid vehicle used to prepare the glyburide suspension. Here, Avicel PH 102 was utilized as carrier material and Aerosil 200 was utilized as a coating material and the mixture of these excipients were incorporated in to the drug suspension and mixed in a mortar. The mixing should avoid the reduction of particle size and over trituration. There are three different stages of mixing in this technique: firstly, slow mixing was done to achieve steady mixing of drug suspension in the system; then, the mixture was evenly spread on the mortar surface (to form a layer) and kept aside for a couple of min. Finally, 2% disintegrant (Na-starch glycolate) and 1% lubricant (Mg-stearate) were added and mixed thoroughly.[30,31] Tablets were made from the final combination. Glyburide liquisolid compacts (LSC: LSC-1 to LSC-9) were compressed into tablets using a direct compression approach (each tablet contains 5 mg of drug). The working formula for all 9 liquisolid systems are shown in Table 2.

All 9 (LSC-1 to LSC-9) formulations of liquisolid compacts were prepared with software generated quantities of Transcutol and carrier: Coating ratio. The response variables, disintegration time and % cumulative drug release (CDR) at 60 min are experimentally obtained. The obtained experimental values were then compared with that of predicted values generated by software. Response variables were analyzed by ANOVA at 0.05. A checkpoint batch and optimized formulation LSC-10 was prepared by using optimized solutions (quantities) for X_1, X_2 and Y_1, Y_2.

Table 1: Amount of X_1, X_2generated by the software tobe added in 9 formulations.

Run	Component 1 Drug Concentration in Transcutol HP(%w/w)	Component 2 Carrier: Coating Ratio (mg)
1	7.5	10
2	7.5	20
3	5	20
4	10	10
5	10	15
6	10	20
7	7.5	15
8	5	10
9	5	15

Evaluation of Pre-Compressible Blend of Liquisolid System

The angle of repose, and Carr's index, were used to determine the flow parameters of liquisolid systems. For the calculation of Hausner's ratio and Carr's Index, the bulk density and tapped densities were calculated.[32,33]

Evaluation of Liquisolid Tablets

The following parameters were assessed in the prepared liquisolid tablets:.[34]

Thickness and Diameter

Vernier caliper was used for determining the thickness and diameter of a tablet. The tablet was placed in between the movable jaw and the stationary jaw. Then the screw was rotated, so as to fit the tablet in between the jaws. Then, reading shown was noted and the average thickness and hardness were determined in mm.

Hardness

Tablets should be as firm as possible to avoid shattering during handling and transit. Also, it should be sufficiently soft to disintegrate accurately after swallowing. A Monsanto hardness tester was used to determine the hardness of manufactured liquisolid compact tablets.

Friability

The friability test denotes the ability of tablets to resist abrasion and chipping of the compacts during

Table 2: Working formula using software generated theoretical amount of X_1, X_2 added in LSC-1- LSC-9.

Ingredients	LSC-1	LSC-2	LSC-3	LSC-4	LSC-5	LSC-6	LSC-7	LSC-8	LSC-9
Drug (mg)	5	5	5	5	5	5	5	5	5
Transcutol HP (mg)	66.6	66.6	100	50	50	50	66.6	100	100
Ca:Co (mg)	10:1	20:1	20:1	10:1	15:1	20:1	15:1	10:1	15:1
Avicel PH102	238.9	269.9	404.8	179.21	193.79	202.4	258.4	358.4	387.5
Aerosil 200	23.89	13.49	20.24	17.92	12.91	10.12	17.22	35.84	25.83

*All formulation consist of 2% SSG and 1% Mg.stearate.Ca:Co= Carrier material: Coating material

packaging, handling and shipping. Samples of tablets corresponding to 6.5 g were used to conduct a friability test since the total weight of tablet is < 650 mg as per IP. A Roche friabilator set to 25 rpm and 100 rotations was used to determine the friability of tablets. The tablets were then dedusted and reweighed, and those with a weight drop of less than 1% were considered compliant. A formula was used to calculate the % weight reduction in tablets.

$$F = \frac{W_{Initial} - W_{Final}}{W_{Initial}}$$

Weight Variation Test

For this, 20 tablets were individually weighed, and their weights were contrasted to the average weight of all twenty tablets. The tablets pass the test if no more than two tablets are outside the % limit and no tablet differs by more than twice the % limit.

Disintegration Time

Each tube (six tubes) of the disintegration test apparatus was filled with single tablets and discs. The water was held at 37± 2°C, and amount of time it took for the complete tablet to disintegrate was recorded.[35]

Content Uniformity

The average weight of ten tablets was calculated. The tablets were then pulverized and the powder approximately equivalent to 5mg of Glyburide was dissolved in 5ml of methanol and further diluted. Absorbance of the solution was taken at 231nm by using UV spectrophotometer with 0.1N HCl as a blank. Using the slope from the calibration curve, the drug content was then estimated.[36]

Dissolution Study

The test was conducted with 900 ml of 0.1N HCl as the dissolution media (USP Type II dissolution unit) at a temperature of 37°C ± 0.5°C temperature and a stirring speed of 50 rpm. At 5, 10, 15, 30, 45, and 60 min, 10ml of medium was withdrawn and replaced with fresh medium to keep the volume steady. The absorbance of the withdrawn media was analyzed by UV spectrophotometer.[35]

RESULTS AND DISCUSSION

Solubility Studies

The results of a saturation solubility study of the drug in various nonvolatile solvents revealed that the drug was most soluble in Transcutol HP and least soluble in water. The order of solubility was Transcutol HP> PEG 600>PEG 400>Labrafil M2125CS> Water. Thus, Transcutol HP was chosen as non-volatile solvent to solubilize the drug and also it has a long history of strong solubilizer with less toxicity which is used as a solvent in pharmaceuticals and food applications.[37]

Determination of Φ-value and

The Φ-value of carrier (Avicel PH 102) as well as coating material (Aerosil 200) in Transcutol HP were shown in Table 3. It was observed that as the carrier: coating ratio (R) decreases (20, 15 and 10), the liquid load factor (0.247, 0.258 and 0.279) increases.

Preparation of Liquisolid Tablets

The direct compression method was used to prepare tablets from Liquisolid compact systems of Glyburide (LSC-1 to LSC-9). The liquisolid systems contained Avicel PH 102 and Aerosil 200 were used as carrier material and coating material respectively, at different powder excipient ratio (R) i.e., 10, 15 and 20. Transcutol HP is a liquid vehicle used to produce liquid medications with drug concentrations of 5, 7.5, and 10% (w/w). Finally, in all systems, 2% disintegrant and 1% lubricant were utilised Table 2.

The mechanism of liquisolid technique involves the incorporation of drug dissolved liquid vehicle into carrier material. On carrier material, both adsorption and absorption processes take place as its interior surface is porous with closely matted fibers. Initially, absorbed liquid at the interior surface of particles is encapsulated by the internal structure of particles and when absorption gets saturated, adsorption process of liquid initiates on both internal as well as external surfaces of carrier particles (porous particles). The expedient flow characteristics for the liquisolid system were achieved by large specific surface area of the selected coating material and greater adsorptive properties.[38]

Evaluation of Pre-Compressible Blend of Liquisolid System

Particle size, shape, porosity, and density all influence bulk powder flow characteristics. Angle of repose,

Table 3: Liquid retention potential (Φ-value) of carrier and coating material inTranscutol HP.

Carrier Material-Avicel PH 102		Coating Material-Aerosil 200	
Θ	Φ-value	Θ	Φ-value
28.8	0.11	27.2	0.21
33.74	0.215	29.1	0.431
29.1	0.15	31.8	0.52
31.7	0.41	33.03	0.63
31.5	0.45	31.2	0.55

*Where, θ= Angle of repose; Φ value= liquid retention potential.

Table 4: Flow properties of the liquisolid systems from LSC-1 to LSC-9.					
Formulation	**Angle of repose (0)**	**Buk density (g/cc)**	**Tapped density (g/cc)**	**Carr's index (%)**	**Hausner's ratio**
LSC-1	34.50±0.34	0.313±0.025	0.400±0.007	21.75±1.2	1.28±0.067
LSC-2	32.78±0.25	0.345±0.009	0.455±0.017	20.18±0.9	1.32±0.021
LSC-3	33.74±0.65	0.385±0.019	0.476±0.021	19.12±1.9	1.23±0.009
LSC-4	30.96±0.89	0.272±0.036	0.346±0.011	18.38±0.97	1.27±0.011
LSC-5	32.00±0.52	0.250±0.014	0.330±0.006	18.24±1.7	1.32±0.006
LSC-6	28.80±1.02	0.267±0.023	0.324±0.019	17.59±2.1	1.21±0.024
LSC-7	28.80±0.35	0.345±0.011	0.416±0.005	17.27±0.6	1.21±0.006
LSC-8	33.20±0.75	0.274±0.008	0.322±0.020	15.62±0.18	1.18±0.025
LSC-9	34.30±0.25	0.355±0.013	0.455±0.017	21.97±0.97	1.28±0.290

*Data are expressed as mean ± SD (n=3)

Table 5: Evaluation parameters of liquisolidtablets LSC-1 to LSC-9.						
Formulation	**Weight Variation (mg)**	**Thickness (mm)**	**Friability (%)**	**Hardness (kg/cm²)**	**Disintegration Time (min)**	**Drug Content (%)**
LSC-1	347.01±6.34	3.7±0.018	0.40±0.12	3.5±0.067	3.45±0.05	98.40±1.0
LSC-2	351.80±6.25	4.0±0.017	0.40±0.90	3.0±0.021	2.96±0.04	97.78±0.5
LSC-3	550.30±7.65	4.35±0.021	0.29±1.90	3.0±0.009	1.97±0.024	99.0±0.8
LSC-4	249.38±0.89	4.0±0.011	0.27±0.97	3.19±0.011	4.72±0.061	98.8±1.2
LSC-5	269.80±8.52	4.15±0.006	0.36±0.07	3.90±0.006	4.41±0.11	98.6±0.56
LSC-6	276.80±4.02	4.25±0.019	0.34±0.21	3.21±0.024	3.93±0.07	101.4±1.9
LSC-7	345.17±9.35	3.90±0.005	0.44±0.60	4.9±0.016	3.16±0.04	99.2±0.87
LSC-8	522.12±3.75	4.10±0.02	0.276±0.18	3.9±0.025	2.76±0.025	100.02±0.8
LSC-9	538.80±5.25	4.20±0.017	0.089±0.97	5.0±0.29	2.29±0.09	96.34±0.7

*Data are expressed as mean ± SD

bulk density, tapped density, Hausner's ratio as well as Carr's index, were all established prior to compression (Table 4) because these influences compressibility, tablet porosity and dissolution. All of the metrics are within acceptable limits, indicating that the liquisolid compact system has good flow properties and compressibility. The enhanced flowability can be attributed to higher porosity as well as specific surface area of the excipients, which allows liquid to penetrate into the pores of the particle that ultimately increases the weight of individual particle with improved flow characteristics. The carrier material used for liquisolid system should have a porous surface and high absorption properties. Because the moisture content of carriers decreases the flowability of powder, coating material is required to cover the surface of the carrier material. Accordingly, the coating material should be extremely fine and absorbent.[30,39]

Evaluation of Liquisolid Tablets

The post-compression parameters of liquisolid tablets revealed that all tablets were white, flat, and free of physical defects. The pharmacotechnical qualities of the produced tablets were satisfactory (Table 5). The thickness of liquisolid tablets was between 3.7± 0. 057 to 4.35 ± 0.0 57mm while, the diameter was found to be between 8 to 11 mm. The prepared liquisolid tablets ware reported to have hardness ranging from 3± 0.009 to 5±0.29 kg/cm^2, that indicates that the liquisolid tablets were hard enough to withstand packing and shipping. Friability for the formulations was found to be in the range of 0.27 ± 0.97% to 0.44± 0.6% which indicated that the liquisolid tablets possessed good mechanical strength. The weight variation test was passed on all of the tablets because the variations were less than 5%. The result of *in vitro* disintegration time for all formulations was reported to be in the range of 1.97 ± 0.024 to 4.72 ± 0.061mins. Since all the tablets disintegrated in less than 15 min, all the formulations passed the disintegration test.

According to USP, Glyburide tablets contain not less than 90% and not more than 110% of the stated amount of Glyburide. For all formulations from LSC-1

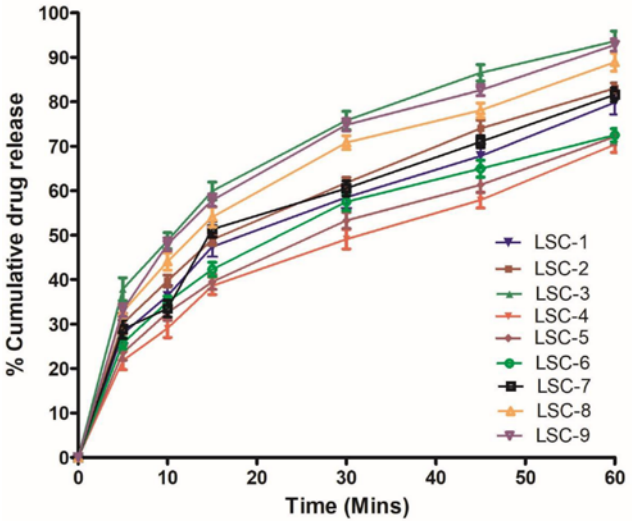

Figure 1: *In-vitro* release profile of Glyburide from liquisolid tablets from formulations LSC-1 to LSC-9.

to LSC-9, the drug content was found to be in the range of 96.34 ± 0.7 to 101.4 ± 1.9%. These results indicate that the drug is uniformly mixed with the excipients. According to USP, the content uniformity test was passed by all formulations.

Dissolution Study

It was observed that *in-vitro* dissolution study that all the 9 formulations showed satisfactory drug release. The results for formulations LSC-1 – LSC-9 at 60 min were in the range of 70.76±1.7% – 94.23±1%. Among the 9 formulations, LSC-3 showed the highest release of 94.23± 1% containing 100mg of Transcutol HP and 20:1 carrier: coating ratio, LSC-4 showed the lowest drug release and contained 50mg of transcutol HP and 10:1 carrier: coating ratio. Hence, these results indicate that high concentration of Transcutol HP and carrier: coating ratio increases the dissolution rate. The *in-vitro* dissolution of formulation LSC-1 – LSC-9 is shown in Figure 1. The compact wettability by the dissolution media is another suggested mechanism for describing the improved dissolution rate of the liquisolid compacts. In liquisolid systems, the nonvolatile solvent increased drug particle wettability by reducing interfacial tension between the dissolving media and the tablet surface.[38]

ANOVA (Analysis of variance) for Disintegration Time in Min (Y_1), % CDR at 60 Min (Y_2)

After Responses Y_1, Y_2 are obtained experimentally, analysis of variance (ANOVA) is done, Actual values (experimental values) and predicted values are compared to evaluate the model and after complete analysis, software generates optimal formula (predicted solutions) of factors with desired responses to give optimized formulation.

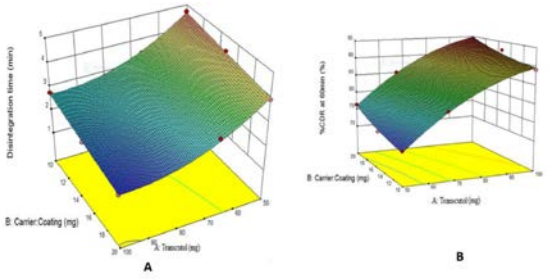

Figure 2: 3D Response surface graph showing effect of independent factors on Disintegration time and B. 3D Response surface graph showing effect of independent factors on %CDR.

Statistical Analysis of Response (Y_1) Disintegration Time in Min

The model has an *F*-value of 106.52, indicating that it is significant. A, B, and A2 are important model terms. The model terms are significant if the "probability values > *F*" 0.0500. The discrepancy between the "Predicted R-Squared" of 0.9375 and the "Adjusted R-Squared" of 0.9851 is less than 0.2. The signal-to-noise ratio is calculated using "Adequate Precision." It is preferable to have a ratio of more than four.

Polynomial equation of response:

$$Y_{1=} 2.78\text{-}1.01*A\text{-}0.35*B\text{-}0.016*AB+0.56*A^2+0.012*B^2$$

Response Surface Plots in 3 Dimensional (3D), Y_1: Disintegration time in Min

Response surface can be visualized with the help of surface plot. With the decrease in the amount of Transcutol HP, there is a decrease in disintegration time, whereas carrier: coating ratio has little effect on disintegration time. The response surface plot for Y_1 is shown in Figure 2 (A).

Statistical Analysis of Response (Y_2) % CDR at 60 Min

The model significance is indicated by the Model *F*-value of 144.5. A, B, and A2 are important model terms. The significance of the model terms is shown by the "Probability values> *F*" < 0.0500. The "Predicted R-Squared" of 0.9383 and the "Adjusted R-Squared" of 0.9890 are in good agreement; the difference is <0.2. The signal-to-noise ratio is calculated using "Adequate Precision." It is preferable to have a ratio of more than four. Polynomial equation of response:

$$Y_{2=} 85.11+9.44*A+2.68*B\text{-}0.012*AB\text{-}3.07*A^2+0.71*B^2$$

Response Surface Plots in 3 Dimensional (3D), Y_1: Disintegration Time in Min

With an increase in the amount of transcutol HP, there is an increase in % CDR at 60min, whereas carrier: coating ratio has little effect on % CDR. The response surface plot for Y_2 is shown in Figure 2 (B).

Optimization

The quadratic model fit's regression analysis revealed that disintegration time and % CDR were 97 % associated with the components X_1, X_2. For the generation of optimal formula, a numerical optimization technique by desirability function was adopted with certain constraints on the response. The software predicted one solution for independent variables X1, X2 with desired responses Y_1, Y_2 based on optimization findings, ANOVA ($p<0.05$), and desirability = 1. Optimized solutions for independent variables as well as response variables are depicted in Table 6. Finally, to demonstrate the validity of the evolved approach, a checkpoint batch LSC-10 (optimal formulation) was created using optimum values, and the working formula of the optimized formulation is provided in Table 6. Pre-compression parameters for optimised formulation LSC-10, such as angle of repose, carr's index, hausner's ratio, and percent porosity, demonstrated that the liquisolid system had good flow properties within the passable limit. Post compression parameters evaluated for optimized formulation LSC-10 thickness, uniformity, hardness, weight variation, friability, and the drug content were reported to be uniform and within the permissible limit. The values are depicted in Table 6. The software generated optimal formulation LSC-10 containing 98.165mg of Transcutol HP, 19.574:1 carrier: coating ratio and showed experimental prominent drug release of 93.19% ±1.5 at 60 min with a shorter disintegration time of 2.017±0.01 min.

Table 6: Predicted solutions (optimized) by the software: Factors and responses, Working formula, Flow properties and Evaluation parameters of optimized formulation LSC-10.

Predicted Solutions (Optimized) by The Software: Factors and Responses			
Factors		Response	
X_1 (mg)	X_2 (mg)	Y_1 (mins)	Y_2(%)
98.165	19.574:1	2.006	94.163
Working Formula for Optimized Formulation LSC-10			
Formulation Ingredients		**Quantities (mg)**	
Glyburide		5.0	
Transcutol		98.165	
Ca:Co (mg)		19.574:1	
Avicel PH102		395.82	
Aerosil 200		20.22	
Flow Properties of The Optimized Liquisolid System (LSC-10)			
Angle of repose (0)		31.8±1.03	
Bulk density (g/cc)		0.274±0.02	
Tapped density (g/cc)		0.322±0.011	
Carr's index (%)		15.62±2.79	
Hausner's ratio		1.18±0.045	
Evaluation Parameters of Optimized Liquisolid Tablets (LSC-10)			
Weight variation (mg)		541±2.3	
Diameter (mm)		11.1	
Thickness (mm)		4.25±0.05	
Friability (%)		.31±0.253	
Hardness (kg/cm²)		4±0.2	
Disintegration Test (min)		2.017±0.01	
Drug content (%)		99.0±0.5	

*Data are expressed as mean ± SD (n=3)

Validation of Design

Comparison of Experimented Values (E) and Predicted Values (P) For the Optimized Formulae

The experimented values were in close agreement with the projected response, showing appropriate fitting and validation of the formula created, according to the results in Table 6.

Comparison of Optimized Formulation with Pure Drug and Marketed Formulation

A comparative study for *in-vitro* release profile of optimized formulation LSC-10 with pure drug and marketed product having the same strength of 5mg Glyburide showed 93.19% ±1.5 (LSC-10), 27.10% ±0.63 and 53.28% ±0.48 drug release respectively at the end of 60min. The optimized formulation shows a higher % CDR than the pure and marketed product. The comparative graph is shown in Figure 3.

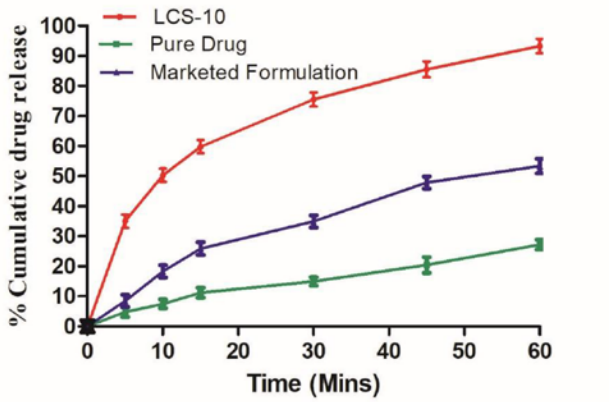

Figure 3: Comparative studies between optimized formulation LSC-10, pure drug and marketed formulation.

CONCLUSION

Two independent variables (factors) concentration of Transcutol HP and carrier: coating ratio were selected to optimize the response variables, i.e., disintegration time (min), % CDR at 60 mins. The prepared liquisolid system showed good flow properties. The prepared liquisolid tablets have good mechanical strength, according to the hardness and friability values. All of the formulations' weight variation, disintegration time, and drug content were substantially within the prescribed limits. The cumulative percent drug release for formulations LSC-1 to LSC-9 was in the range of 70.76% to 94.23% at 60 min. A checkpoint batch is created based on the optimization results to demonstrate the validity of the evolved approach. Thus, it may be concluded that the results demonstrate the feasibility of the model in the development of an oral drug delivery system for liquisolid compacts of Glyburide. The experimented values were found to be closer to the anticipated values, indicating that the model is valid and reproducible. The optimized formulation LSC-10 was compared with pure drug and marketed formulation and showed better *in-vitro* dissolution release study of the drug. Hence, the liquisolid technique was discovered to be a potential strategy for optimising the dissolution profile and thereby increasing the drug's solubility.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

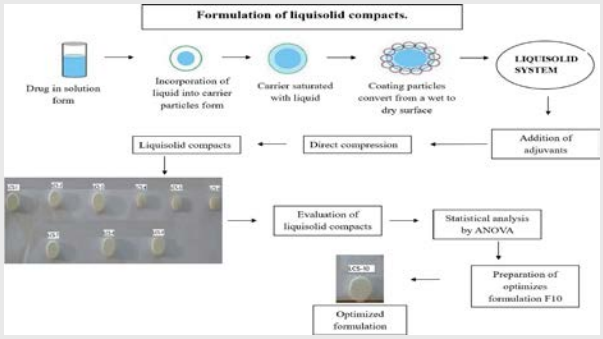
LSC: Liquisolid Compacts; **PEG:** Poly(ethylene glycol; **Conc:** Concentration; **CDR:** Cumulative drug release; **%:** Percentage; **µg:** Microgram; **mg:** Milligram; **rpm:** Rotation per minute; **DSC:** Differential scanning calorimetry; **FTIR:** Fourier transform infrared; **hr:** Hour; **λ_{max}:** Maximum absorbance; **nm:** Nanometer; **R^2:** Regression coefficient.

REFERENCES

1. Krishnaiah YSR. Pharmaceutical Technologies for Enhancing Oral Bioavailability of Poorly Soluble Drugs. JBB;02(2). doi: 10.4172/jbb.1000027.
2. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: Importance and enhancement techniques. ISRN Pharm. 2012;2012:195727. doi: 10.5402/2012/195727.
3. Brahmankar DM. Sunil B. Biopharmaceutics and pharmacokinetics A Treatise. 1st ed. VallabhPrakashan, Delhi 2005. Vol. 27. p. 5-6.
4. Lachmann L, Libermann H. The theory and practice of industrial pharmacy. New Delhi: CBS Publications; 2009. p. 293-7.
5. Sucheta B, Dyandevi M, Patil VK, Rajendra VB. Solubility enhancement of antihypertensive agent by solid dispersion technique. Int J Pharm Life Sci. 2011;2(8):970-5.
6. Kala NP, Shastri DH, Shelat PK. Design and characterization of buccoadhesive liquisolid system of an antihypertensive drug. J Drug Deliv. 2015;2015:574247. doi: 10.1155/2015/574247, PMID 26579235.
7. Lu M, Xing H, Jiang J, Chen X, Yang T, Wang D, *et al.* Liquisolid technique and its applications in pharmaceutics. Asian J Pharm Sci. 2017;12(2):115-23. doi: 10.1016/j.ajps.2016.09.007, PMID 32104320.
8. Simard JM, Sheth KN, Kimberly WT, Stern BJ, Del Zoppo GJ, Jacobson S, *et al.* Glibenclamide in cerebral ischemia and stroke. Neurocrit Care. 2014;20(2):319-33. doi: 10.1007/s12028-013-9923-1, PMID 24132564.
9. Caffes N, Kurland DB, Gerzanich V, Simard JM. Glibenclamide for the treatment of ischemic and hemorrhagic stroke. Int J Mol Sci. 2015;16(3):4973-84. doi: 10.3390/ijms16034973, PMID 25749474.
10. World Health Organization (WHO). Model list of essential medicines; 2015 [cited Apr 24 2020]. Available from: http://www.who.int/medicines/publications/essentialmedicines/en/index.html.
11. Chalk JB, Patterson M, Smith MT, Eadie MJ. Correlations between *in vitro* dissolution, *in vivo* bioavailability and hypoglycaemic effect of oral glibenclamide. Eur J Clin Pharmacol. 1986;31(2):177-82. doi: 10.1007/BF00606655, PMID 3100314.
12. Neugebauer G, Betzien G, Hrstka V, Kaufmann B, Von Möllendorff E, Abshagen U. Absolute bioavailability and bioequivalence of glibenclamide (Semi-Euglucon N). Int J Clin Pharmacol Ther Toxicol. 1985;23(9):453-60. PMID 3932228.
13. Glyburide. Drug bank. Available from: http://www.drugbank.ca/drugs/DB01016 [cited 4/3/2022] [Assessed on May 28 2015].
14. Kumar P, Bioavailability KB CS. Bioavailability and dissolution enhancement of glyburide nanosuspension. Asian J Pharm Clin Res. 2019;12(4):111-8.
15. Mudgal SS, Jayaprakash S, Nagrajan M, Pancholi SS. Formulation and evaluation of tablets of micronized glibenclamide (glyburide) in industrial set-up. Int J Pharmacol Res. 2010;2:25-9.
16. Betageri G. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. International Journal of Pharmaceutics. 1995;126(1-2):155-60. doi: 10.1016/0378-5173(95)04114-1.
17. Shrinivas RD, Reddy PV. Dissolution and bioavailability enhancement of glyburide. 2013;95(3):445-57.
18. Tejas BP, Patel LD, Patel TB, Makwana SH, Patel TR. Formulation and characterization of solid dispersions containing glibenclamide. 2010;2(3):138-41.
19. Tabbakhian M, Hasanzadeh F, Tavakoli N, Jamshidian Z. Dissolution enhancement of glibenclamide by solid dispersion: solvent evaporation versus a supercritical fluid-based solvent -antisolvent technique. Res Pharm Sci. 2014;9(5):337-50. PMID 25657806.
20. Prashant U, Pandit KP, Upadhyay S, Ghosh AK. Studies on formulation and optimization of gastro retentive multiparticulates of glibenclamide and metformin hydrochloride for the treatment of type II diabetes mellitus using gelucire: A review. J Pharm Sci Res. 2010;2(6):351-4.
21. Bachhav YG, Patravale VB. SMEDDS of glyburide: Formulation, *in vitro* evaluation, and stability studies. AAPS PharmSciTech. 2009;10(2):482-7. doi: 10.1208/s12249-009-9234-1, PMID 19381824.
22. Albertini B, Sabatino MD, Melegari C, Passerini N. Formulation of spray congealed microparticles with self-emulsifying ability for enhanced glibenclamide dissolution performance. J Microencapsul. 2015;32(2):181-92. doi: 10.3109/02652048.2014.985341, PMID 25423165.

23. Cirri M, Roghi A, Valleri M, Mura P. Development and characterization of fast-dissolving tablet formulations of glyburide based on solid self-microemulsifying systems. Eur J Pharm Biopharm. 2016;104:19-29. doi: 10.1016/j.ejpb.2016.04.008, PMID 27091783.
24. Seedher N, Kanojia M. Micellar solubilization of some poorly soluble antidiabetic drugs: A technical note. AAPS PharmSciTech. 2008;9(2):431-36. doi: 10.1208/s12249-008-9057-5, PMID 18431666.
25. Gavali SM, Pacharane SS, Sankpal SV, Jadhav KR. Liquisolid compact: A new technique for enhancement of drug dissolution. Int J Res Pharm Chem. 2011;1(3):705-13.
26. Chella N, Shastri N, Tadikonda RR. Use of the liquisolid compact technique for improvement of the dissolution rate of valsartan. Acta Pharmaceutica Sinica B. 2012;2(5):502-8. doi: 10.1016/j.apsb.2012.07.005.
27. Kapoor D, Sharma S, Patel M, Vyas RB, Chaitali L. Solubility Enhancement and Dissolution Improvement-liqisolid Technique. J Drug Delivery Ther;3(6). doi: 10.22270/jddt.v3i6.673.
28. Thakkar HP, Vasava D, Patel AA, Dhande RD. Formulation and evaluation of liquisolid compacts of itraconazole to enhance its oral bioavailability. Ther Deliv. 2020;11(2):83-96. doi: 10.4155/tde-2019-0050, PMID 31955698.
29. Spireas S, Wang T, Grover R. Effect of powder substrate on the dissolution properties of methyclothiazide liquisolid compacts. Drug Dev Ind Pharm. 1999;25(2):163-8. doi: 10.1081/ddc-100102156, PMID 10065349.
30. Spireas S, Bolton SM. Liquisolid systems and methods for preparing same. United States patent 5,800,834; 1998.
31. Patil SS, Verma AS, Doddayya H, Udupi RH. Development and *in-vitro* evaluation of liquisolid compacts of lornoxicam. Int J Pharm Sci Res. 2020;12(6):2135-46.
32. Lumay G, Boschini F, Traina K, Bontempi S, Remy J-C, Cloots R, *et al*. Measuring the flowing properties of powders and grains. Powder Technol. 2012;224:19-27. doi: 10.1016/j.powtec.2012.02.015.
33. Government of India, Ministry of Health and Family Welfare. The Indian pharmacopoeia commission. Ghaziabad Indian Pharmacopoiea. 2014;1:251-8.
34. Javadzadeh Y, Musaalrezaei L, Nokhodchi A. Liquisolid technique as a new approach to sustain propranolol hydrochloride release from tablet matrices. Int J Pharm. 2008;362(1-2):102-8. doi: 10.1016/j.ijpharm.2008.06.022, PMID 18647643.
35. The United States pharmacopeial convention. Glyburide Tablets. 2010:1-3.
36. Dua JS, Kaur B, Prasad DN. Development and Characterization of Fenofibrate Tablet by Comaparing two Different Solubility and Dissolution Enhancement Methods. Asian J Pharm Res Dev;6(5):32-40. doi: 10.22270/ajprd.v6i5.423.
37. Sullivan DW Jr, Gad SC, Julien M. A review of the nonclinical safety of Transcutol®, a highly purified form of diethylene glycol monoethyl ether (DEGEE) used as a pharmaceutical excipient. Food Chem Toxicol. 2014;72:40-50. doi: 10.1016/j.fct.2014.06.028.
38. Tiong N, Elkordy AA. Effects of liquisolid formulations on dissolution of naproxen. Eur J Pharm Biopharm. 2009;73(3):373-84. doi: 10.1016/j.ejpb.2009.08.002, PMID 19679184.

PICTORIAL ABSTRACT



SUMMARY

- Diabetes mellitus (type II) was chosen as a model drug as it is practically insoluble in water and low dissolution rate, while high permeability. The aim of the study was to formulate and evaluates liquisolid compacts of glyburide by using optimization technique.
- The development and formulation of liquisolid tablets, Transcutol HP was used as the non-volatile solvent, Avicel PH 102 as the carrier material and Aerosil 200 as the coating material.
- Nine formulations LSC-1–LSC-9 were prepared and experimentally responses were obtained, the two responses (Y_1) disintegration time, (Y_2)% CDR at 60 min were subjected to one way ANOVA (statistical analysis) using software Design-Expert for the construction of polynomial equation.
- In addition, the formulations were evaluated using a variety of parameters, viz thickness uniformity, friability, hardness, weight variation and the drug content and all were within the approvable limit. The formulations were also subjected for *in vitro* dissolution study.
- The software generated one solution for independent variables X_1, X_2 with desired answers Y_1, Y_2 using ANOVA ($p<0.05$) and desirability = 1. To validate the model, optimized formulations LSC-10 was prepared using the predicted solutions and evaluated.
- LSC-10 was compared to both the pure medication and the commercial formulation. When comparing the optimal formulation LSC-10 to the pure and commercialised formulation, it was discovered that the *in-vitro* dissolution profile of the optimised formulation LSC-10 was higher.
- Thus, the developed liquisolid technique was proven to be a potential technique for enhancing the dissolution profile and thereby increasing the drug's solubility.

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