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DESIGN, DEVELOPMENT AND OPTIMIZATION OF VALSARTAN LIQUISOLID TABLETS USING BOX-BEHNKEN DESIGN

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ABSTRACT

The aim of the present study was to investigate the applicability of liquisolid technique in improving the dissolution properties of Valsartan in a solid dosage form. This study was designed to optimize and evaluate the effects of different formulation variables: amount of liquid vehicle (X_1), ratio of carrier to coating material(X_2) and amount of magnesium oxide(X_3) on angle of repose (Y_1), hardness(Y_2) and in-vitro release(Y_3) of formulation using three level three factor Box-Behnken statistical design. The non-linear quadratic model generated by the design is of the form: $Y = A_0 + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_1X_2 + A_5X_2X_3 + A_6X_1X_3 + A_7X_1^2 + A_8X_2^2 + A_9X_3^2 + E$, where Y is the measured response associated with each factor level combination. Contour and response surface plots were depicted based on the equation given by the model. The optimization procedure generated the maximum overall desirability value. The optimized formula yields observed values close to the predicted values. Furthermore, the commonly used carrier and coating materials in liquisolid systems Avicel® and Aerosil® were replaced by Neusilin®, an amorphous magnesium aluminometasilicate with an extremely high specific surface area of 339 m^2/g to improve the efficiency of liquisolid approach.

INTRODUCTION: The poor dissolution rate of water insoluble drugs is still a substantial problem confronting the pharmaceutical industry. A great number of new and, possibly, beneficial chemical entities do not reach the public merely because of their poor oral bioavailability due to inadequate dissolution.

Over the years, various solid dosage formulation techniques, to enhance the dissolution of poorly soluble substances, have been introduced with different degrees of success. The technique of 'liquisolid compacts' is a new and promising addition towards such a novel aim [1].

Liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications. The term 'liquid medication' implies oily liquid drugs and solutions or suspensions of water insoluble solid drugs carried in suitable nonvolatile solvent systems termed the liquid vehicles.

Using this new formulation technique, a liquid medication may be converted into a dry-looking, non-adherent, free flowing and readily compressible powder by a simple blending with selected powder excipients referred to as the carrier and coating materials.

Various grades of cellulose, starch, lactose, etc., may be used as the carriers, whereas very fine particle size silica powders may be used as the coating (or covering) materials [2].

A formulation mathematical model by Spireas 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 (Ø-value) and the Compressible (ψ-number) Liquid Retention Potentials of the constituent powders [3].

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 Ø-value is determined by recording powder flow [3, 4]. 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 ψ-number of powders can be determined by using pacticity theories [3, 5]. The excipient ratio R of the powder substrate is defined in the following equation as:

$$R = Q/q$$

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' (L_f) as shown in the following equation:

$$L_f = W/Q$$

For a given excipient ratio R, there exists a specific Flowable L_f factor denoted as ${}^{\emptyset}L_f$, as well as a specific compressible L_f factor denoted as ${}^{\psi}L_f$.

The optimum liquid load factor L_o that produces acceptable flow and compression characters is equal to either ${}^{\emptyset}L_f$, or ${}^{\psi}L_f$, whichever possesses the lower value [3].

In the present research work an attempt has been made to replace commonly used carrier and coating materials in liquisolid systems Avicel® and Aerosil®, respectively by Neusilin® to improve the efficiency of liquisolid approach. Neusilin have extremely high specific surface area of 339 ± 1 m^2/g as well as its good flow and tableting properties [6], this magnesium aluminometasilicate was assumed to allow a considerably higher liquid load factor, thereby enabling the preparation of liquisolid compacts with lower tablet weights.

Due to significantly increased wetting properties and surface area of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release characteristics and, consequently, improved oral bioavailability. Since dissolution of a non-polar drug is often the rate limiting step in gastrointestinal absorption, better bioavailability of an orally administered water-insoluble drug is achieved when the drug is already in solution, thereby displaying enhanced dissolution rates [7].

That is why soft gelatin elastic capsules containing solutions of such medications demonstrate higher bioavailability when compared to conventional oral solid dosage forms [8]. A similar principle underlies the mechanism of drug delivery from liquisolid compacts and is chiefly responsible for the improved dissolution profiles exhibited by these preparations. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution properties.

In the present work, Valsartan, a very slightly water soluble angiotensin-receptor blocker (ARB), was formulated into liquisolid tablets consisting of similar powder excipients and liquid vehicle and different drug concentrations in their liquid medications. The in-vitro drug dissolution rates of such preparations were compared to those of conventionally prepared, directly compressed, tablets using a USP dissolution apparatus II in 900 ml of different dissolution medias like 0.1 N HCl aqueous solution and 6.8 pH Phosphate buffer.

MATERIALS AND METHODS

Materials: Valsartan was received as a gratis sample from Alembic Research Center (Baroda, India). Neusilin® US2 (magnesium aluminometasilicate), Fuji Chemical Industry, Toyoma, Japan. Polyethylene glycol 200 (PEG 200), PEG 400, Propylene glycol, Tween 20, Tween 40, Tween 80, Avicel PH101 (Microcrystalline Cellulose), Avicel PH102, Aerosil 200 (Colloidal Silica), Crosspovidone were purchased from S. D. Fine Chemicals Ltd, Mumbai, India. All other chemicals used were of reagent grade. Double-distilled water was used for all experiments.

Saturation Solubility Studies: The solubility of Valsartan in different non-volatile liquid vehicles that are commonly used for the formulation of liquisolid com pacts, namely, propylene glycol, polyethylene glycol 200 (PEG 200), and PEG 400, Tween 20, Tween 40 and Tween 80 was determined by preparation of saturated solutions of the drug in these solvents and measuring the solubilized drug concentration. Excess Valsartan was stirred in the above mentioned solvents for 48 h at 25˚C. Accurately weighed quantities of the filtered supernatants were further diluted with methanol and analyzed spectrophotometrically at 250 nm for their drug content. From these results, the solubility of Valsartan in the respective liquid vehicle was calculated. Each experiment was carried out in triplicate [9, 10].

Determination of the angle of slide and Flowable Liquid Retention Potential for Carrier and Coating Material: In constant weight of carrier/ coating material, increasing amount of solvent was incorporated and on each addition, angle of repose was determined. The flowable liquid-retention potential (Ø -value) of each liquid/powder admixture was calculated using the following equation.

$$Ø\text{ -value} = \text{weight of liquid/weight of solid}$$

The Ø -values were plotted against the corresponding angle of repose (for optimal flow properties). Corresponding to 33^o of a liquid/powder admixture represented the flowable liquid-retention potential [3, 11].

Determination of Liquid Load Factors (L_f): The appropriate amounts of carrier and coating materials to produce acceptable flowing and compactable powders will be calculated using Eqs.

$$L_f = Ø_{CA} + Ø_{CO}\ (1/R)$$

Based on the physical properties of powders termed ‘‘flowable liquid-retention potential” (Ø-value). The maximum amount of liquid loads on the carrier material, termed ‘‘load factor” (L_f).

Preparation of Liquisolid Compacts: Several liquisolid systems of Valsartan (denoted as F1 to F15) were prepared and compressed into tablets each containing 40 mg drug, using the single punch tablet press. A three-factor, three-level Box-Behnken design was used for constructing a second-order polynomial models using Design Expert (Version 8.0.6.1; Stat-Ease Inc, Minneapolis, Minnesota). A design matrix comprising 15 experimental runs was constructed, for which the nonlinear computer-generated quadratic model is defined as:

$$Y = A_0 + A_1X_1 + A_2X_2 + A_3X_3 + A_4X_1X_2 + A_5X_2X_3 + A_6X_1X_3 + A_7X_1^2 + A_8X_2^2 + A_9X_3^2 \quad \ldots\ldots (1)$$

Where, Y is the measured response associated with each factor level combination; A_0 is constant; A_1, A_2, A_3 are linear coefficients, A_{12}, A_{13}, A_{23}, are interaction coefficients between the two factors and are computed from the observed experimental values of Y from experimental runs; and X_1, X_2, and X_3 are the coded levels of independent variables. The terms X_1X_2 (i = 1, 2 or 3) represent the interaction effect and X_1^2, X_2^2, X_3^2 represent the curvature effects.

The concentration range of independent variables under study is shown in **table 1** along with their low and high levels, which were selected based on the results from preliminary experimentation. The range of amount of liquid (X_1), ratio of carrier to coating material (X_2), and amount of magnesium oxide (X_3) used to prepare the 15 formulations and the respective observed responses are given in **table 2.**

TABLE 1: FACTORS AND THEIR DIFFERENT LEVELS FOR BOX BEHNKEN DESIGN FOR PREPARATION LIQUISOLID TABLETS

Independent Variables	Levels		
	Low (-1)	Medium (0)	High (+1)
Amount of Liquid (mg) (X_1)	50	75	100
Ratio of carrier to coating material (R) (X_2)	5	10	20
Amount of magnesium oxide (%w/w) (X_3)	2.5	5	7.5
Dependent Variables		Goal	
Angle of Repose (Y_1)		Minimize	
Hardness (kg/cm^2) (Y_2)		Optimize	
% CDR in 6.8 pH in 60 min (Y_3)		Maximize	

TABLE 2: EXPERIMENTAL MATRIX AND RESULTS

Run	Independent Variables			Responses		
	X1	X2	X3	Y1	Y2	Y3
F1	-1	-1	0	36.1 ± 1.2	5.2 ± 0.2	72.42 ± 1.9
F2	-1	+1	0	33.3 ± 0.5	6.2 ± 0.3	73.79 ± 2.3
F3	+1	-1	0	38.3 ± 0.6	2.5 ± 0.4	89.37 ± 3.1
F4	+1	+1	0	35.1 ± 0.9	3.5 ± 0.1	95.05 ± 2.5
F5	-1	0	-1	34.2 ± 1.4	5.5 ± 0.5	75.86 ± 1.6
F6	-1	0	+1	33.8 ± 0.9	5.8 ± 0.2	74.27 ± 2.1
F7	+1	0	-1	37.9 ± 0.4	2.7 ± 0.3	97.05 ± 3.1
F8	+1	0	+1	37.3 ± 0.2	2.5 ± 0.2	94.98 ± 2.5
F9	0	-1	-1	36.9 ± 0.9	3.2 ± 0.3	91.73 ± 2.6
F10	0	-1	+1	36.2 ± 0.3	3.4 ± 0.2	88.85 ± 1.7
F11	0	+1	-1	34.2 ± 0.5	5.2 ± 0.3	92.10 ± 2.4
F12	0	+1	+1	33.9 ± 0.3	5.5 ± 0.2	92.70 ± 2.6
F13	0	0	0	35.1± 0.8	4.3 ± 0.4	93.26 ± 1.3
F14	0	0	0	35.6 ± 0.9	4.4 ± 0.2	92.67 ± 2.1
F15	0	0	0	35.3 ± 0.6	4.3 ± 0.3	91.44 ± 2.3
FN	0	+1	+1	33.5 ± 0.2	5.6 ± 0.1	93.73 ± 1.9

X1, Amount of liquid (mg) ; X2 , Ratio of carrier to coating material; X3, Amoumt of magnesium oxide (%w/w), Y1, Angle of repose; Y2, hardness(kg/cm2); Y3, % CDR in 6.8 pH in 60 min (%). FN, formulation containing Neusilin as carrier material. Results are expressed as mean ± SEM.

All liquisolid formulations contained microcrystalline cellulose "Avicel® PH 102" as the carrier powder and silica (Aerosil 200) as the coating material at different powder excipient ratio (R) using Box-Behnken design. Propylene glycol was used as the liquid vehicle in different amounts as 50mg, 75mg, and 100mg to prepare the liquid medications with a different drug concentration.

Different amount of propylene glycol 50mg, 75mg, and 100mg were used. Different liquid load factor, L_f, 0.225, 0.30 and 0.4w/w were employed. Different percentage of magnesium oxide 2.5, 5, and 7.5 % (w/w) were used as a flow activator. Finally, standard 5% crosspovidone was used as a disintegrant and 1% magnesium stearate as a lubricant in all systems.

Liquisolid tablets were prepared as follows, Valsartan was dispersed in propylene glycol and the mixture of Avicel PH102- Aerosil 200 and magnesium oxide were added to the mixture under continuous mixing in a mortar. Finally, crosspovidone was mixed and mixture was blended for a period 10 minutes and then magnesium stearate was added before compression as a lubricant [12]. After optimization of formulation from statistics, another formulation was prepared replacing Avicel PH 102 by Neusilin US 2 to reduce the tablet weight.

Evaluation:

1. **Flowability of Valsartan Liquisolid Powders:** The flowability evaluation (expressed as the angle of repose, Y_1) of each formula was carried out by fixed height method. As a general guide, powders with angles of repose greater than 50° have unsatisfactory flow properties, whereas minimum angles close to 25° correspond to very good flow

properties [13]. The tablets were also evaluated for other different parameters like weight variation, friability, hardness, disintegration time.

2. **Content uniformity Valsartan Liquisolid Tablets:** Drug content uniformity was determined by dissolving the tablets in methanol and filtering with Whatman filter paper (0.45 µm). Then by employing suitable dilution, drug concentration was analyzed at 250 nm using a UV spectrophotometer (UV-1700, shimadzu Inc. Japan). The experiments were performed in triplicate, and average values were reported [14, 15].

3. ***In-vitro* release of Valsartan from Liquisolid Tablets:** The test was performed on the prepared Valsartan liquisolid tablets using the USP dissolution apparatus II. Six individual tablets from each formula were tested. Test was performed in 900ml of two different dissolution medium (0.1 N HCL, 6.8 pH phosphate buffer). In all studies, the temperature of the dissolution medium was maintained at 37±0.5 °C. The aliquots of 5ml were withdrawn at regular time intervals 10, 20, 30, 40, 50 and 60minutes, filtered, and analyzed spectrophotometrically at 250 nm [10, 16].

   For assessment and comparison, drug dissolution rates (D_R) of drug were used. For this, amount of drug (in µg) dissolved per min that presented by each tablet formulation during the first 10 min were calculated as follows [10, 17]:

$$D_R = (M \times D) / 1000$$

   Where, M is the total amount of Valsartan in each tablet (in this study, it is 40000 µg) and D denotes percentage of drug dissolved in first 10 min.

4. **Effect of aging on tableting properties:** Stability testing of drug products begins as part of the drug discovery process and ends with the rejection of the compound or its acceptance as a commercial product. The FDA and ICH specify the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. The study was performed under accelerated stability conditions at 40˚C ± 2˚C/75% RH ± 5% RH for three months [9].

RESULTS

Solubility Studies of Valsartan: Solubility of valsartan was determined in different solvents and reported in **table 3** and it was observed that it has greater solubility in propylene glycol than other solvents. So it was selected for further formulation. **Figure 1** shows comparison of solubility of Valsartan in different solvents.

TABLE 3: SOLUBILITY OF VALSARTAN IN DIFFERENT SOLVENTS

Solvent	Solubility (mg/ml)
Water	0.079 ±0.002
1.2 pH	0.0248 ±0.003
6.8 pH	0.082 ± 0.01
Propylene glycol	134.37 ±2.3
PEG 200	52.50 ±1.2
PEG 400	68.43 ±1.5
Tween 20	63.40 ±1.3
Tween 40	73.75 ±1.2
Tween 80	91.25 ±1.4

Results are expressed as mean ± SEM

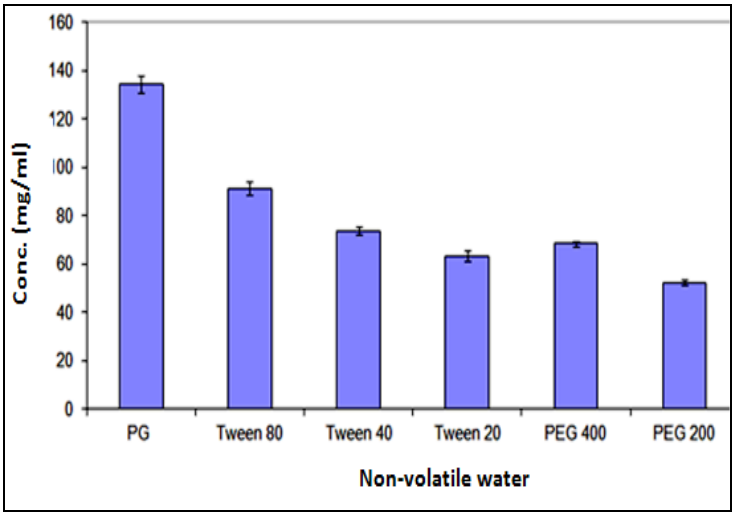


FIG. 1: COMPARISON OF SOLUBILITY OF VALSARTAN IN DIFFERENT SOLVENTS

Flowable liquid retention potential (Ø-value) and liquid load factor (L_f): Angle of repose was measured for powder containing Avicel PH101, Avicel PH102, Neusilin and Aerosil 200. As Avicel PH102 had shown higher liquid retention maintain good flow than Avicel PH101 it was used for preparation of liquisolid tablets (F1-F15). **Figure 2** shows the relationship between the angle of repose and corresponding $Ø_{CA}$- value and $Ø_{CO}$-value of propylene glycol. **Table 4** shows different liquid load factors (L_f) which were determined by employing different ratios (R) of Carrier to coating material.

TABLE 4: DIFFERENT L_F VALUES FOR DIFFERENT RATIOS OF CARRIER TO COATING MATERIAL

Carrier to coating Material Ratio (R)	Liquid load factor (L_f) of Avicel PH 102	Liquid load factor (L_f) of Neusilin US 2
5	0.45	0.52
10	0.30	0.37
15	0.225	0.3

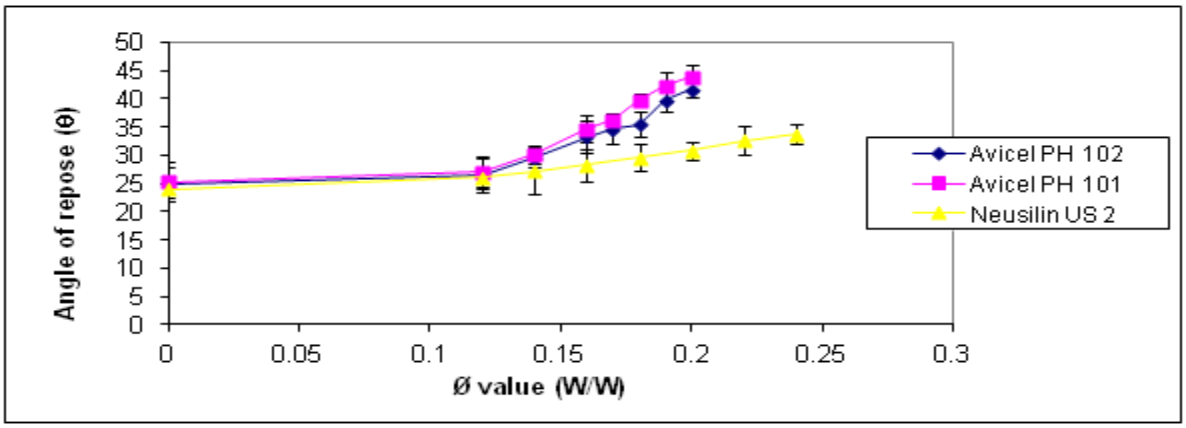


FIG. 2: (A) RELATIONSHIP BETWEEN ANGLE OF REPOSE AND CORRESPONDING $Ø_{CA}$- VALUE OF DIFFERENT CARRIER MATERIAL FOR PROPYLENE GLYCOL

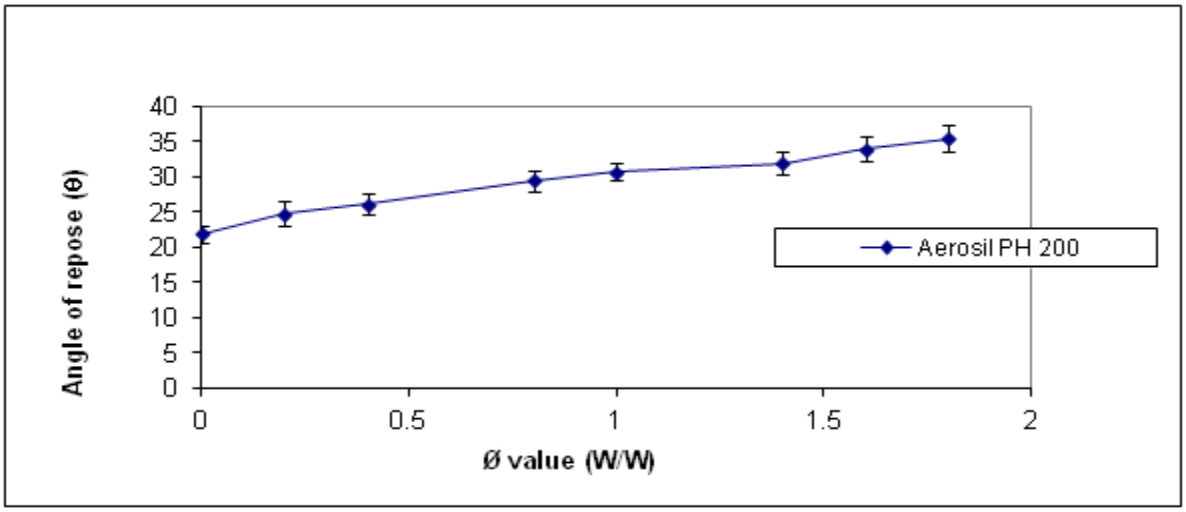


FIG. 2: (B) RELATIONSHIP BETWEEN ANGLE OF REPOSE AND CORRESPONDING $Ø_{CO}$- VALUE OF COATING MATERIAL (AEROSIL 200) FOR PROPYLENE GLYCOL

Angle of Repose of Liquisolid Powders (Y_1): Angle of Repose for all liquisolid powders were determined by using fixed height method. The angle of repose of various Valsartan liquisolid powders are presented in **table 2**. The smallest angle of repose was observed for Valsartan liquisolid powders F6 (33.8 ± 0.9), whereas the maximum was obtained as 38.3 ± 0.6 for F3.

Weight Variation and Content Uniformity: All liquisolid tablets complied with the USP weight uniformity test. Also, all tablets had met USP content uniformity criteria. The results were reported in **table 5.**

Tablet Hardness (Y_2), friability and Disintegration Time: The mean hardness of all formulations is presented in **table 2**. Hardness of all formulations was between 1.5-7 kg/cm^2. The maximum hardness 6.2 ± 0.3 kg/cm^2 was obtained for F2 and minimum hardness 2.5 ± 0.4 kg/cm^2 for F3.

All liquisolid tablets passed friability test as all shows less than 1% friability.

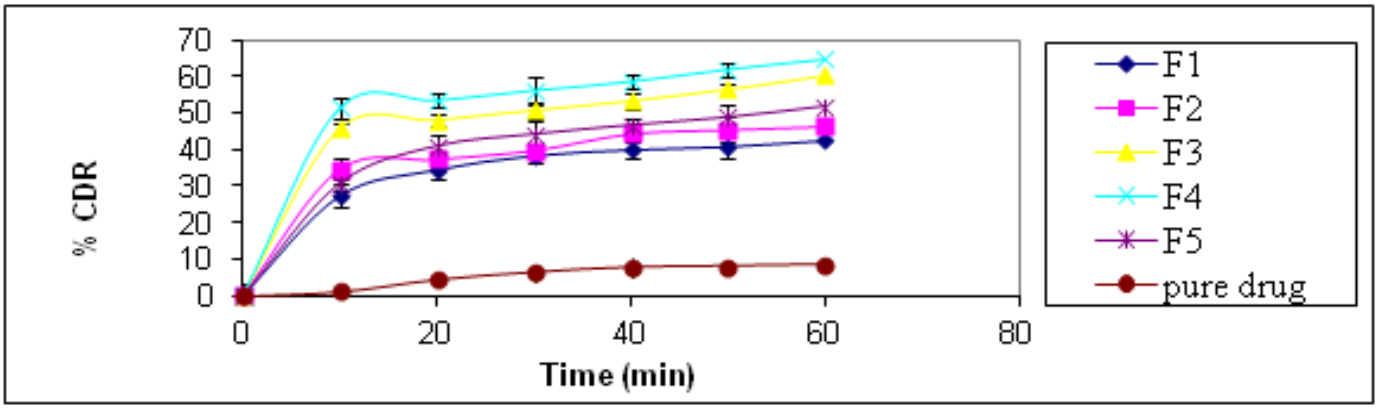
The mean disintegration time for all formulations is presented in **table 5**. The disintegration time were observed between 46-116 sec.

TABLE 5: EVALUATION OF LIQUISOLID TABLETS

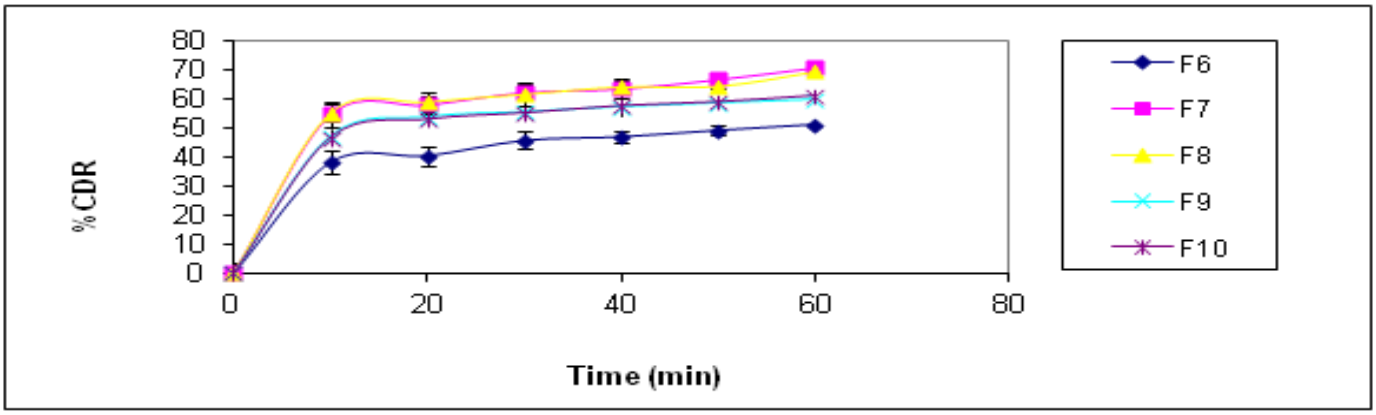
Formulation	Thickness (mm)	%Friability	Disintegration time (sec)	% Content Uniformity	Weight Variation
F1	2 ± 0.1	0.46	90 ±5	97.18 ±0.78	Pass
F2	3.1 ± 0.2	0.0	135 ±3	98.43 ±1.43	Pass
F3	3.1 ±0.1	0.88	46 ±6	100.15 ±2.56	Pass
F4	5.1±0.1	0.19	71 ±2	97.3 ±2.36	Pass
F5	2.7±0.2	0.37	106 ±4	94.07 ±0.86	Pass
F6	2.8 ±0.2	0.0	112 ±6	99.37 ±0.28	Pass
F7	4.1 ±0.2	0.24	50 ±3	101.10 ±1.42	Pass
F8	4.2 ±0.1	0.23	59 ±4	95.16± 1.71	Pass
F9	2.7 ±0.2	0.38	69 ±7	95.63 ±0.45	Pass
F10	2.8 ± 0.2	0.35	72 ±5	98.28 ±1.91	Pass
F11	4.1 ±0.1	0.24	90 ±6	99.37 ±2.78	Pass
F12	4.2 ±0.2	0.24	116 ±3	98.28 ±1.13	Pass
F13	3.3 ±0.2	0.23	87 ±5	99.37 ±1.47	Pass
F14	3.3 ±0.1	0.23	93 ±4	98.28 ±2.61	Pass

Results are expressed as mean ± SEM.

***In-vitro* release study:** The amount of drug release from the different liquisolid tablets was found to be ranging between from 42.48 % to 70.59 % in 0.1 N HCL and 72.42 % to 97.09 % in 6.8 pH phosphate buffer. The release profile of all formulations is shown in the **figure 3** and **figure 4** respectively. F4 and F7 showed the maximum release as 64.67, 70.59 and 95.05 % , 97.07 % at 0.1 N HCL and 6.8 pH phosphate buffer respectively. The comparison of dissolution rates (D_R) of all formulations are shown in **figure 5**. Comparison of release of Valsartan through F12 and FN is shown in **figure 6.**



(A)



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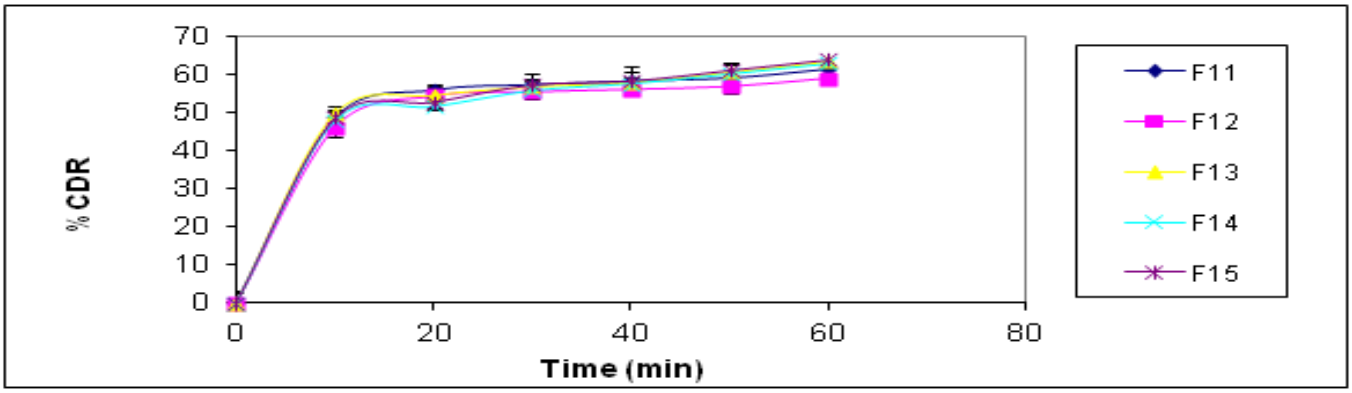
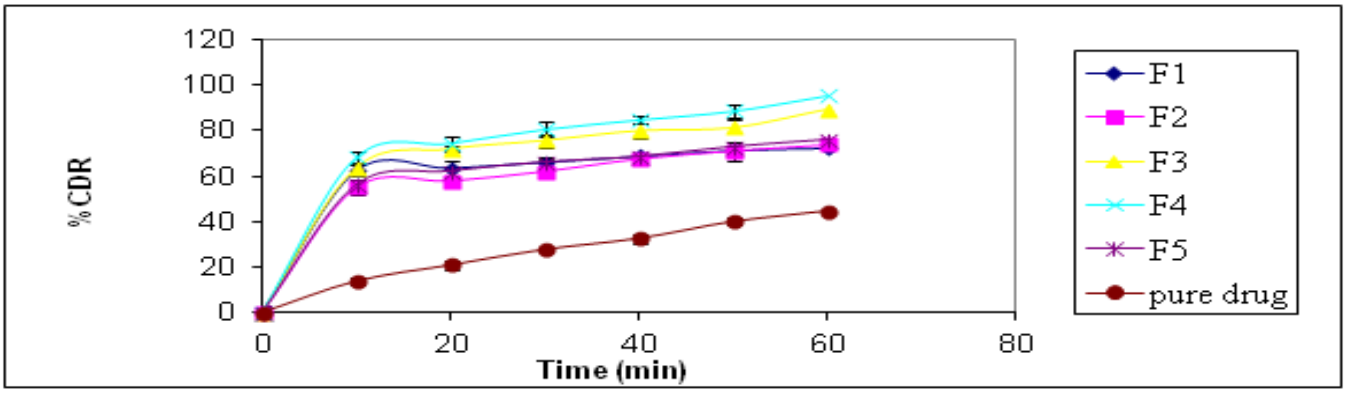
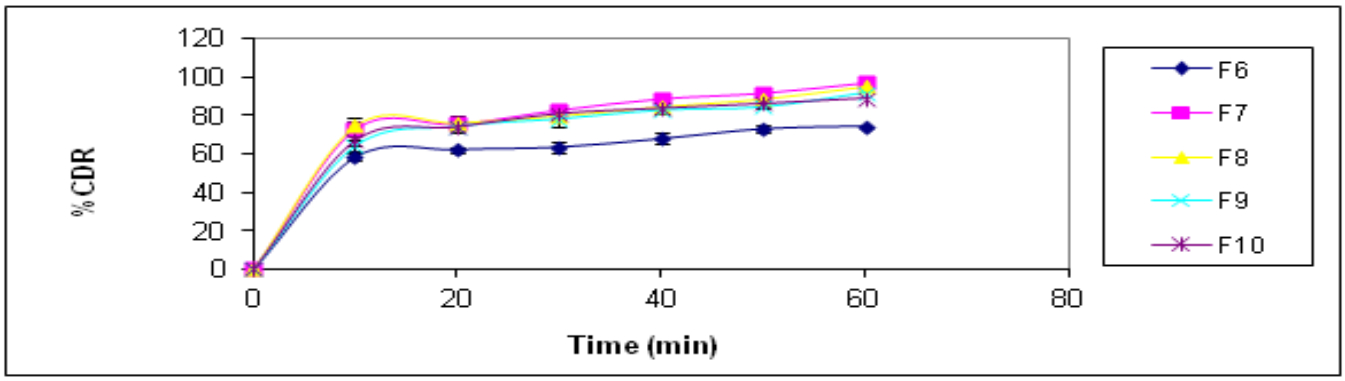


(C)

FIG. 3: RELEASE PROFILE OF VALSARTAN FROM LIQUISOLID TABLET IN 0.1 N HCL (A) F1 TO F5 AND PURE DRUG (B) F6- F10 AND (C) F11- F15



(A)



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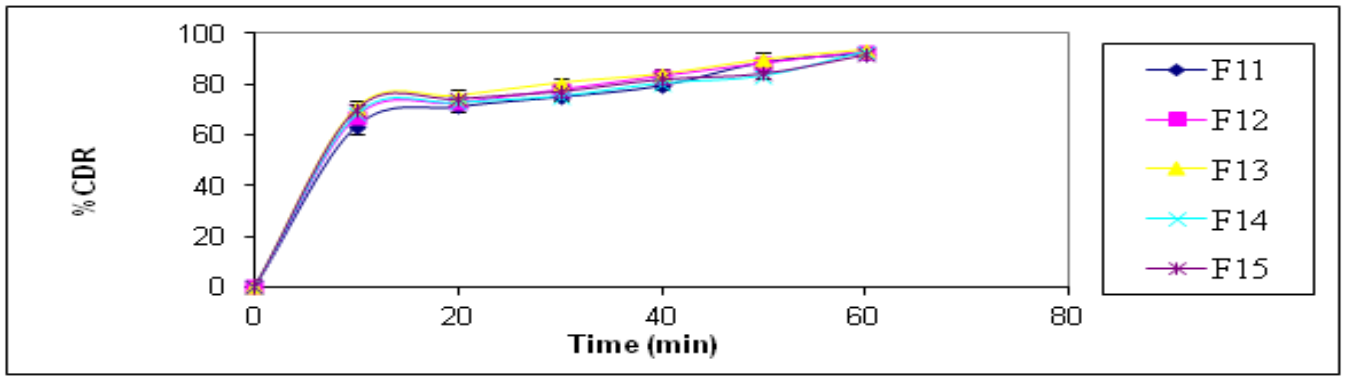

(C)

FIG. 4: RELEASE PROFILE OF VALSARTAN FROM LIQUISOLID TABLET IN 6.8 PH PHOSPHATE BUFFER (A) F1 TO F5 AND PURE DRUG (B) F6- F10 AND (C) F11- F15

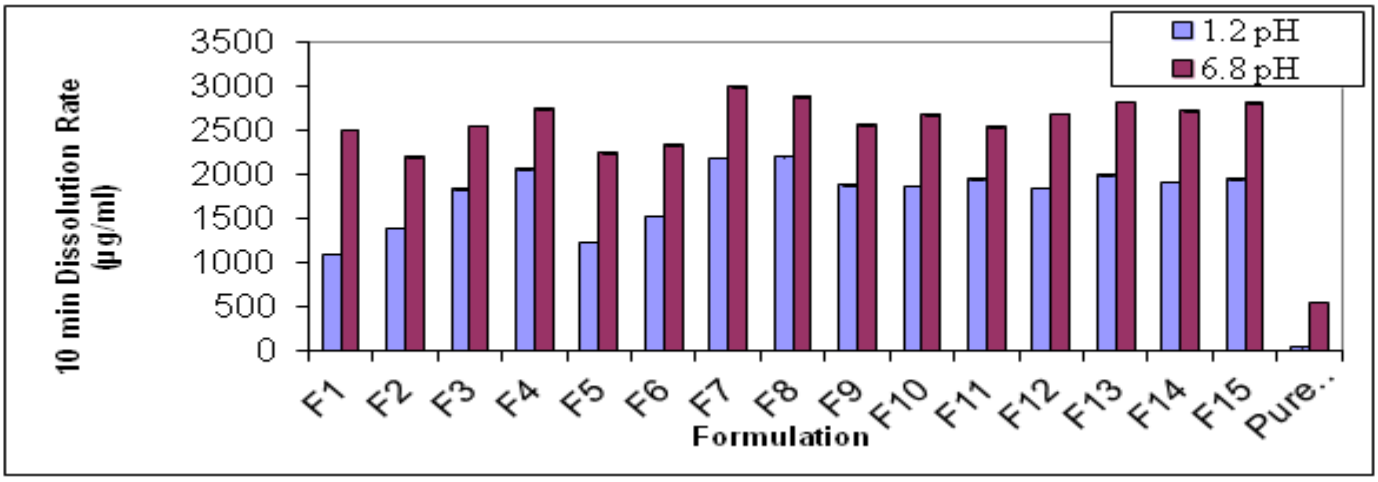

FIG. 5: COMPARISION OF THE 10 MIN DISSOLUTION RATE OF VALSARTAN EXHIBITED BY LIQUISOLID TABLETS AND PURE DRUG AT DIFFERENT DISSOLUTION MEDIA

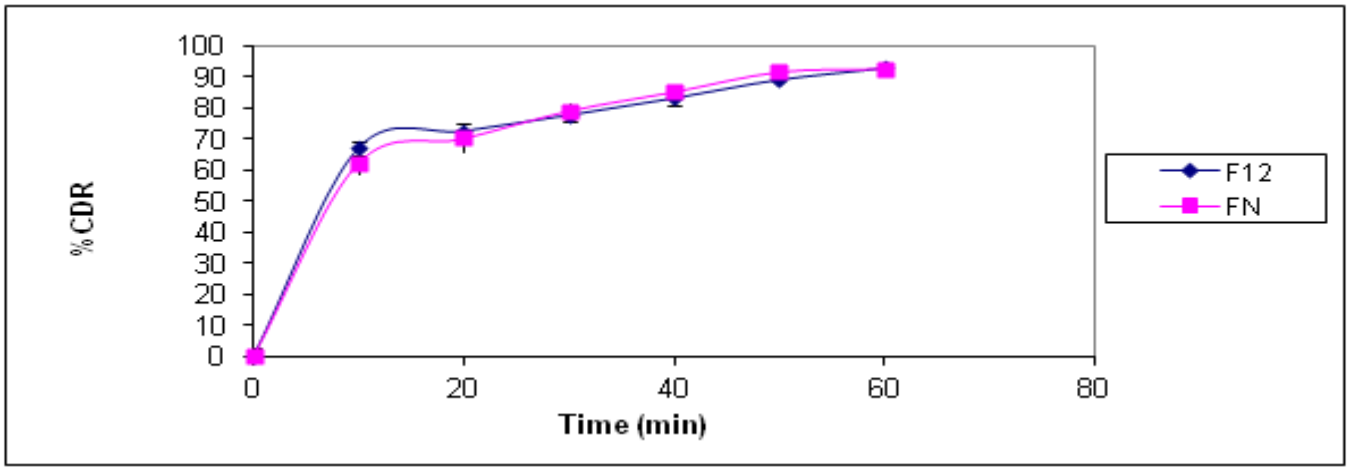

FIG. 6: COMPARISION OF RELEASE OF VALSARTAN THROUGH LIQUISOLID TABLETS F12 AND FN

Effect of aging on Tabletting Properties: Stability studies of liquisolid compacts indicate that there is no major difference in hardness (2.9±0.1 kg/cm^2) and disintegration time (50±3 s) after storing the formulations for three months under accelerated storage conditions. The dissolution profile (**Figure 7**) of fresh and aged Valsartan liquisolid tablets compacts showed no significant effect on drug release ($P > 0.05$). Stability studies show that the physical and chemical properties of the tested compacts were not altered significantly and all the tested formulations were found to be stable.

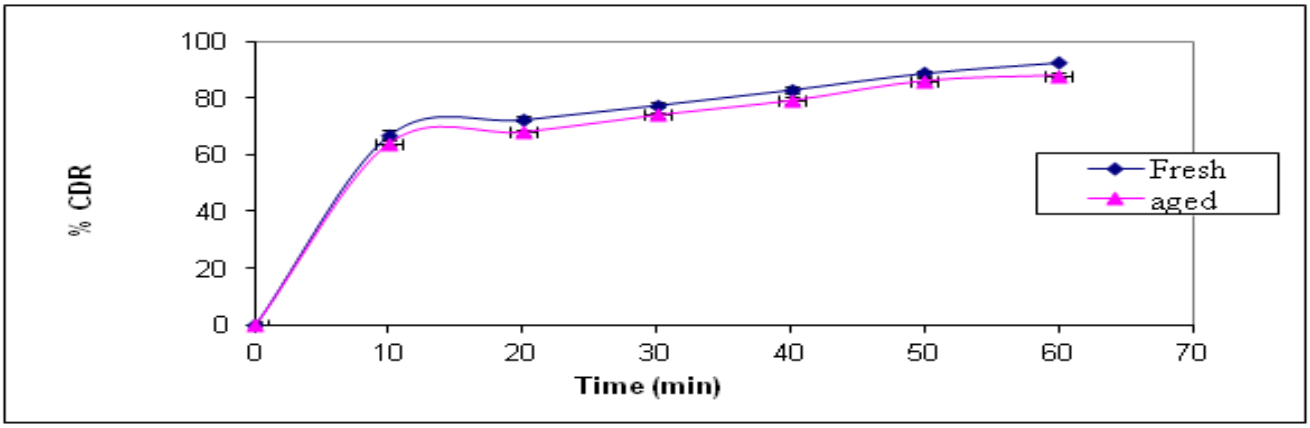

FIG. 7: RELEASE OF OPTIMIZED VALSARTAN LIQUISOLID TABLETS (FRESH AND AGED)

DISCUSSION:

Angle of Repose of liquisolid powders (Y_1): Figure 8 showed the response surface plot, which displayed the effect of X_1 and X_2 on the angle of repose Y_1. From the figure, at fixed level of X_3 (5%), increasing X_1 up to 100 mg along with decreasing X_2 to 5 results in increasing the angle of repose of the formulation to the maximum 38.3. On the other hand, decreasing the X_1 to 50 mg and increasing X_2 up to 20 results in decreasing the angle of repose to the minimum 33.3. Also, it was found that, at low level of X_2 (5), the angle of repose of the formulation will maximized either at low 2.5 % or high 7.5% of X_3, where the angle of repose of the formulation were 36.9 and 36.2.

Contour plot represented in **figure 9** gave an idea about the exact percent of X_1 and X_2 at which the angle of repose becomes at minimum level.

Figure 10 showed the linear correlation plot of predicted and actual values of angle of repose and these values are near by each other.

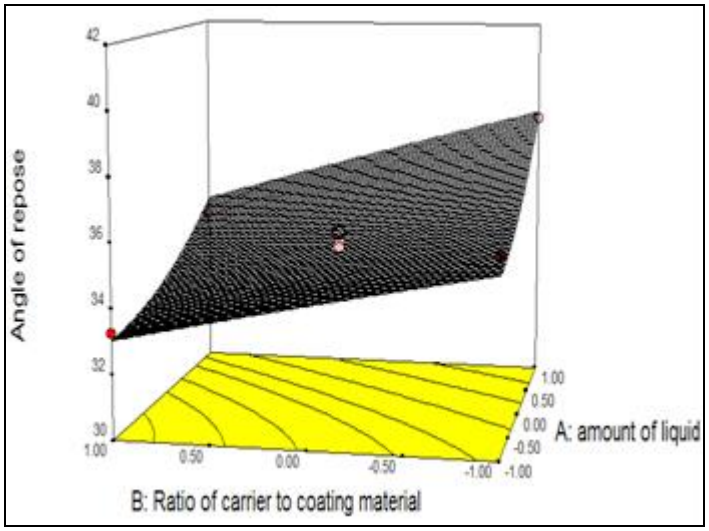

FIG. 8: RESPONSE SURFACE PLOT SHOWING THE EFFECT OF X_1 AND X_2 ON ANGLE OF REPOSE

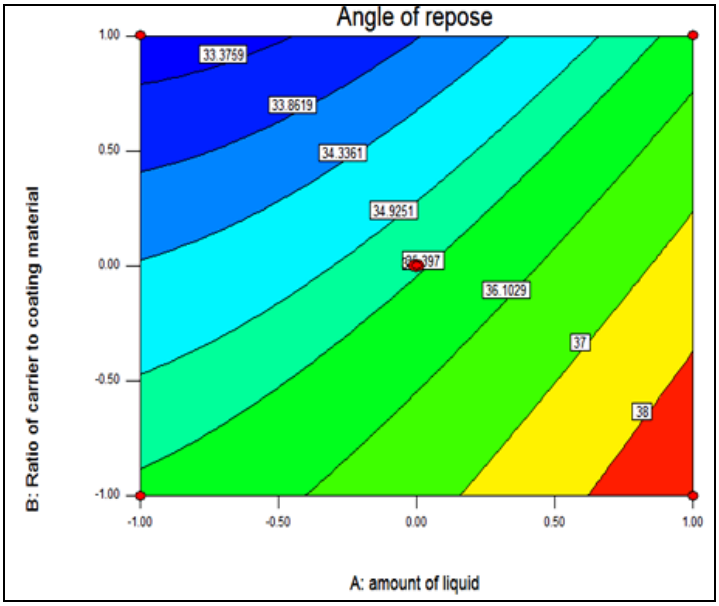

FIG. 9: CONTOUR PLOT SHOWING THE EFFECT OF X_1 AND X_2 ON ANGLE OF REPOSE

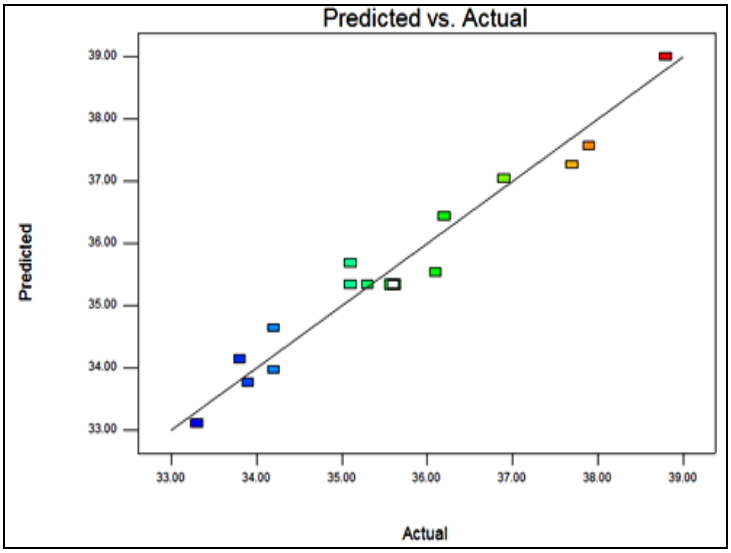

FIG 10: LINEAR CORRELATION PLOTS BETWEEN ACTUAL AND PREDICTED VALUES OF ANGLE OF REPOSE

Hardness of liquisolid tablets (Y_2): Figure 11 showed the response surface plot, which displayed the effect of X_1, and X_2 on the hardness Y_2. From the figure, at fixed level of X_3 (5%), increasing X_1 up to 100 mg along with decreasing X_2 up to 5 results in decreasing the hardness Y_2 of the formulation to be 1.7. On the other hand, using the low level of X_1 (50 mg) along with decreasing X_2 up to 5 results in increasing the hardness Y_2 to 6.2, and this value increased to 7.2 when X_2 will increase to 20. Also, it was found that, at fixed level of X_1(50 mg) and X_2 (5), the hardness of the formulation will remain approximately same either at low 2.5 % or high 7.5% of X_3, where the hardness of the formulation were 6.5 and 6.7.

Contour plot in **figure 12** gives an idea about the exact percent of X_1, and X_2 at which the hardness Y_2 becomes at optimum level at fixed level of X_3 (5%). From the figure, using X_1 from 50 to 75 along with percent of X_2 ranging from 5 to 10 can produce a formulation having hardness Y_2 from 5 to 6.5. While using X_1 from 75 to 100 along with low percent of X_2 produce a formulation having the hardness from 2.5 to 4.2.

Figure 13 showed the linear correlation plot of predicted and actual values of hardness and these values are near by each other.

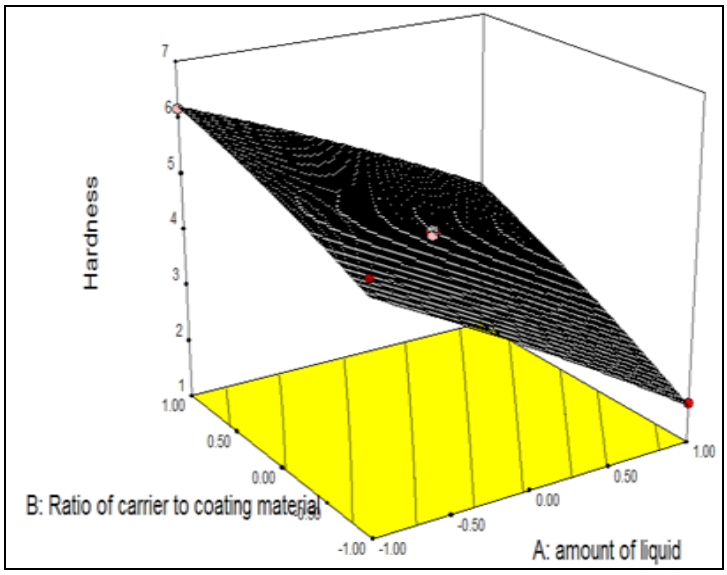

FIG. 11: RESPONSE SURFACE PLOT SHOWING THE EFFECT OF X_1 AND X_2 ON HARDNESS

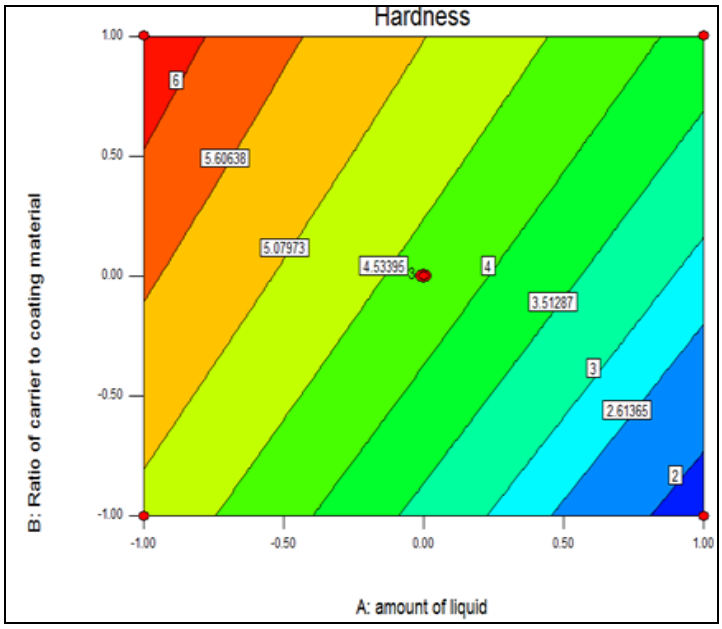

FIG. 12: CONTOUR PLOT SHOWING THE EFFECT OF X_1 AND X_2 ON HARDNESS

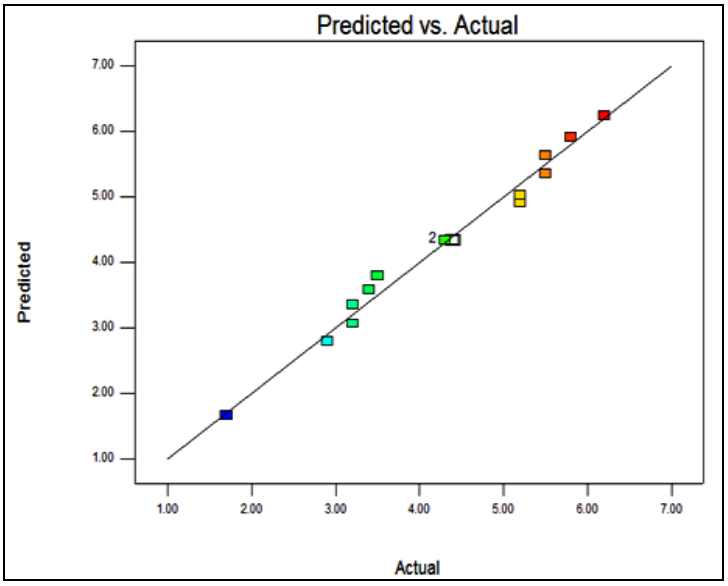

FIG. 13: LINEAR CORRELATION PLOTS BETWEEN ACTUAL AND PREDICTED VALUES OF HARDNESS

***In-vitro* release study (Y_3): Figure 14** showed the response surface plot, which displayed the effect of X_1, and X2 on the in vitro release study Y_3. From the figure, it can be observed that at fixed level of X_2 (10), increasing X_1 from 50 to 100 mg results in a formulation having in vitro release from 75.86 to 97.05. On the other hand, increasing X_2 up to 20 results in a formulation having decrease *in vitro* release 95.05.

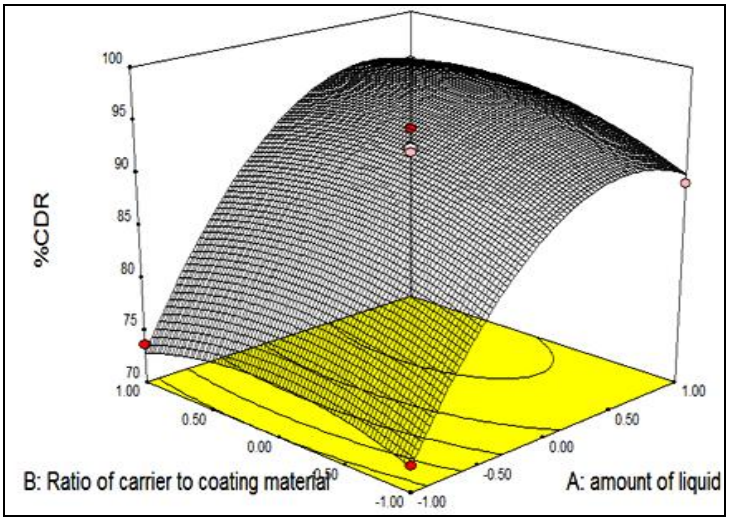

FIG. 14: RESPONSE SURFACE PLOT SHOWING THE EFFECT OF X_1 AND X_2 ON %CDR

Contour plot in **figure 15** gives an idea about the exact percent of X_1, and X_2 at which the in-vitro release Y_3 becomes at maximum level at fixed level of X_3 (5%). From the figure, using X_1 from 50 to 75 along with percent of X_2 ranging from 5 to 10 can produce a

formulation having in-vitro release Y_3 from 72.42 to 91.73.

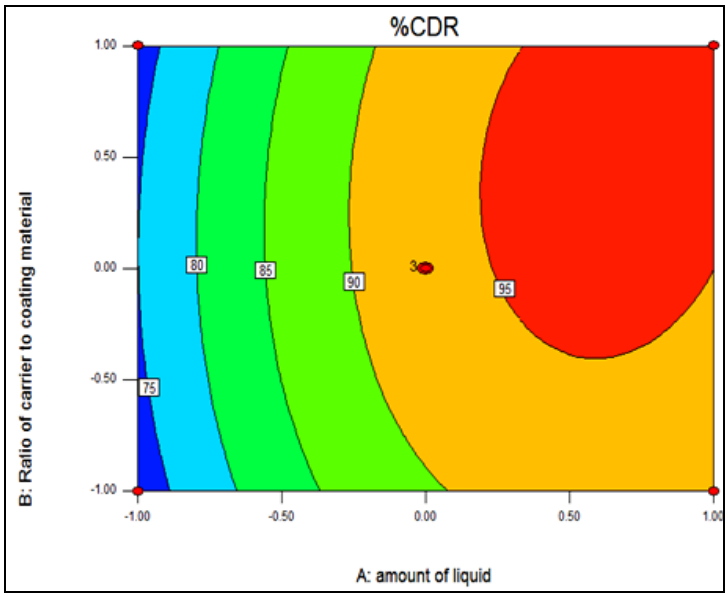

FIG. 15: CONTOUR PLOT SHOWING THE EFFECT OF X_1 AND X_2 ON %CDR

While using X_1 from 75 to 100 along with low percent of X_2 produce a formulation having the in-vitro release from 93.26 to 97.05.

Figure 16 showed the linear correlation plot of predicted and actual values of % CDR and these values are near by each other.

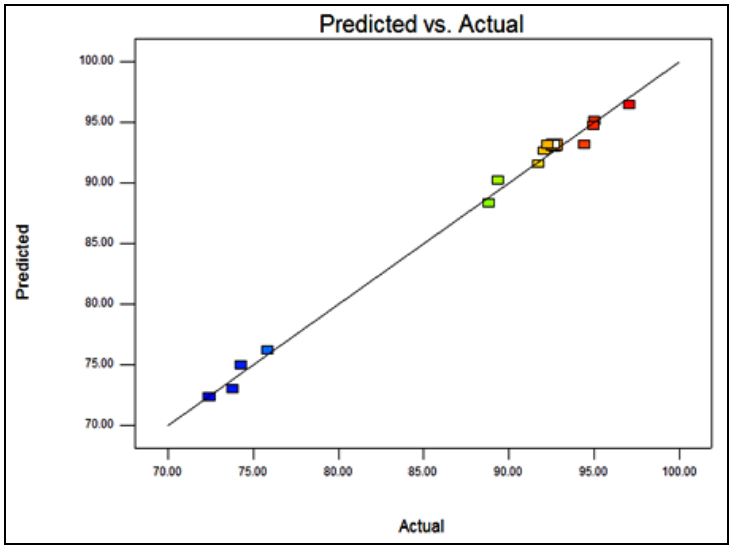

FIG. 16: LINEAR CORRELATION PLOTS BETWEEN ACTUAL AND PREDICTED VALUES OF % CDR

CONCLUSION: The liquisolid tablet technique can prove to be an effective and efficient way for dissolution rate improvement of water insoluble drugs such as Valsartan as it shows faster release than that of pure drug. Propylene glycol was used as a liquid vehicle. Enhanced dissolution rates obtained in the present study can be attributed to increased wetting and surface area available for dissolution. This novel approach to the formulation may be helpful to improve oral bioavailability. Use of a highly adsorptive carrier such as Neusilin US 2 resulted in reduction in tablet weight compared to formulations prepared using Avicel PH 102. This might be due to the carrier's physical properties such as particle size, surface area and liquid retention capacity.

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REFERENCES:

1. Spireas S, Sadu S: Enhancement of prednisolone dissolution properties using liquisolid compacts. International Journal of Pharmaceutics 1998; 166:177–188.
2. Kulkarni AS, Nagesh H, Aloorkar, Mane MS, Gaja JB: Liquisolid Systems: A Review. International Journal of Pharmaceutical Sciences and Nanotechnology 2010; 3(1):795-802.
3. Louis D, Tayel SA, Soliman II: Improvement of dissolution properties of Carbamazepine through application of the liquisolid tablet technique. European Journal of Pharmaceutics and Biopharmaceutics 2008; 69:342–347.
4. Gold G, Duvall RN, Palermo BT, and Slater JG: Powder flow studies II: Effects of gliadants on flow rate and angle of repose. Journal of pharmaceutical sciences 1996; 55:1291-1295.
5. Spireas SS, Sadu S, and Grover R: *In-vitro* release evaluation of hydrocortisone liquisolid tablets. Journal of pharmaceutical sciences 1998; 87:867-872.
6. Hentzchel CM, Sakmann A, and Leopold CS: Suitability of various excipients as carrier and coating materials for liquisolid compacts. Drug Development and Industrial Pharmacy, 2011,doi:10.3109/03639045.03632011.03564184.
7. Nelson E: Physicochemical and pharmaceutical properties of drugs that influence the results of clinical trials. Clinical Pharmacology and Therapeutics 1962; 3:673-681.
8. Ebert WR: Soft elastic gelatin capsules: unique dosage form. Pharmaceutical Technology, 1, 44-50.
9. Gubbi SR, Jarag R: Formulation and characterization of atorvastatin calcium liquisolid compacts. Asian Journal of Pharmaceutical Sciences 2010; 5(2):50-60.
10. Nokhodchi A: Effect of type and concentrate of vehicles on the the dissolution rate of a poorly soluble drug (Indomethacin) from liquisolid compacts. Journal of Pharmacy and Pharmaceutical Sciences 2005; 8(1): 18-25.
11. Tiong N and Elkordy AA: Effects of liquisolid formulations on dissolution of naproxen. European Journal of Pharmaceutics and Biopharmaceutics 2009; 73:373-384.
12. Gavali SM, Pacharane SS, Sankpal SV, Jadhav KR and Kadamet VJ. Liquisolid Compact: A New Technique for Enhancement Of

Drug Dissolution. International Journal Of Research In Pharmacy And Chemistry 2011; 1(3):705-713.
13. Martin A. Physical Pharmacy, Philadelphia: Lippincott Williams and Wilkins; Edition 4, 1993, 444.
14. Sharma A and Jain CP: Preparation and characterization of solid dispersions of Valsartan with Poloxamer 188, Der Pharmacia Lettre 2010; 2(2):54-63.
15. Patel M, Patel M, Patel N and Bhandari A: Formulation and evaluation of lipid based formulation of valsartan. International Journal of Current Pharmaceutical Research 2011; 3(4):76-81.
16. Burra S and Galipelly SK: Enhancement of solubility and dissolution rate of frusemide through liquisolid technique. Der Pharmacia Lettre 2010; 2(6):321-328.
17. Mahajan HS, Dhamne MR, Gattani SG, Rasal AD, Shaikh HT: Enhanced Dissolution Rate of Glipizide by a Liquisolid Technique. International Journal of Pharmaceutical Sciences and Nanotechnology, 2011; 3(4):1205-1213.

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