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Improvement of solubility and dissolution rate of Repaglinide by Liquisolid Compact technique: QbD approach

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ABSTRACT: The bioavailability and therapeutic efficacy of several active molecules is limited due to poor solubility. Repaglinide is used to lower plasma glucose levels, especially in type II diabetes mellitus, and its activity is low due to extensive first-pass metabolism and poor solubility. The current research focused on improving the solubility and thus accelerating the dissolution rate of repaglinide for its antidiabetic effect. Liquisolid Compact technique was used for potent therapeutic molecules, which improved the solubility, dissolution rate and thus bioavailability using non-volatile solvents. Repaglinide was readily soluble in PEG 200 at 241 mg/ml. Incorporation of PEG 200 resulted in conversion of solid drug to liquid drug and conversion back to powder form was achieved by incorporation of carrier and coating agents. The compatibility of repaglinide with all excipients was tested by FTIR and the compatibility with excipients was confirmed. Before compression, all powder mixtures were tested for their flow properties such as Carr index and angle of repose, etc. Optimization was performed using Design of Expert, applying 32 Box-Behnken designs consisting of 3 independent parameters (DCP, Aerosil 200 and CP) and reliable parameters (decay and dissolution time). The optimized batch F1 showed good flow properties, low disintegration time and higher dissolution rate of 99.56% within 30 minutes. In addition, the optimized batch successfully passed the stability test.

KEYWORDS: Repaglinide; Liquisolid technique; solubility enhancement; Box Behnken design.

1. INTRODUCTION

Several new therapeutic molecules have been invented in clinical trials possess high lipophilicity aiming to cross the gastrointestinal (GIT) barrier and thus showed poor solubility [1]. The low solubility of active ingredients is big challenge for pharmaceutical industry which resulted in poor therapeutic efficacy. Moreover, the absorption of therapeutic moieties and their bioavailability is mainly depends on the solubility and dissolution characteristics [2]. Around 40 % of the approved products in the market and 90 % of the new chemical entities faced the hurdle of low solubility in GIT [3, 4]. According to the ''Lipinski's Rule of Five '' these agents can't produce enough therapeutic efficacy [5]. When solubility of active agents were less than 100 µg/ml, then the agent is considered as poorly soluble and require the improvement in solubility [6].

Oral drug delivery is widely acceptable over other routes for offering ease of convenience, economical, high patient comfort, accuracy and safety. Upon administration through oral route, the active ingredient must dissolve in presence of gastric juice and failure is resulted due to poor solubility characteristics. Hence, solubility is the rate-limiting step towards the absorption and bioavailability of drugs [7]. As per recommendation provided by Biopharmaceutics classification system (BCS) and Biopharmaceutics drug disposition classification system (BDDCS), the agents with poor solubility is categorized in class II and IV respectively [8].

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Solubility of active ingredients can be modify by utilizing several enhancement techniques such as solid dispersion, ionic liquids, micronization, supercritical fluid (SCF), nanomatrix, micellar solubilization, self-microemulsifying drug delivery system, solid lipid nanoparticles (SLN), and polymeric nanoparticles etc. [9]. Liquisolid Compact technique firstly described by Spireas for enhancement of solubility and dissolution rate of the poor soluble agents. These techniques mainly utilized non-volatile solvent for the improvement and convert solid drug into the liquid medication. Then liquid medicaments are converted into the freely flowing compressible powder by the addition of carrier and coating agents [10, 11]. The liquid load is allowed to adsorb on the surface of carrier agents and further addition of coating agents improves the flowing characteristics of the powder. The Liquisolid Compact system describe the development of tablets for rapid or sustained release by addition of super disintegrants and polymers. The higher solubility and dissolution of poorly soluble active ingredients are achieved through enhancing the wettability of solid particles with non-volatile liquid, rising drug surface area [12].

Diabetes mellitus (DM) is the second largest chronic disease affecting large number of populations in the world. There are two types of DM, insulin dependent (Type 1) and non-insulin dependent (Type 2). Both these types are responsible for occurrence of several associated diseases and which may be fatal to the person [13]. Repaglinide is an antihyperglycemic agent belongs to meglitinide class recommended for type 2 DM. Repaglinide belongs to BCS class II and having log P value 3.97. Thus, Repaglinide is poorly soluble in water and also have short half-life (1 hr.). The therapeutic efficacy of Repaglinide is restricted due to its poor absorption and bioavailability in the plasma. Hence, current research was focused on the improvement of solubility, dissolution rate of Repaglinide and thus enhanced absorption and bioavailability was achieved. The marked antihyperglycemic action was attained by improving solubility and dissolution rate of poorly water soluble Repaglinide by Liquisolid Compact technique [14, 15].

''Quality-by-design (QbD) defined the systematic development of a pharmaceutical product involving predefined objectives and comprises of product understanding, control and prompt recognition of risk assessments''. QbD mainly comprised of essential components such as quality targeted product profile (QTPP), critical quality attributes (CQA), critical material attributes (CMA), critical process parameters (CPP), design space and risk assessments (RA). The designing of tablets involving dosage form, route of administration, dosage strength considered as QTPP parameters and disintegration time, dissolution are CQA [16].

The optimization of the Liquisolid Compact analysis was performed by response surface methodology using the Box-Behnken design. In this model, 3 factors were selected and considered as independent parameters, such as the concentration of the carrier (dibasic calcium phosphate), the coating agent (Aerosil 200), and the supercolorant (Cross Povidone), while the decay time and resolution were reliable parameters. A quadratic model was selected for the BBD, which was determined using the Design of expert (version 11) software [17, 18].

2. RESULT AND DISCUSSION

2.1. Evaluation of preformulating parameters

Repaglinide is white amorphous powder. The melting point was recorded in the range of 132-134^0 C and LOD value observed about 0.5 %.

2.2. Estimation of solubility

The weighed quantity of Repaglinide was transferred to the solution of different non-volatile solvents and best suitable solvent for improvement of solubility and dissolution was identified. PEG 200 was selected as best one for solubilization of Repaglinide completely in comparison with other non-volatile solvents. The solubility of Repaglinide in PEG 200 recorded as 24.1 mg/ml, whereas in Tween 80 was 13.7 mg/ml and in PG was found to be 19.3 mg/ml.

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2.3. Compatibility study

The identification of powder sample of Repaglinide was carried out with the FTIR spectra. The characteristic peak observed at 3309.85 cm $^{-1}$ for N-H stretching, C=O stretching at 1687.71 cm $^{-1}$, bands for C-O stretching at 1217.08 cm $^{-1}$, and O-H bending at 920.05 cm $^{-1}$. The FTIR spectrum were showed in Fig.1 indicated above functional groups.

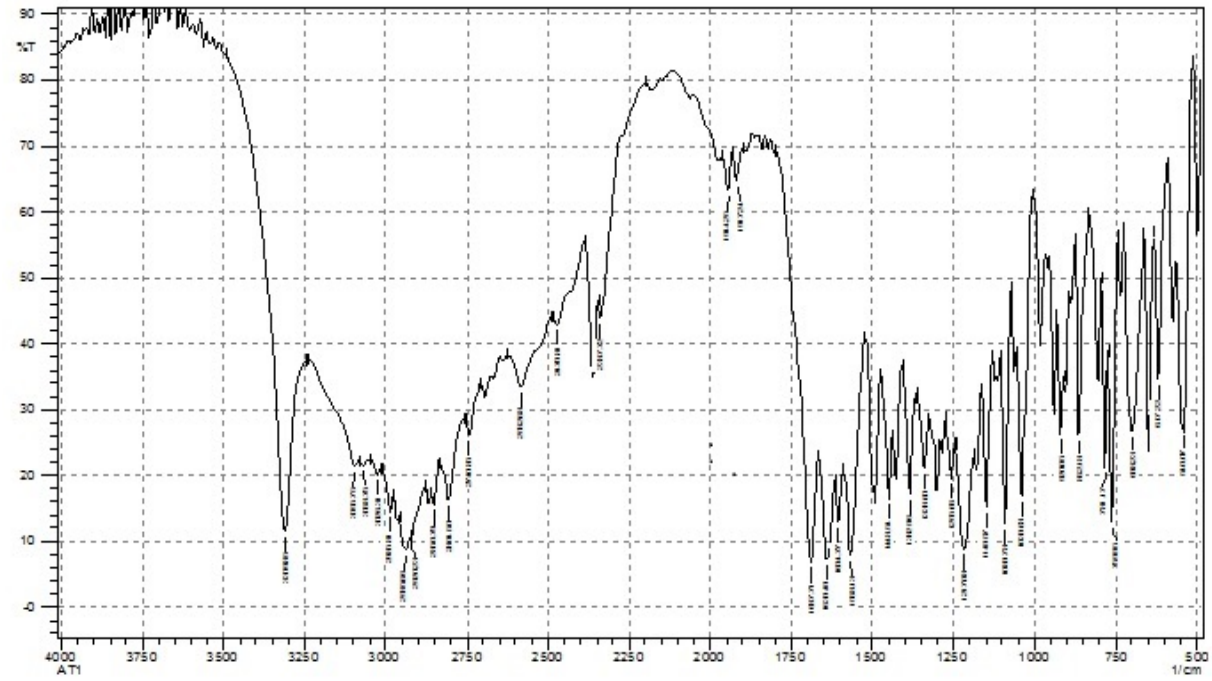

Figure 1. FTIR Spectra of Repaglinide

These bands and stretching observed for different functional groups confirmed for the presence of pure Repaglinide samples. Moreover, the Repaglinide was found compatible with carrier and coating agents, recognized with identification of above functional groups without changing their stretching band. The FTIR spectrum were showed in Fig. 2 to 4.

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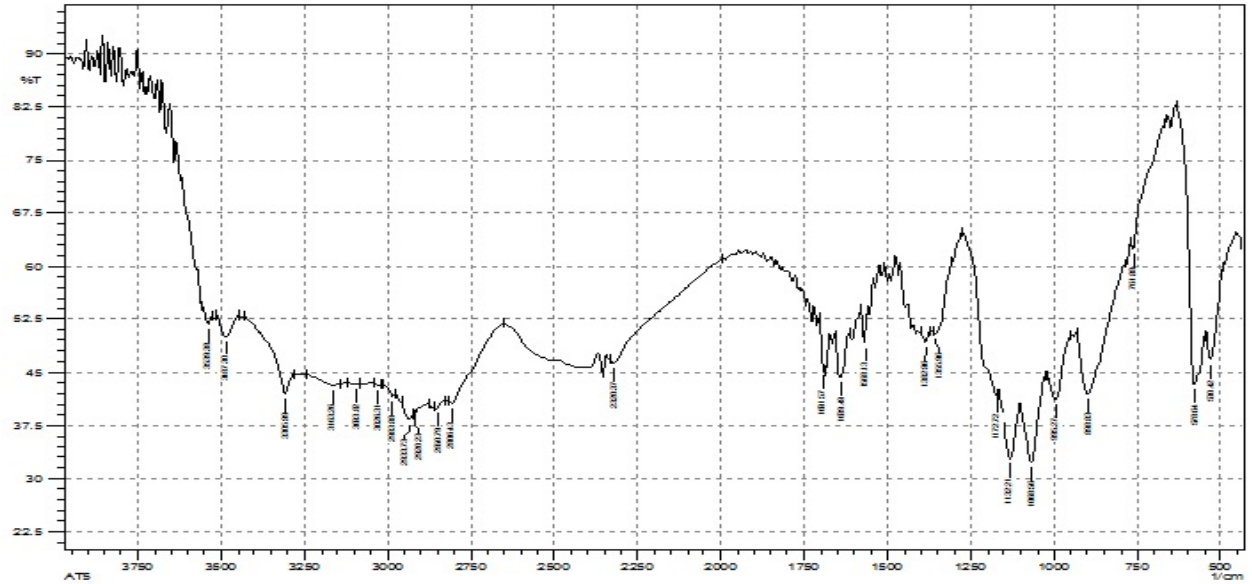

Figure 2. FTIR spectrum of Repaglinide and DCP

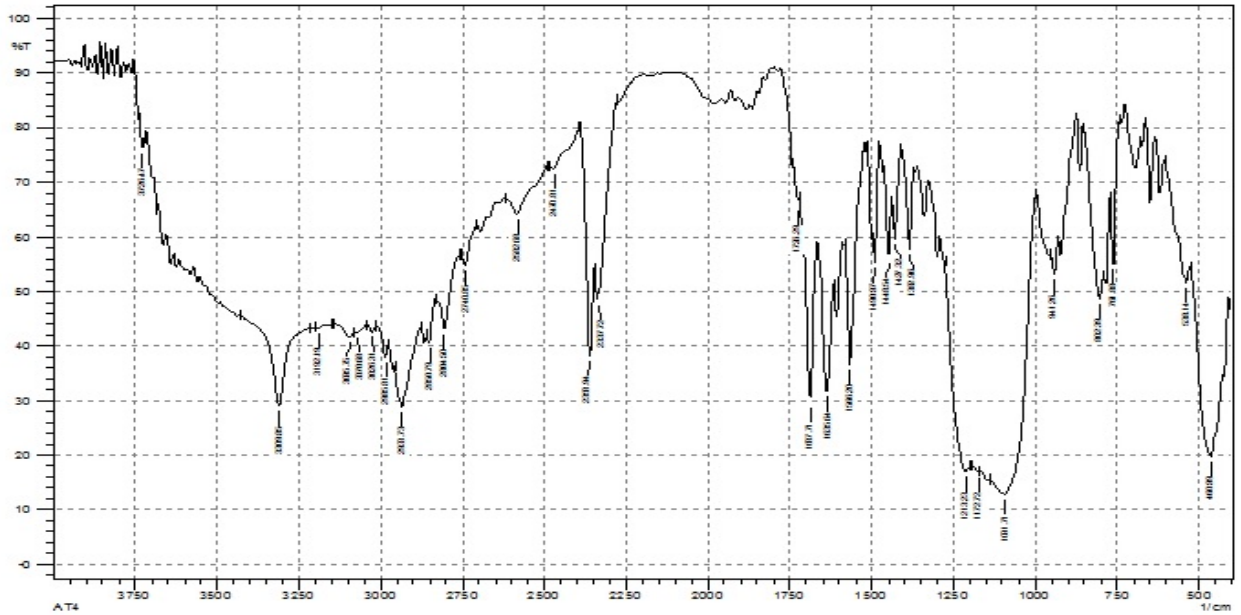

Figure 3. FTIR spectrum of Repaglinide and Aerosil 200

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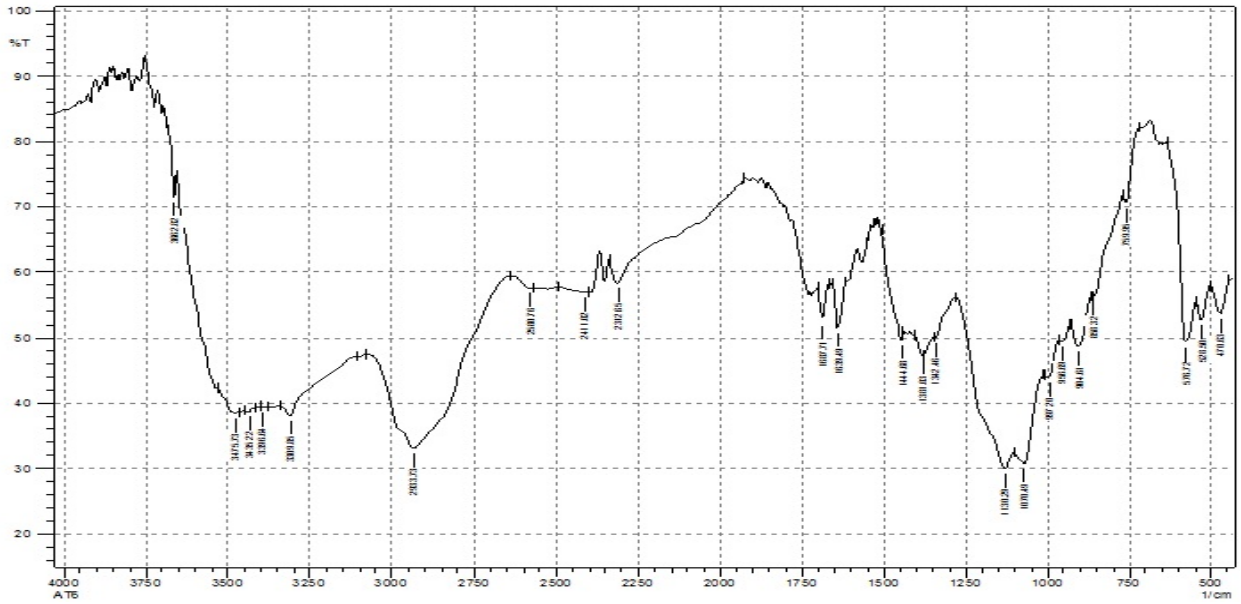

Figure 4. FTIR interaction study of core formulation

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2.4. Optimization analysis

The optimization study was analyzed with Design of Expert software (Stat Ease, Version 11). The independent parameters such as DCP, Aerosil 200 and CP with their low and high values and disintegration time and dissolution time as dependable parameters fitted into the DoE and accordingly 3^2 Box-Behnken design was applied. The BBD predicted 12 runs depicted in Table 1.

Table 1: Optimization study by BBD for Repaglinide tablet

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Std	Run	A:DCP	B:Aerosil 200	C:Cross Povidone	Disintegration time	Dissolution
		mg	mg	mg	min	%
11	1	160	40	7.5	2.29	99.56
4	2	170	50	6.25	2.38	98.64
2	3	170	40	6.25	2.37	98.27
3	4	150	50	6.25	2.4	98.23
1	5	150	40	6.25	2.4	98.41
8	6	170	45	7.5	2.3	99.48
7	7	150	45	7.5	2.29	99.28
5	8	150	45	5	2.44	98.32
9	9	160	40	5	2.46	98.25
10	10	160	50	5	2.45	98.36
6	11	170	45	5	2.46	98.88
12	12	160	50	7.5	2.3	99.1

The critical step involved in the QbD is the selection of an appropriate model. This model was successful after prediction from the regression analysis such as p-value and R^2. The predicted R^2 value was 0.9839 for disintegration time and for dissolution was 0.9658 respectively. The model Quadratic equations were discussed as follows.

For Disintegration time (Dependable parameters-1)

$DT = +2.36 - 0.0025\ A + 0.0012\ B - 0.0788\ C + 0.0025\ AB - 0.0025\ AC + 0.0050\ BC + 0.0125\ A^2 + 0.0150\ B^2 + 0.0000\ C^2$.

For Dissolution (Dependable parameters-2)

$Dissolution = +99.42 + 0.1287A - 0.0200\ B + 0.4513\ C + 0.1375\ AB - 0.0900\ AC - 0.1425\ BC - 0.4300\ A^2 - 0.6025\ B^2 + 0.0000\ C^2$.

The above mathematical equations for both dependable parameters suggested coefficients comprising one factor indicated effect of one parameter and with two factors represent interactions among two parameters. The equations indicating plus sign have synergistic effects and with negative sign showed antagonistic effects on the dependable parameters. For disintegration time, increased concentration of dibasic calcium phosphate has antagonistic effects and also with cross povidone but not at significant level. The synergistic effect found with Aerosil 200. Moreover, in case of dissolution parameters, concentration of DCP and CP have synergistic effect and Aerosil has antagonistic effect.

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When the formulation parameters are coded between low to high concentration range (-1,0 and +1) for DCP, Aerosil 200 and CP, results showed that optimum concentration of DCP, low concentration of Aerosil and high concentration of CP provided least disintegration and higher dissolution release compared with other combinations.

The response surface (3-D) and contour (2-D) plots are the graphical illustrations indicated relationship between formulation parameters (DCP, Aerosil 200 and CP) and dependable response parameters (DT and Dissolution). The design was applied for ANOVA study and the dependable parameters such as disintegration (p-value: 0.0131) and dissolution time (p-value: 0.0390) were found to be significant predicted by the p-value less than 0.05. The Quadratic model using ANOVA for DT and dissolution was depicted in Table 2 and 3 respectively.

ANOVA for Quadratic model (Aliased)

Table 2: Response 1: Disintegration time using BBD

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.0503	8	0.0063	22.88	0.0131	significant
A-DCP	0.0001	1	0.0001	0.1818	0.6986	
B-Aerosil 200	0.0000	1	0.0000	0.0455	0.8448	
C-Cross Povidone	0.0496	1	0.0496	180.41	0.0009	
AB	0.0000	1	0.0000	0.0909	0.7827	
AC	0.0000	1	0.0000	0.0909	0.7827	
BC	0.0001	1	0.0001	0.3636	0.5890	
A^2	0.0003	1	0.0003	1.14	0.3646	
B^2	0.0005	1	0.0005	1.64	0.2908	
C^2	0.0000	0				
Residual	0.0008	3	0.0003			
Cor Total	0.0512	11				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 22.88 implies the model is significant. There is only a 1.31% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case C is a significant model term. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

ANOVA for Quadratic model (Aliased)

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Table 3: Response 2: Dissolution using BBD

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	2.72	8	0.3405	10.59	0.0390	significant
A-DCP	0.1326	1	0.1326	4.12	0.1353	
B-Aerosil 200	0.0032	1	0.0032	0.0995	0.7731	
C-Cross Povidone	1.63	1	1.63	50.66	0.0057	
AB	0.0756	1	0.0756	2.35	0.2227	
AC	0.0324	1	0.0324	1.01	0.3895	
BC	0.0812	1	0.0812	2.53	0.2102	
A^2	0.3698	1	0.3698	11.50	0.0427	
B^2	0.7260	1	0.7260	22.58	0.0177	
C^2	0.0000	0				
Residual	0.0965	3	0.0322			
Cor Total	2.82	11				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 10.59 implies the model is significant. There is only a 3.90% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case C, A^2, B^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

The RSM design followed second-order polynomial order. The relationship amongst the dependable and independent parameters for both 3-D and 2-D were reflected in Fig. 5 and 7 for DT time. Similarly, 3-D and 2-D plots for dissolution release was showed in Fig. 6 and 8 respectively.

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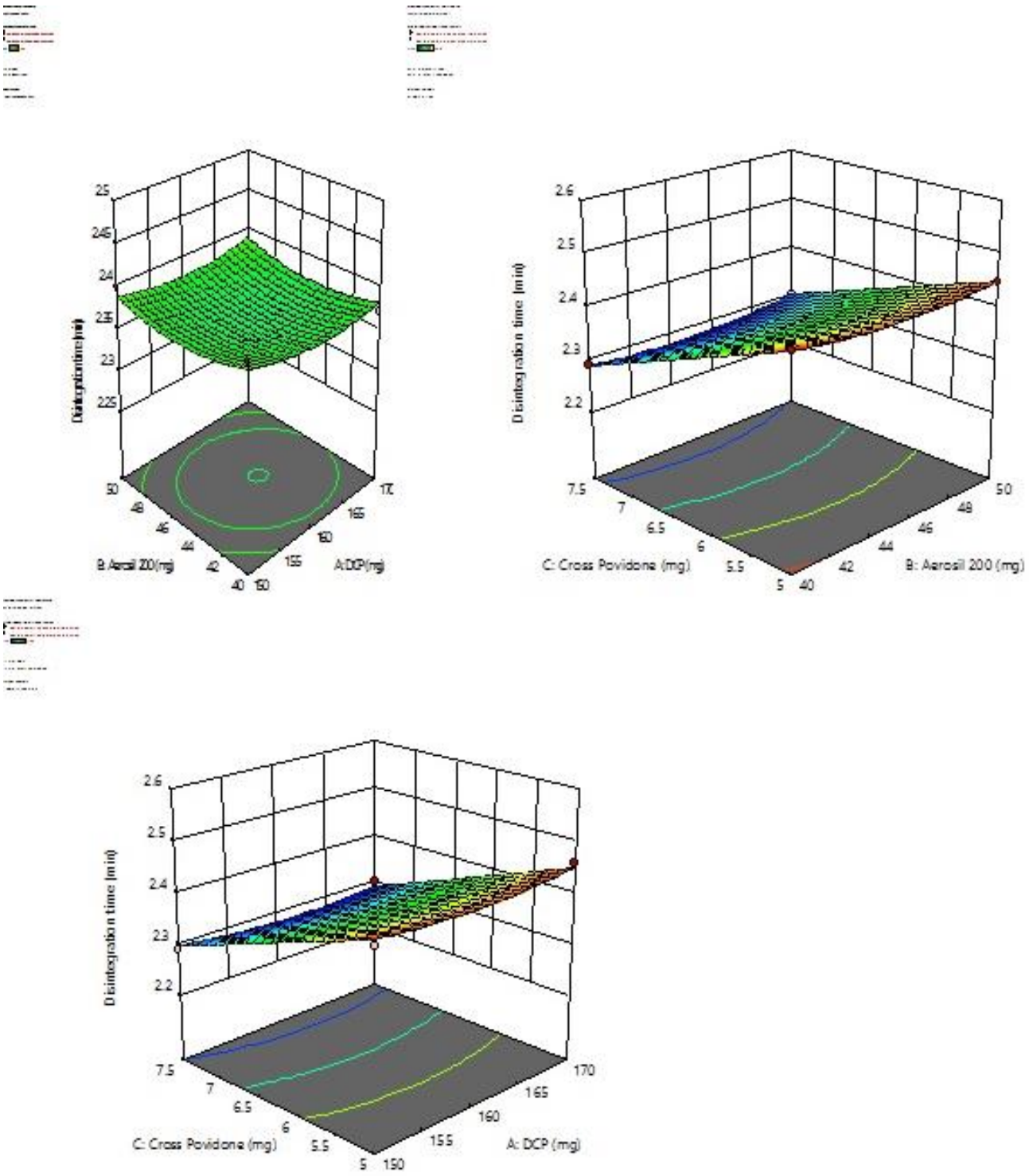

Figure 5. Response surface graph for Disintegration time

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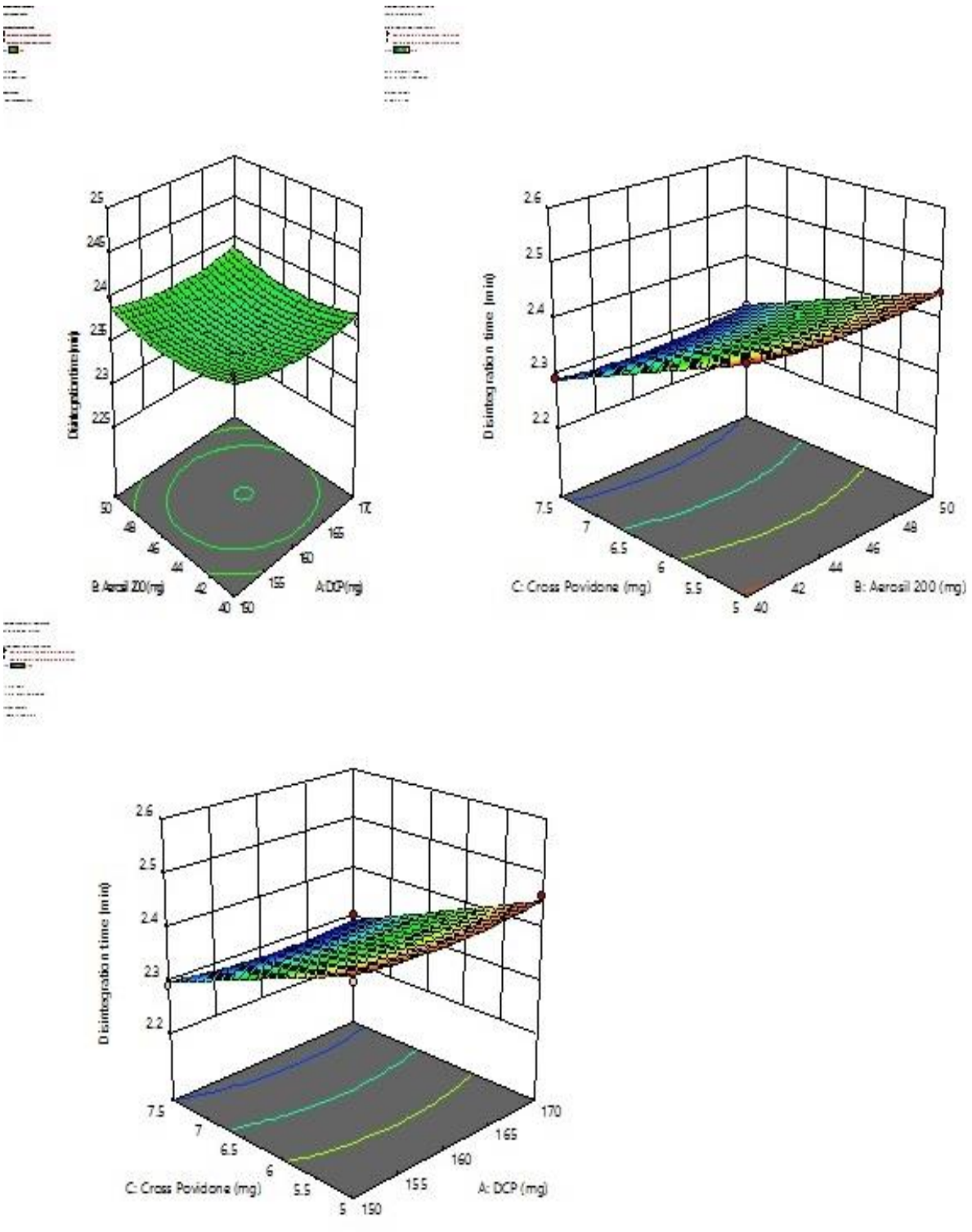

Figure 6. Response surface graph for dissolution

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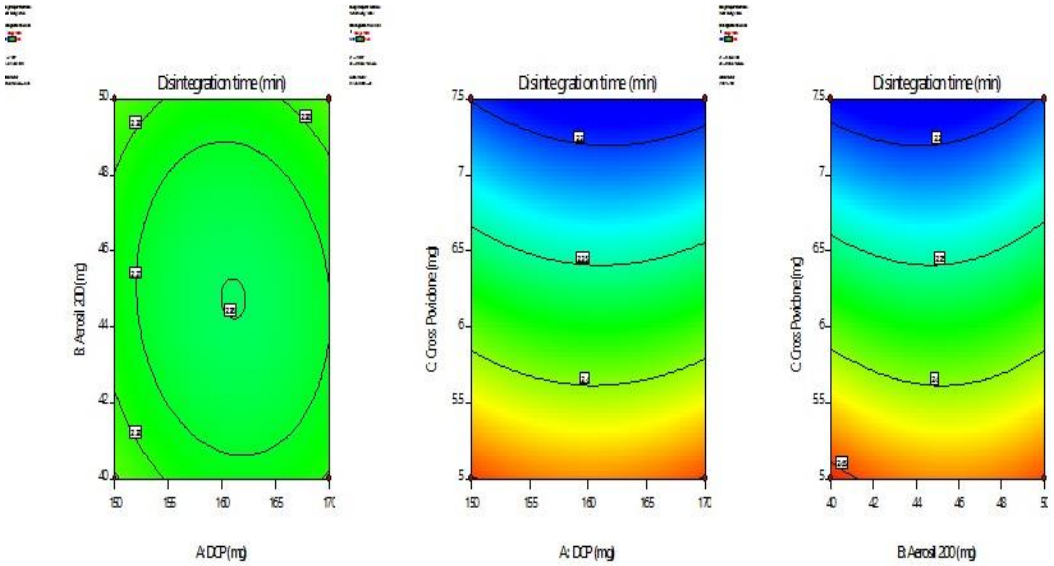

Fig. 7. Contour plots for Disintegration time

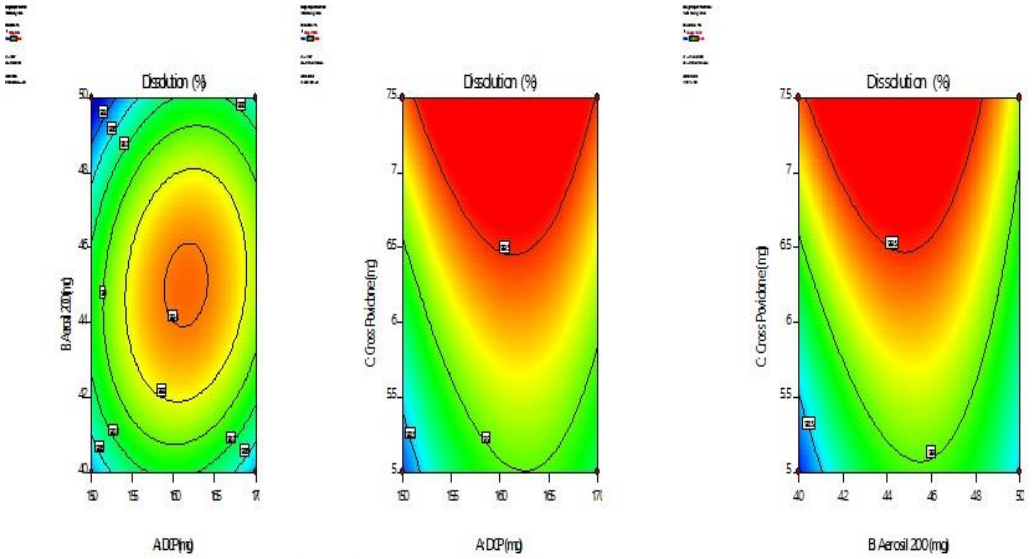

Fig. 8. Contour Plots for dissolution

For disintegration time, the increase in parameters AB resulted in increase in DT time. The optimum concentration of A (160 mg) and low concentration of B (40 mg) given lowest disintegration time of 2.29 min. In BC, rise in concentration of C showed decrease in disintegration time while keeping B at lower level.

In contour plots, horizontal and vertical lines indicated independent factors and middle one represented iso-response value. Moreover, contour plots also confirmed design space and indicated proved acceptable range for dependable parameter. All the images of contour plots reflected in Fig. 7 given 2.35 min time for disintegration time and optimized batch matches within the limit.

For dissolution parameters, with rise in concentration of AB dissolution increases up to certain limit and thereby decreases. The increase concentration of C was synergistic effect and accelerates the dissolution

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process. The contour plots also supported the data and provided design space value of 99.5 % for AB, BC and AC which was showed in Fig. 8.

2.5. Evaluation of flow characteristics of powder blends

The powder blends were evaluated for their flowing characteristics such as bulk density, tapped density, compressibility index, angle of repose and Hausner's ratio. The formulated batches were passed the flow characteristics. The Carr's index of all batches was observed in the range of 12.5 ± 0.14 to 17.39 ± 0.12%. The angle of repose was observed in the range of 24.69 ±0.11 to 29.31±0.13. Hausner's ratio were observed in the range of 1.14 ± 0.09 to 1.21 ± 0.08.

Aerosil 200 is hydrophilic fused silica and have fine particle size with greatest surface are and good compressibility. As the concentration of Aerosil 200 increases the flowing characteristics was found to be improved. The higher concentration in all batches containing Aerosil 200 have showed excellent flow characteristics of powder recognized with Carr's index and angle of repose values. Similarly, the low concentration of DCP showed good to passable characteristics for Carr's index and angle of repose. Whereas, moderate to high concentration showed very good to excellent flow properties. The results of all batches were depicted in Table 4.

Table 4: The evaluation of flow characteristics of powder blends

Batch	Tapped density	Bulk density	Carr's index (%)	Angle of repose (θ)	Hausner's index
F1	0.48 ± 0.09	0.41 ± 0.05	14.58±0.27	26.8 ±0.12	1.17 ± 0.05
F2	0.46 ± 0.04	0.39 ± 0.07	15.21±0.10	27.4 ±0.19	1.17 ± 0.07
F3	0.48 ± 0.06	0.40 ±0.08	16.66±0.20	28.37 ±0.18	1.20 ± 0.03
F4	0.47 ± 0.05	0.40 ± 0.12	14.89 ± 0.04	27.05 ±0.15	1.17 ± 0.11
F5	0.46 ± 0.07	0.38 ± 0.11	17.39 ± 0.12	29.31±0.13	1.21 ± 0.08
F6	0.48 ± 0.03	0.40 ± 0.21	16.66 ± 0.06	27.07 ±0.14	1.17 ± 0.06
F7	0.47 ± 0.07	0.39 ± 0.12	17.02 ± 0.05	27.57±0.02	1.18 ± 0.16
F8	0.47 ± 0.11	0.40 ± 0.08	14.89 ± 0.20	27.34 ±0.13	1.17 ± 0.14
F9	0.46 ± 0.04	0.39 ±0.08	15.21 ± 0.13	27.37 ±0.14	1.17 ± 0.06
F10	0.48±0.01	0.42 ± 0.12	12.5 ± 0.14	24.69 ±0.11	1.14 ± 0.09
F11	0.47 ± 0.06	0.39 ± 0.17	17.02 ± 0.12	27.87±0.13	1.20 ± 0.12
F12	0.46 ± 0.03	0.39 ± 0.21	15.21 ± 0.06	27.48 ± 0.14	1.17 ± 0.06
F13	0.48± 0.07	0.40± 0.20	16.66± 0.10	28.42± 0.21	1.20± 0.09

All values are n =3 ±SD.

2.6. Evaluation of post compression parameters

The prepared tablets of Repaglinide were assessed for weight variation, hardness, friability, disintegration time and content uniformity. The prepared batches were passed the weight variation test. The hardness of tablets differs from 3.7±0.04 to 4.1±0.11 kg/cm^2. The hardness of tablets from batch to batch slightly varies due to different composition and number of materials. The friability of tablets from all the batches were observed in the range of 0.53±0.15 to 0.73±0.13 %. The friability of tablets generally depends upon the tablet hardness. Hence, tablets with lower hardness resulted in slightly more friable compared with higher hardness value.

Moreover, the disintegration time for the batches were showed in the range of 2.29±0.07 to 2.46±0.11 min. The variations in tablets disintegration time were predicted due to the variable concentration of

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superdisintegrants. As the concentration of cross povidone increases the disintegration time was less due to prompt swelling characteristics and burst release. The content uniformity of the several tablets were identified in the range of 97.89±0.95 to 99.18±0.61 %. The results of all post compression characteristics were depicted in Table 5.

Table 5: The post compression evaluations of Repaglinide Tablets

Batch	Weight variation (mg)	Hardness (kg/cm²)	Friability (%)	Disintegration (m)	Content uniformity (%)
F1	249±0.57	3.9±0.06	0.61±0.22	2.29±0.07	98.71±0.53
F2	268±0.45	4.1±0.11	0.53±0.15	2.38±0.03	98.34±0.30
F3	258±0.36	4.0±0.09	0.57±0.25	2.37±0.06	98.78±0.42
F4	250±0.26	3.8±0.06	0.60±0.18	2.4±0.09	98.56±0.78
F5	239±0.74	3.7±0.04	0.73±0.13	2.4±0.10	98.04±0.56
F6	266±0.48	4.0±0.08	0.59±0.20	2.3±0.06	98.23±0.51
F7	245±0.34	3.8±0.05	0.60±0.14	2.29±0.08	97.89±0.95
F8	242±0.50	3.7±0.12	0.66±0.17	2.44±0.10	98.34±0.46
F9	246±0.62	3.7±0.10	0.63±0.21	2.46±0.05	99.18±0.61
F10	257±0.35	3.8±0.07	0.56±0.10	2.45±0.09	98.58±0.39
F11	261±0.24	4.0 ±0.15	0.58±0.24	2.46±0.11	98.72±0.66
F12	260±0.40	4.1±0.05	0.56±0.15	2.3±0.07	98.60±0.54

All values in n=3 ±SD

2.7. Dissolution study

The in-vitro dissolution study of Repaglinide was carried out in phosphate buffer of pH 5 using USP dissolution apparatus II at 50 rpm. The randomly selected 3 tablets from each batch were placed in the dissolution apparatus containing 900 ml of dissolution media. The samples were withdrawn frequently at an interval of 5 min and replaced with phosphate buffer for maintaining stock solution. The samples were filtered through 0.45 µ Whatman filter paper and analyzed spectrophotometrically at 241 nm using UV visible spectrophotometer.

The Repaglinide was released quickly due to the change of solid form of the drug in the liquid medication. The drug release from the F1 batch was found to be 99.56% after 30 min. Whereas, the cumulative amount of 98.64 % of Repaglinide was recored in F2 batch. The release rate was slighly less in the F2 batch comparatively with the F1. The speedy release of Repaglinide was attributed due to the greater concentration of superdisintegrants in the batch F1 due to rapid swelling characteristics upon ingress of dissolution media. Similarly, the cumulative percentage of drug released from the batches F3 to F6 were 98.27 %, 98.23%, 98.41% and 99.48 % respectively. Among all these batches the slight variations in the drug release was due to the variable concentration of superdisintegrant and hardness of the tablets.

In F7 batch, the drug dissolution was comparatively higher with the other batches and found to be 99.28 % after 30 min. Moreover, the drug released within 30 min in the batches of F8 to F12 and observed as 98.32%, 98.25%, 98.36%, 98.88 % and 99.1% respectively. The release rates from the liquisolid compact tablets were very similar to one another and variations was due to the processing parameters and concentration of superdisintegrants.

The significant improvement in the dissolution release was attributed due to the availability of Repaglinide in the molecular dispersion form and greater surface area provided by the non-volatile solvent PEG. The non-volatile solvent worked as surfactant which have tendency to minimise the interfacial tension occurred between repaglinide and dissolution media. Moreover, PEG facilitates diffusion of the active ingredients from the dissolving surfaces. The greater concentration gradient among the diffusion layer and

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bulk medium was exist resulted in higher dissolution as per the modified Noyes-Whitney equation. Among all the batches F1 batch was considered as optimized because of rapid and greater amount of drug released in 30 min as well as lower material required than batch remaining batches. The in-vitro dissolution profile of Repaglinide was depicted in the Fig. 9 and 10 respectively.

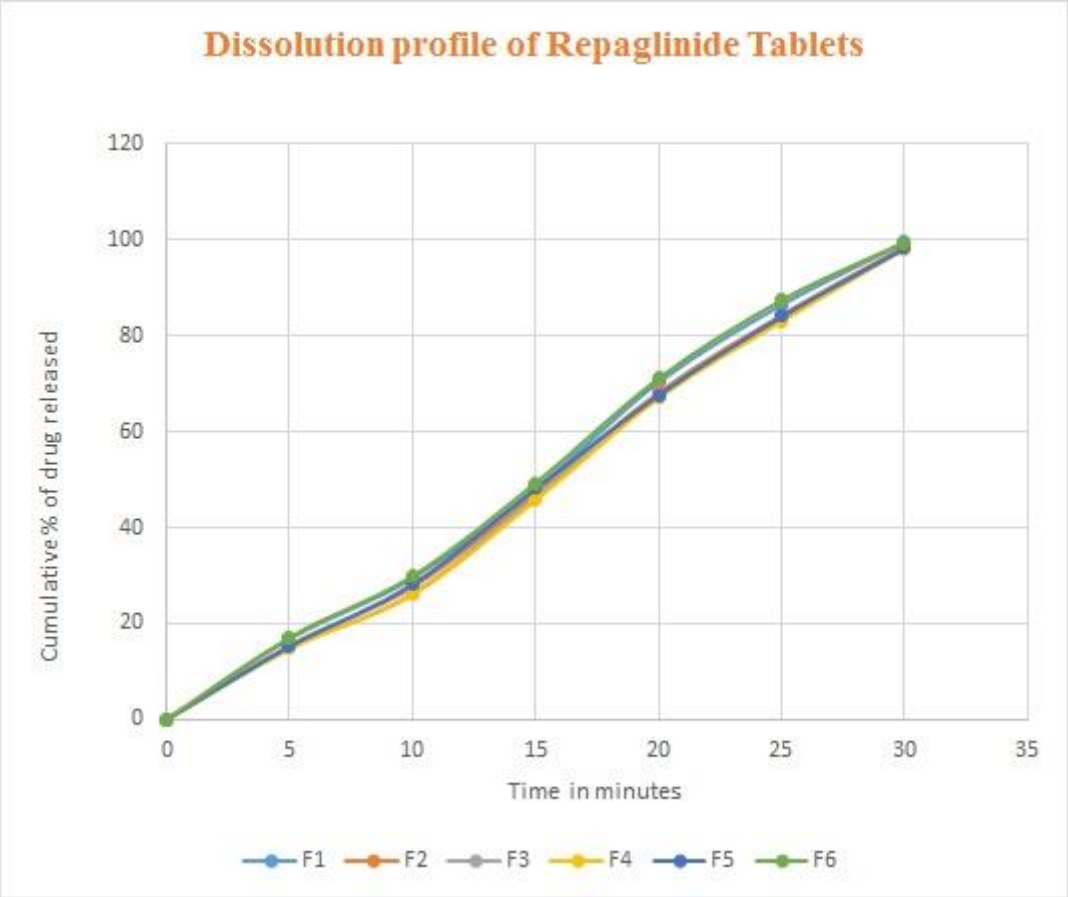

Figure 9. In-vitro dissolution release of Repaglinide tablets

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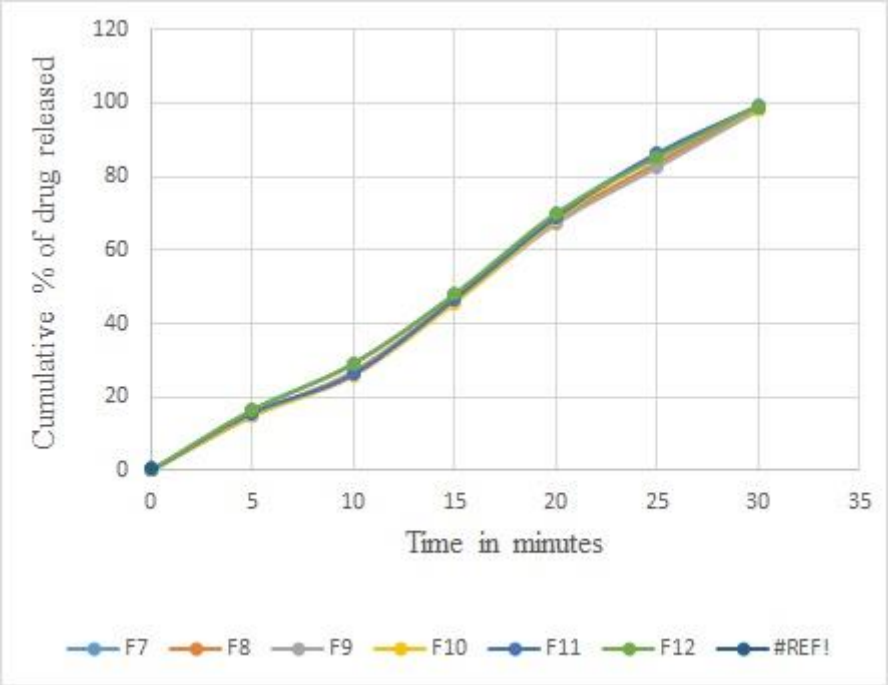

Figure 10. In-vitro dissolution release of Repaglinide

2.8. Stability studies

The optimized batch F2 was tested for their stability and passes the test. The results were depicted in Table 6.

Table 6: Stability study of an optimized batch F2

Parameters	After 1 month	After 2 month	After 3 month
Physical appearance	No change	No change	No change
Hardness(kg/cm^2)	3.9±0.15	3.8±0.06	3.7±0.10
Friability (%)	0.63±0.13	0.71±0.26	0.79±0.30
Disintegration (min)	2.29±0.05	2.24±0.06	2.21±0.09
Drug content (%)	98.60 ±0.29	98.52±0.44	98.43±0.39

n =±3, SD

3. CONCLUSION

Repaglinide is routinely used in the therapy of type II diabetes mellitus. But, due to rapid biotransformation and poor solubility, its bioavailability and efficacy was limited. Liquisolid-Compact technique is cost effective technique for the improvement of solubility and dissolution characteristics of BCS class II and IV molecules and thereby enhancing bioavailability. This technique utilizes several non-volatile

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solvent for enhancement of solubility and dissolution rate. The marked rise (>650 times compared with original solubility) in solubility was observed in PEG 200. Further incorporating DCP as carrier agent and Aerosil 200 as coating agent helps in the prompt adsorption due to small particle size and thus resulted in development of freely flowable powder and subsequent formulation of tablets of Repaglinide.

QbD-based design assisted minimal number of runs and confirmed about quality as well as safety of processed formulation. The optimized batch was F1 which showed excellent flowing characteristics, lesser disintegration time and higher dissolution release comparatively with other batches. The faster release observed during in-vitro dissolution was due to presence of Repaglinide in liquid form and adsorbed on the solid surface. Moreover, F1 batch showed very good results with less number of materials than others which enabled the formulation cost-effective and competitive in the market. Hence, significant antidiabetic activity can be achieved with Liquisolid Compact technique.

4. MATERIALS AND METHODS

4.1. Materials

Repaglinide was received as gift sample from Torrent Pharmaceuticals, Ahmedabad. Tween 20 (Polysorbate 20), Polyethylene glycol 200, 400 were purchased from Merck chemicals, Mumbai. Anhydrous dibasic calcium phosphate and sodium steraryl fumarate were provided by Nitika Chemicals, Nagpur. Microcrystalline cellulose was supplied by NB entrepreneurs, Nagpur. All other chemicals used were of analytical grade only.

4.2. Methods

4.2.1. Preformulation studies

Repaglinide was characterized for their organoleptic characteristics, melting point and loss on drying (LOD).

4.2.2. Estimation of solubility

The solubility of Repaglinide was estimated in several non-volatile solvents such as Tween 20, Span 20, propylene glycol (PG), polyethylene glycol (PEG) 200 and PEG 400. Further, saturation solubility study was carried out by the addition of excess amount of the active ingredients in the non-volatile vehicles and subjected for orbital shaker for about 48 h at 37 ^{0}C with continuous vibration. The drug solution was further diluted, filtered through 0.45 µm and analyzed by UV visible spectrophotometer (Shimadzu-1900, Japan). The results were calculated in triplicate [19].

4.2.3. Calculation of load factor

The powders have tested for their capability to load the liquid medicaments to achieve good flowability and compressibility characteristics. Hence, it was necessary to recognize the extreme loading capacity without conceding compressibility. These were found out with flowing potential of liquid (Φ) and compressible potential of liquid (¥). The excipient ratio (R) can be calculated by diving the quantity of carrier (Q) to the coating material (q). The liquid load factor was calculated from the following equations [20, 21].

$R = Q/ q$ ……1

$Lf = \Phi_{ca} + \Phi_{co} \quad x\ 1/R$ ……2

$Q = W/L_f$ ……3

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4.2.4. Compatibility study

The physical interactions among the active ingredients with carrier and coating agent were analyzed with FTIR (IRAffinity-1s, Shimadzu). The accurately weighed quantity of Repaglinide with formulation components (MCC, DCP, and Aerosil 200) as well as Liquisolid Compact mixture was characterized for any possible interactions. The mixture was subjected for scanning between the ranges of 400 to 4000 cm^{-1} [22].

4.2.5. Flowing characteristics of powder

The flexible quantity of carrier and coating materials were transfer to the liquid medicaments encompassing active ingredient to convert it freely flowable. The powder blends were evaluated for their flowing characteristics such as Carr's index and angle of repose (Fixed funnel method) [23].

4.2.6. Formulation of tablets from powder blends

Precisely weighed amount of the Repaglinide was transfer in the mortar subsequent addition of selected non-volatile solvents. To the liquid medicaments precalculated quantity of carrier agent's namely anhydrous dibasic calcium phosphate were added. Subsequently, the coating agent Aerosil 200 was added to make the powder blends in their compressible form. Before compression, cross povidone (CP), sodium steraryl fumarate (SSF) was added and blended without any friction. The powder mass was subjected for compression and tablets were prepared with 9 mm punch size on 12 station multi-tooling machine (Rimek mini press-II, Karnavati Engineering, Ahmadabad) [24, 25]. The formulation components were depicted in Table 7.

Table 7: Formulation of Repaglinide tablets

Std	Run	Repaglinide	PEG 200	A:DCP	B:Aerosil 200	R	LF	C:CCS	SSF	Total
		mg	mg	mg	mg			mg	mg	Mg
4	1	1	39	160	40	4	0.25	7.5	2.5	250
12	2	1	39	170	50	3.4	0.23	6.25	2.5	269
5	3	1	39	170	40	4.25	0.25	6.25	2.5	259
14	4	1	39	150	50	3	0.26	6.25	2.5	249
10	5	1	39	150	40	3.75	0.26	6.25	2.5	239
17	6	1	39	170	45	3.77	0.25	7.5	2.5	265
9	7	1	39	150	45	3.33	0.26	7.5	2.5	245
15	8	1	39	150	45	3.33	0.26	5	2.5	242
6	9	1	39	160	40	4	0.25	5	2.5	247.5
11	10	1	39	160	50	3.2	0.25	5	2.5	257.5
13	11	1	39	170	45	3.77	0.25	5	2.5	262.5
3	12	1	39	160	50	3.2	0.25	7.5	2.5	260

4.2.7. Optimization study

Quality-by-design approach (QbD) was applied with the objective of developing the product lacking any error and protects the materials as well as time. The critical quality attributes for designing Liquisolid Compact was the disintegration and dissolution time, whereas the independent parameters were variations of carrier and coating agents. The 3^2 Box-Behnken design (BBD) was .applied and suggested 12 runs to find out the optimized batch [26]. QbD design was depicted in the Table 4. The ANOVA applied for the BBD was depicted in Table 5, and 6 respectively.

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4.2.8. Evaluation of tablets

4.2.8.1. *Weight variation test*

The ready tablets about 20 were randomly chosen and accurately weighed. The mean weight of an individual tablets was noted with standard derivations. The weight variation test passes within 2.5 % variations from the average tablets [27].

4.2.8.2. *Hardness*

The hardness of tablets from each batch was tested by Monsanto hardness tester and values were reported by average of three [28].

4.2.8.3. *Friability*

The tablets from each batch were weighed accurately equivalent to 6.5 g and further kept in the Roche friabilator which was rotated at a speed of 25 rpm for 100 rotations. After rotation, tablets were collected and reweighed. The percentage of friabilator was calculated by deducting the weight of initial from final weight [29].

4.2.8.4**.** *Disintegration time*

The 6 tablets were randomly picked and placed in the disintegration test apparatus containing 900 ml of simulated gastric fluid at 37±0.5° C. The time required to pass all the particles from the sieve number 10 were recorded [30].

4.2.8.5. In-vitro dissolution

The dissolution study of Repaglinide tablets were performed with USP Dissolution apparatus II (Paddle) using pH 5 phosphate buffer. The paddle was allowed to rotate at a speed of 50 rpm, at 37±0.5° C. The samples were withdrawn at an interval of 5 minutes, diluted, filter through 0.45 µm membrane filter and analyzed spectrophotometrically at 241 nm [31].

4.2.8.6**.** *Content uniformity*

The prepared tablets about 10 were randomly selected and converted into the powder after crushing. The average weight of tablet containing a powder was taken and dissolved with pH 5 phosphate buffer. The solution was further diluted and filter through 0.45 µ membrane filter and analyzed spectrophotometrically at 241 nm [32, 33].

4.2.8.7. Stability study

The stability study of an optimized formulation was carried out according to the ICH guidelines. The optimized batch was kept at 40^0 C and 75 % RH for about 3 months. The samples were withdrawn at an interval of one month and estimated for drug content, disintegration and dissolution time [34].

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