RESEARCH PAPER

Development and Optimization of Repaglinide Amorphous Solid Dispersion Using Polymer Blends and Factorial Design for Enhanced Solubility and Dissolution

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Abstract
The present study focuses on the fabrication and evaluation of an amorphous solid dispersion (ASD) system of repaglinide, a BCS Class II antidiabetic drug with poor aqueous solubility. The aim was to enhance the dissolution behavior and potential bioavailability of repaglinide using a polymer-based ASD approach. A polymer blend consisting of hydroxypropyl methylcellulose (HPMC), Pluronic F127, and polyethylene glycol (PEG 400) was used to prepare solid dispersions by reactive ball milling employing 1.7 mm zirconium beads. A 323^232 full factorial design was applied for formulation optimization. The prepared formulations were characterized using FTIR, XRD, and DSC to evaluate drug–excipient compatibility, amorphous nature, and stability. FTIR studies indicated good compatibility, while XRD and DSC confirmed the conversion of crystalline repaglinide into a stable amorphous form. In vitro dissolution studies showed significant enhancement in drug release. The optimized batch achieved more than 95% drug release and exhibited acceptable short-term stability.

Keywords: Repaglinide; Amorphous solid dispersion; Reactive ball milling; Polymer blend; Dissolution enhancement.
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INTRODUCTION

Poor aqueous solubility remains one of the major challenges in the oral delivery of many contemporary drug molecules. A significant proportion of newly developed and marketed drugs belong to Biopharmaceutics Classification System (BCS) Class II, characterized by low solubility and high permeability, where drug dissolution becomes the rate-limiting step for absorption.[1] Inadequate solubility often leads to poor and variable bioavailability, delayed onset of action, dose escalation, and reduced therapeutic efficacy, thereby necessitating advanced formulation strategies. Repaglinide, a BCS Class II antidiabetic drug widely used in the management of type 2 diabetes mellitus, exhibits low aqueous solubility and rapid metabolism, resulting in limited and inconsistent oral bioavailability.[2] Various formulation approaches such as particle size reduction, inclusion complexes, lipid-based systems, and conventional solid dispersions have been explored to overcome these limitations. Among these, amorphous solid dispersion (ASD) has emerged as a promising and effective strategy due to its ability to convert crystalline drugs into a high-energy amorphous state, thereby significantly enhancing solubility and dissolution rate.[3]

Recent advances in ASD technology emphasize the use of hydrophilic polymer blends to improve drug–polymer miscibility, inhibit recrystallization, and ensure long-term physical stability of the amorphous system. Polymers such as hydroxypropyl methylcellulose (HPMC), Pluronic F127, and polyethylene glycol (PEG) have shown potential in stabilizing amorphous drugs through hydrogen bonding and steric hindrance mechanisms.[4] However, despite these advancements, challenges remain related to systematic optimization of polymer concentration, processing variables, and stability, which are critical for achieving a robust and reproducible formulation. A review of existing literature reveals that while repaglinide solid dispersions have been reported, limited studies have employed a structured experimental design approach to optimize formulation variables and understand their combined influence on solubility and dissolution behavior. The lack of factorial design–based optimization represents a significant research gap, as traditional trial-and-error methods fail to provide comprehensive insight into factor interactions and process robustness.[5]

The present research work focuses on the development and optimization of repaglinide amorphous solid dispersion using hydrophilic polymer blends, employing a factorial design approach to systematically evaluate the effect of formulation and processing variables. The study aims to enhance solubility and dissolution performance while ensuring amorphous stability through appropriate polymer selection and solid-state characterization. This research is expected to contribute to the rational design of stable ASD

systems and provide a scalable formulation strategy for improving the oral performance of poorly soluble antidiabetic drugs.

Material and Method

Repaglinide was obtained form Jay Jalaram Enterprises. GIDC Ankaleshwar Gujrat. HPMC E15 and Polaxamer (Pluronic F127) purched from Research Lab Fine Chem, Pvt. Ltd Mumbai and Lotto Chemical Pvt Ltd Mumbai and other chemicals and solvents were procured from commercial sources were purified and sterilized using standard procedures from literature whenever required.

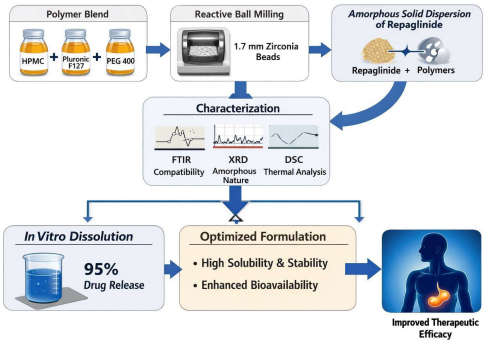
Preformulation Studies

Pre-formulation research was carried out to ensure that the medication and polymer were in a stable and pure state before being formulated into a dosage form also for determinations of characteristics which may play important role in dosage form development.

Formulation Development

Preparation of Polymer Blends using Reactive Ball Milling:

The preselected polymers were mixed uniformly in plastic bag in 1:1 ratio. Then these polymers physical mixture were subjected to reactive ball milling using 1.7mm zirconium beads for 3 hours in Ball Milling equipment. In Ball milling combination sufficient amount of methanol or PEG 400 was added as reactive media. After ball milling the polymer samples were dried then passed through sieve no 40. The FTIR, XRD and DSC studies were performed to confirm the qualitative parameters. Then these polymer blends were used as solid dispersion media for repaglinide drug.



Preparation of amorphous Solid dispersions (ASD) using Reactive ball Milling:

The ASDs were all prepared using a drug-to-carrier ratio of 1:4 and labelled as ASD PVP-P and ASD HPMC-P, corresponding to the carriers utilized (PVP K30 + Pluronic F127 and HPMC + Pluronic F127). This ratio was based on previous reported studies.[6] The drug and polymer blend sample taken into 2.50 g, underwent 3.00 hours of milling using Ball Milling equipment (Remi Instruments Pvt Ltd Mumbai) with zirconium beads (1.7 mm external diameter) at a 4:1 (w/w) ball-to-powder ratio. Obtained sample further sieved through a 40 no mesh sieve.

Table 1: Composition of samples prepared by Reactive Ball Milling

Sample	Drug	Carrier	Total Weight (gm)
Repaglinide: (PVP K30 + Pluronic F12) ASD PVP-P			
1:4	0.5	2.0	2.5gm
Repaglinide: (HPMC + Pluronic F12) ASD HPMC-P			
1:4	0.5	2.0	2.5gm

Preparation of physical mixtures

Repaglinide and carriers were combined in Physical Mixtures (PMs) through basic spatulation, maintaining the 1part of drug and 4 of polymer blend (i.e 1.0:4.0 ratio). drug-to- carrier ratio. The samples labelled as PVP K30 + Pluronic F127 and HPMC + Pluronic F127, corresponding to the carrier employed.

Determination of Repaglinide Content:

Concentration of repaglinide within the ASDs had analysed using a UV spectroscopy method technique with Jasco V630 UV–Visible spectrophotometer. Specific quantities of ASDs, matching to 5.00 mg of repaglinide, had added to separate vol flasks then further diluted water and methanol mixture to attain a conc. of 500µg per ml.[7] Required subsequent dilutions were carried out using solvents, resulting in a required conc. of 10µg per ml. Test solutions then passed from 28µm membrane and UV spectrum was recorded in triplicate at 240.00 nm.

In vitro dissolution studies:[8]

Release study of Repaglinide Pure drug, ASD samples, and Physical mixtures (PM) were conducted in pH 5 phosphate buffer with the help of USP dissolution testing apparatus Type-I (Basket) at 50.00 rpm. Three capsules (Powder-filled) were randomly chosen from various batches added in the dissolution testing apparatus containing 900.00 ml of the disso medium. Analytical Samples were taken withdrawn at 5-minute intervals, with replacement by phosphate buffer to maintain the solution volume. The analytical samples were filtered thr 0.45 micron Whatman paper and investigated using a UV spectrophotometer at 240.00 nm. Dissolution experiments were performed in triplicate.

Optimization of Formula using Design of Experiment (DoE):[9]

Optimization study for best formulation design was analyzed using Design of Expert software" (Stat Ease, Version 11). Independent parameters, including the concentrations of HPMC & Pluronic F127 and ball milling time, were assigned low, median, and high values, while dissolution time served as the dependent parameter. These values were tailored into the DoE software into a 32 Box-Behnken design was applied accordingly.

Result

Preformulation Studies:

a) λmax Determination:

It was done by using UV-Spectrophotometer

I. The wavelength of repaglinide at 240.00 nano meter in distilled water.

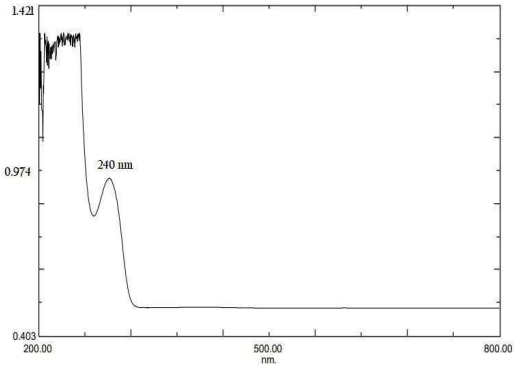


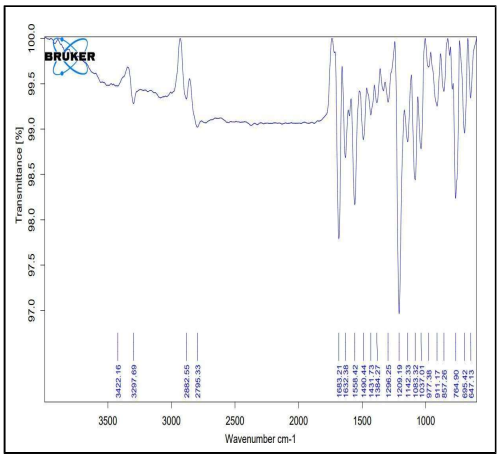
Figure 1: UV Spectrum of Repaglinide (in Water) (DW)

b) Saturation Solubility:

Saturation solubility of repaglinide in the solvent

Table 9.3: Solubility Profile of Repaglinide in different Solvents

Sr. No	Solvent System	Solubility of Repaglinide
1.	Purified Water	Sparingly Soluble
2.	Methanol	Highly soluble
3.	Ethanol	Highly soluble
4.	Distilled Water + Methanol	Freely Soluble



c) FTIR Spectroscopy:

Figure 2: Infra-Red Spectrum of Repaglinide

Table 2: Spectrum interpretation of Repaglinide

Functional Group	Wavenumber per cm
Primary amine (N-H) stretching group	3422
> C= O stretching within in CooH group	1683
-O-H stretching	2500-3000
-CH stretching	2882
➢ C = C stretching in aromatic ring	1430-1630
C=C stretching	1490
C-N stretching	1209
ether linkage (R-O-R	1142
C-N amine stretching	1083

DSC:

The DSC analysis on pure API was performed, and the graphs shown below.

The differential scanning calorimetry (DSC) curves of the initial Repaglinide sample, in its as-received state from the producer, revealed a melting point at 137.8°C, and no glass transition event was detected. These findings point towards the prevailing crystalline nature of the original sample. This aligns well with the observed crystalline needle-like structure under scanning electron microscopy (SEM) analysis. (Previously reported articles).

Figure 3: DSC thermogram of Pure Repaglinide API

XRD:

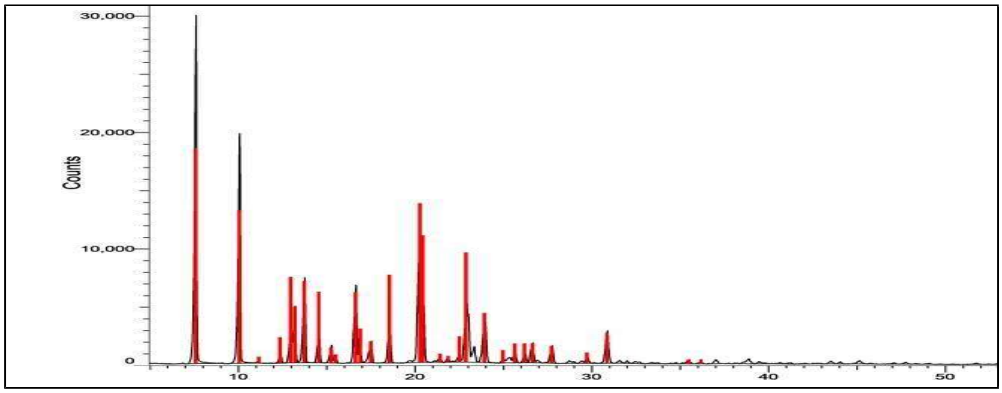


Figure 4: X-ray Diffractogram of Pure Repaglinide API

XRD pattern of crystalline repaglinide is shown in Figure 5.12. Crystalline repaglinide displayed their characteristic diffraction peaks at 7.58^0, 10.06^0, 13.75^0, $16.62^{0,}$ 20.24^0,22.90^0 and 30.81^0 respectively and which are correlating with the previously reportedly reference values which confirms the crystalline nature of repaglinide.

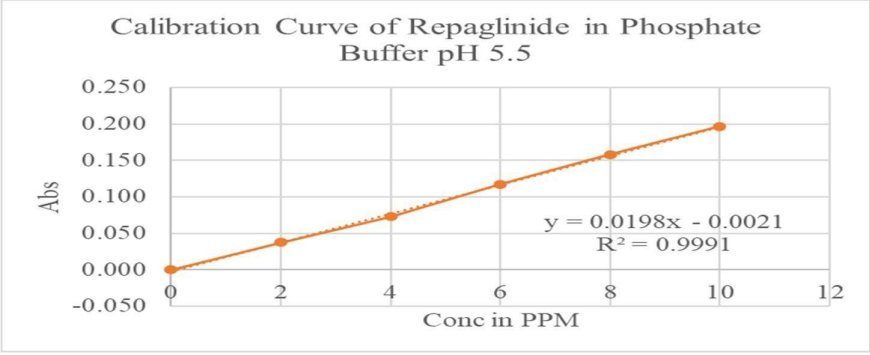
a) Standard Calibration Curve of Repaglinide in buffer system pH 5.5:

Calibration curve observation at 240 nm

Table 3: Calibration curve observation in buffer pH 5.5(Phosphate buffer)

Sr. No	Conc. in µg per ml	Read 1	Read 2	Read 3	Mean value
1	0	0	0	0	0.000
2	2	0.035	0.038	0.04	0.038
3	4	0.072	0.076	0.071	0.073
4	6	0.115	0.118	0.119	0.117
5	8	0.156	0.16	0.158	0.158
6	10	0.198	0.201	0.191	0.197

Figure 5: Standard curve of Repaglinide in buffer pH 5.5



9.1 Optimisation Study using Design of Experiments:

Table 4: Variable Factors for Box-Behnken design:

Factors	**Levels for study, As Coded**	
	Low (-1)	**High (1)**
Independent Variables		
X-1= Conc. Of Polymer Blend (% w by w)	40	80
X-2=Ball Milling time (Min)	60	180
Dependent Variables	**Constraints**	
Y1= Drug Release (%)	Maximize	
Y2= Crystallinity of Repaglinide (%)	Minimize	

Statistical Analysis:

Full 3^2 factorial design had chosen, with sufficient two factors examined at three levels each. The independent variables were Polymer Blend Concentration (X1) and Ball Milling Time (min) (X2), while the dependent variables were Drug Release (%) (Y1) and Crystallinity of Repaglinide (%) (Y2). The collected data was studied using Design Expert 7.1.6 software and statistically evaluated through analysis of variance (ANOVA).

Table 5: Design and Response summary Repaglinide ASD batches

Sr. No	**Batch Nos**	**Factor-1 (X1) Conc. Of Polymer Blend (%w/w)**	**Factor-2 (X2) Ball Milling time (Min)**	**Response-1 Drug Release (%)**	**Response-2 Crystallinity of Repaglinide (%)**
1	Rep SD 01	40	60	54.87	10.14
2	Rep SD 02	60	60	70.15	9.36
3	Rep SD 03	80	60	96.03	12.06
4	Rep SD 04	40	120	57.66	9.45
5	Rep SD 05	60	120	78.05	10.96
6	Rep SD 06	80	120	82.85	13.06
7	Rep SD 07	40	180	58.02	8.32
8	Rep SD 08	60	180	74.12	11.58
9	Rep SD 09	80	180	89.45	14.25

Table 6: Response 1 Valeus: Drug Release

Source	Std Dev.	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS	
Linear	4.58	0.9268	0.9024	0.8323	288.39	Suggested
2FI	4.52	0.9406	0.9050	0.7797	378.77	
Quadratic	5.73	0.9427	0.8471	0.4300	980.01	
Cubic	6.84	0.9728	0.7826	-3.9520	8514.21	Aliased

ANOVA considering the Quadratic model:

Table 7: Response for Factor No 1: Drug Release of Repaglinide

Source	Sum of Squares	df	Mean Square	F Value	p-value prob> F	
Model	27.78	5	5.56	11.15	0.0374	Significant
A-conc.of polymer Blend	21.89	1	21.89	43.93	0.0070	
B-Ball Milling time	1.12	1	1.12	2.24	0.2311	
AB	4.02	1	4.02	8.07	0.0656	
A^2	0.67	1	0.67	1.35	0.3293	
B^2	0.084	1	0.084	0.17	0.7088	
Residual	1.49	3	0.50			
Cor Total	29.28	8				

The Model. F-value of 9. 86 indicates significance of model. There will be only a 4.42% probability that this such a large. F-value could result from randomness. .Model terms with p- values below 0.05 are to eb considered significant.

Table 8: Fit Statistics for % Drug Release

Std. Dev.	5.73	R-Squared	0.9427
Mean	73.47	Adj R-Squared	0.8471
C.V. %	7.80	Pred R-Squared	0.4300
PRESS	980.01	Adeq Precisior	8.002

"Predicted R-Squared" value of 0.4300 deviates from "Adjusted R-Squared" of 0.8471, suggesting a substantial block effect or also a potential issue with the model and/ or data. Factors such as design model simplification, responded transformation, and outlier examination should be taken into account. "Adequate Precision" assesses signal-to-noise ratio, and a ratio over 4.00 is desirable. In this study ratio of 8.002 signifies an acceptable signal suggesting that this model is suitable for the design space.

Table 8: Coefficients of coded factors for the percentage of drug release

Factor	Coefficient Estimate	df	Standard Error	95% CI Low	95% CI High	VIF
Intercept	73.49	1	4.27	59.89	87.09	
A-Conc. Of Polymer Blend	46.30	1	2.34	8.85	23.74	1.00
B-Ball Milling time	0.090	1	2.34	-7.36	7.54	1.00
AB	-2.43	1	2.87	-11.55	6.69	1.00

A^2	-0.96	1	4.05	-13.86	11.94	1.00
B^2	0.92	1	4.05	-11.98	13.82	1.00

The coefficient estimate indicates the anticipated alteration in the response for each unit shift in factor. As a general suggestion, VIFs value below 10.00 are acceptable.
The Final equation expressed in coded factors is as follows:
Drug Release = +73.49 +16.30 * A +0.090 * B -2.43 * A * B -0.96 * A2 +0.92 * B2

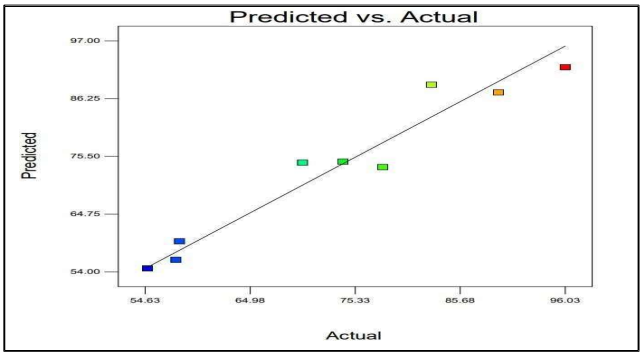


Figure 6: Report for % Drug Release

Table 10: Response 2 Values: Crystallinity of Repaglinide

Source	Std. Dev.	R-Squared	Adjusted R-Squared	Predicted R-Squared	PRESS	
Linear	1.02	0.7858	0.7144	0.3811	18.12	
2FI	0.67	0.9231	0.8770	0.6754	9.50	Suggested
Quadratic	0.71	0.9489	0.8639	0.3908	17.84	
Cubic	0.28	0.9972	0.9778	0.4944	14.80	Aliased

ANOVA for Quadratic model

Table 9.14: Response 2: Crystallinity of Repaglinide

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	27.78	5	5.56	11.15	0.0374	
A-Conc. Of Polymer Blend	21.89	1	21.89	43.93	0.0070	Significant
B-Ball Milling time	1.12	1	1.12	2.24	0.2311	
AB	4.02	1	4.02	8.07	0.0656	
A^2	0.67	1	0.67	1.35	0.3293	
B^2	0.084	1	0.084	0.17	0.7088	
Residual	1.49	3	0.50			
Cor Total	29.28	8				

Significance of this used model is shown by the std F-value of 11.15. Probability that such a high "Model F-Value" could .occur due to noise is only 3.74%. Model terms with "Prob > F" values below 0.0500 are considered significant, and in this instance, term A might be significant.

Table 11: Fit statistics for Crystallinity of Repaglinide

Std. Dev.	0.71	R-Squared	0.9489
Mean	11.02	Adj R-Squared	0.8639
C.V. %	6.41	Pred R-Squared	0.3908
PRESS	17.84	Adeq Precisior	10.107

3Dimensional Response Surface & Contour Plot:

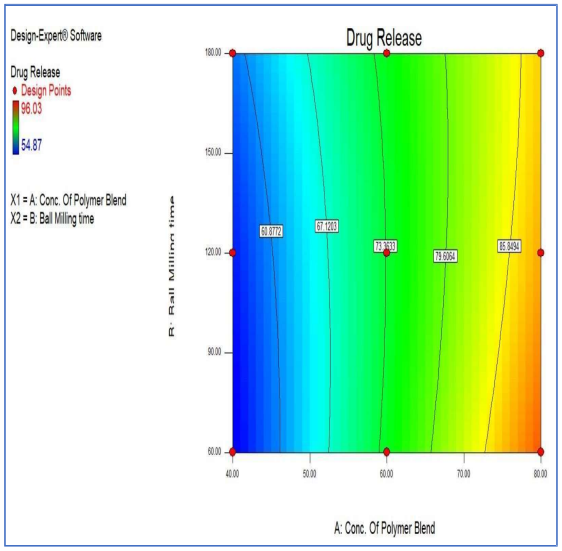


Figure 7: A contour plot illustrates the correlation between different concentrations of the polymer blend and ball milling time with respect to drug release.

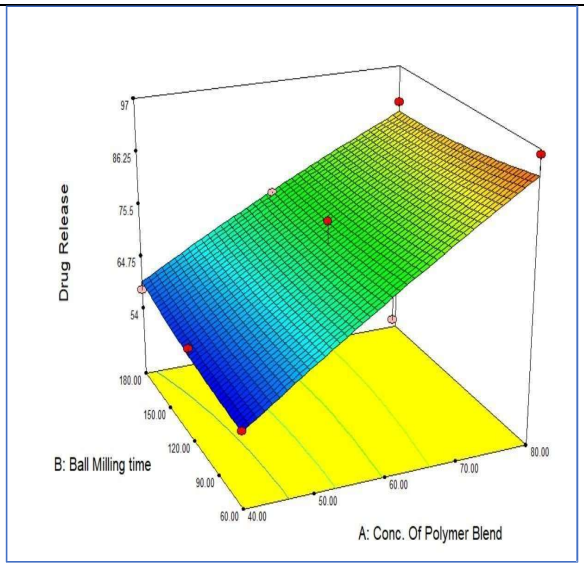


Figure 8: Response 3D surface plot show the effect of levels of conc. of polymer blend and ball milling time on drug release

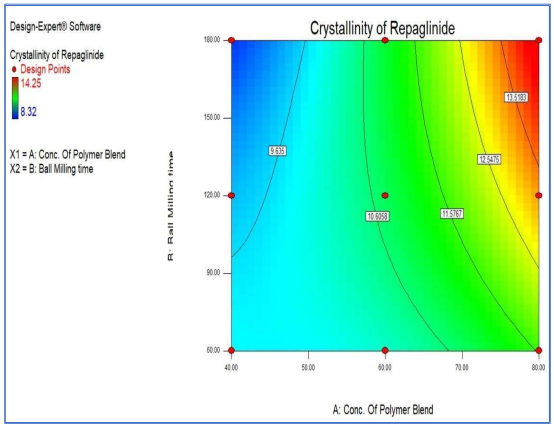


Figure 9: A contour plot demonstrates the connection between different concentrations of the polymer blend and ball milling time concerning the crystallinity of repaglinide

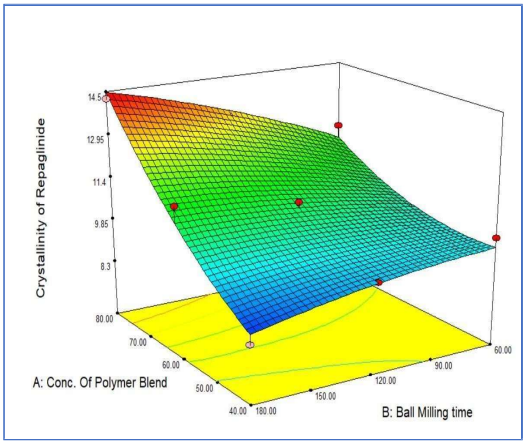


Figure 10: Response 3D surface plot show the effect of levels of conc. of polymer blend and ball milling time on crystallinity of repaglinid

9.2 Evaluation of ASD formulations:

A) Solid- state studies of ball-milled ASDs:

X RD powder diffraction (XRPD:

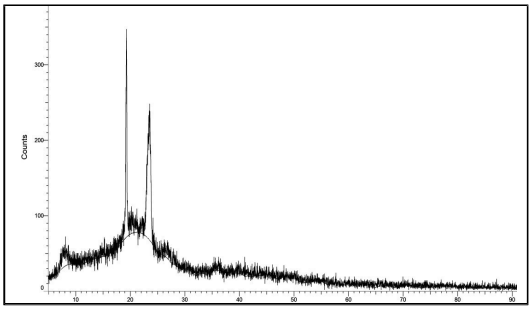


Figure 11: X-RD Diffractogram of Polymer Blend of HPMC + Pluronic F127 developed by Reactive Ball Milling

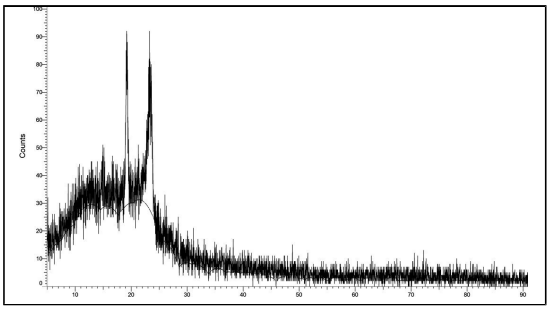


Figure 12: XRD Diffractogram of Polymer Blend of PVP K30 + Pluronic F127 developed by Reactive Ball Milling

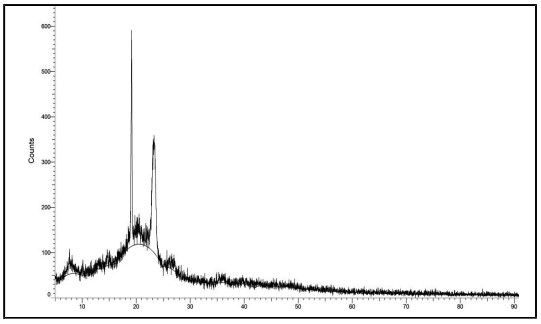


Figure 13: X-ray Diffractogram of Amorphous Solid Dispersion of Repaglinide + (HPMC + Pluronic F127) developed by Reactive Ball Milling

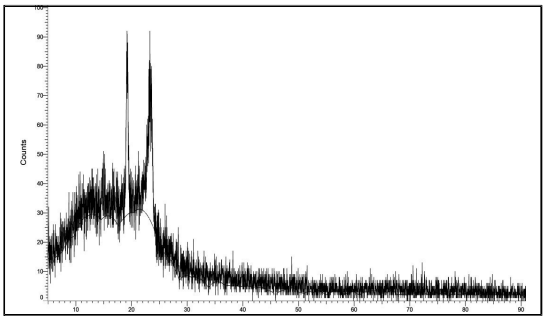


Figure 14: X-ray Diffractogram of Amorphous Solid Dispersion of Repaglinide +(PVP K30 + Pluronic F127) developed by Reactive Ball Milling

9.2.1 DSC-TGA Analysis:

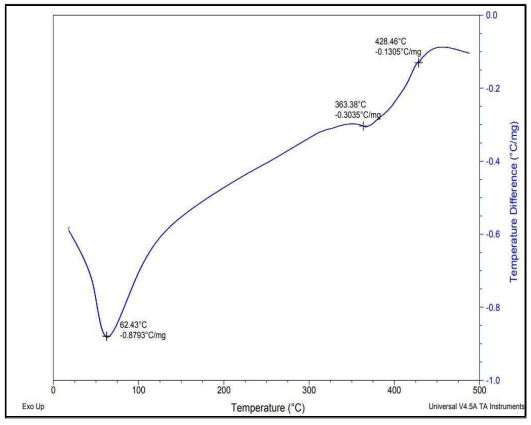


Figure 15: Thermogram of Polymer Blend of HPMC + Pluronic F127 developed by Reactive Ball Milling

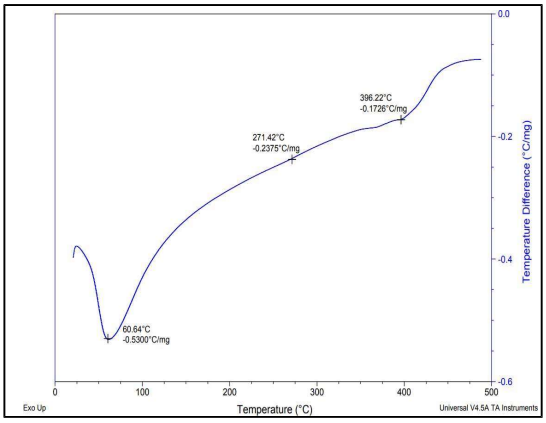


Figure 16: Thermogram of Polymer Blend of PVP K30 + Pluronic F127 developed by Reactive Ball Milling

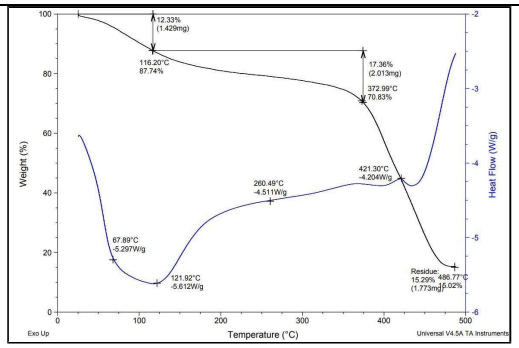


Figure 17: Thermogram of Amorphous Solid Dispersion of Repaglinide + (HPMC + Pluronic F127) developed by Reactive Ball Milling

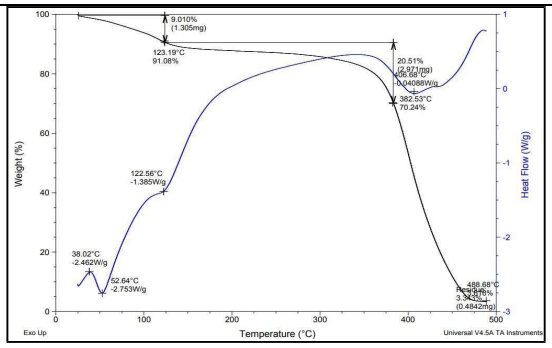


Figure 18: Thermogram of Amorphous Solid Dispersion of Repaglinide +(PVP K30 + Pluronic F127) developed by Reactive Ball Milling

9.1 Cumulative % drug release study for Repaglinide:

Repaglinide release demonstrated rapid also shows complete release within 90 minutes in phosphate buffer at pH 5.5. The drug release profiles of amorphous solid dispersions (ASDs) has compared to that of the neat drug and its physical mixture.

Table 12: Cumulative % drug release of ASD Batches, Neat drug, its Physical mixture

Time Point in Min	Pure Drug	Physical Mixture	REP-SD-1	REP-SD-2	REP-SD-3	REP-SD-4	REP-SD-5	REP-SD-6	REP-SD-7	REP-SD-8	REP-SD- 9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	3.45	5.87	10.11	15.78	22.14	9.88	17.05	16.36	7.88	16.87	15.45
20	8.89	11.25	17.12	25.12	31.47	18.15	28.45	30.04	17.22	24.45	31.67
30	15.25	18.89	26.77	33.64	39.85	28.89	36.89	41.89	25.25	35.78	42.38
45	21.12	27.35	35.49	47.32	60.55	36.65	49.19	59.45	35.87	50.15	58.47
60	29.14	36.15	44.38	57.78	78.52	47.89	67.16	71.18	48.00	61.78	72.65
90	36.45	44.28	54.87	70.15	96.03	57.66	78.05	82.85	58.02	74.12	89.45

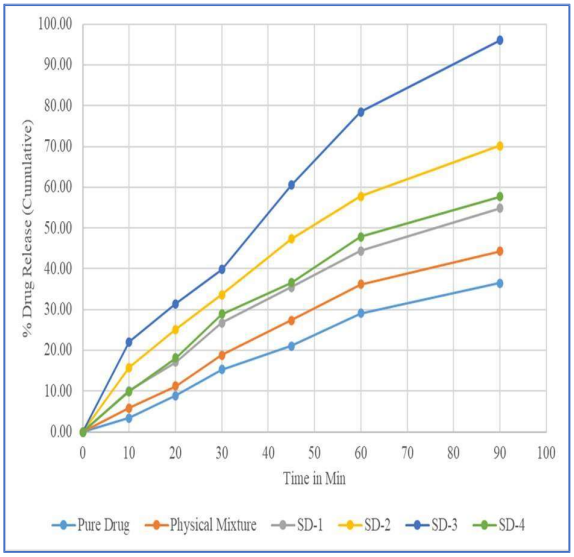


Figure 19: Cumulative % of drug release of Amorphous solid dispersion Batches (SD- 1 to SD 4), Pure drug, Physical mixture

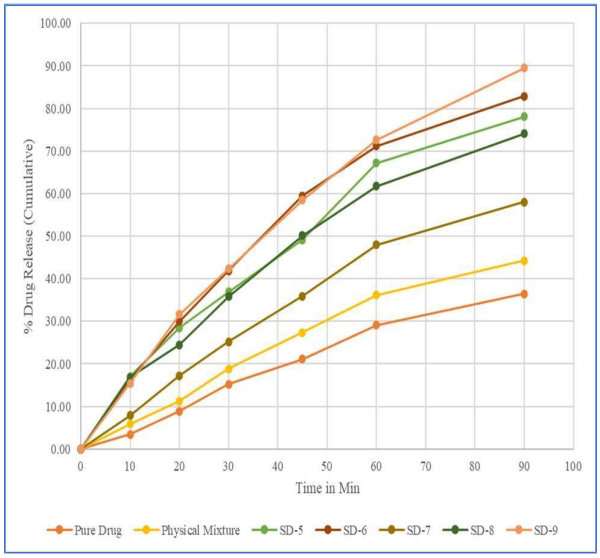


Figure 20: Cumulative % of drug release of Amorphous solid dispersion Batches (SD- 5 to SD-9), Pure drug, Physical mixtur

Repaglinide Drug-Content:

Table 13: % Drug content of Repaglinide ASD batches

Sr. No	ASD Batches	Drug-Content (%)
1	REP-SD-1	88.45
2	REP-SD-2	98.60
3	REP-SD-3	99.78
4	REP-SD-4	100.05
5	REP-SD-5	92.85
6	REP-SD-6	97.68
7	REP-SD-7	96.25
8	REP-SD-8	98.65
9	REP-SD-9	99.14

The repaglinide drug content of solid dispersion formulations are within acceptable range. The percentage drug content in the formulations ranged from 88.45 to 100.05, indicating a uniform distribution of drug in ASD's.

Conclusion

Amorphous solid dispersion of repaglinide with the use of HPMC E15, pluronic F27 was made successfully utilising reactive ball milling. The PEG 400 act as reactive media for converting the crystalline drug to amorphous form. The polymer blend formulation blend and their process were optimised. DoE platform was utilised to optimize the processing cum stability parameters. The neat drug, its physical mixture and finally prepared ASD were evaluated for visual inspection, drug content study by UV spectroscopy, FTIR, X-ray diffraction, DSC, dissolution study and short -term stability study. A pure drug's DSC thermogram shows that crystallization predominated in the initial sample, which is compatible with the crystal's needle-shaped morphology and low water solubility. The developed amorphous system is mostly of an amorphous character, stabilized by a crystal formation inhibitor such HPMC, as confirmed by an X-ray diffractogram. When related to the neat drug and its physical mixture of repaglinide, in-vitro dissolution analysis showed that batch REP SD-3, in which the polymer blend concentration was 80% weight-for-weight and the milling period was 60 min, offered the perfect solid dispersion with an outstanding release profile greater than 95%. The batch's short-term stability falls within allowable limits.

Conflict of Interest –No any conflict of interest

Funding Sources- No

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