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Quality-by-design based development of fast dispersible nimodipine tablets: Formulation attributes and release kinetic assessment

Hira Akhtar[1], Ghazala Raza Naqvi[1], Farya Zafar[2], Huma Ali[3], Rehana Saeed[2], Shaheen Parveen[3] and Shazia Alam[4]

[1]Department of Pharmaceutics, Faculty of Pharmacy, Federal Urdu University of Arts, Science &Technology, Karachi, Pakistan
[2]Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, Pakistan
[3]Department of Pharmaceutics, Institute of Pharmaceutical Sciences, Jinnah Sindh Medical University, Karachi, Pakistan
[4]Department of Pharmaceutics, Faculty of Pharmacy, Ziauddin University, Karachi, Pakistan

Abstract: In the present study fast dispersible nimodipine tablets were developed by direct compression method using quality by design (QbD) approach as per the central composite design by selecting avicel PH 102 (X_1) and crospovidone (X_2) as independent variables while % friability (R_1), disintegration (R_2) and hardness (R_3) as output variables. Powder blends were assessed for flow characterization. At post compressional stage, several quality assessments were carried out. Particles morphology was observed using scanning electron microscopy (SEM). The stability study on the drug and optimized formulation were determined using thermal gravimetric analysis (TGA) and differential thermal analysis (DTA). RSM plots expressed the interaction of avicel PH 102 and crospovidone to determine the adequate quantities of excipients for the optimized formulation. Polynomial equations were used to validate the experimental design. The optimized formulations were evaluated for friability, disintegration, and hardness. Results indicated that formulation (F4) containing avicel PH 102 (35%) and crospovidone (5%) was selected as best optimized formulation having friability 0.59%, disintegration 9 sec, % dissolution 95.703% and hardness 4.14 kg. Results of kinetics models indicated that all the developed formulations followed weibull model.

Keywords: Fast dispersible, direct compression, quality by design, central composite design and release kinetics.

INTRODUCTION

From last few years several innovative tablet manufacturing technology have provided significant substitutes for patients struggling in administrating conventional tablets. Fast dispersible tablets are one of the considerable alternatives (Marroof *et al*., 2016). Upon exposure to physiological fluids, fast dispersible tablets disintegrate and dissolve completely within a short period of time (Qureshi *et al*., 2017). These formulations are very desirable where a fast onset of action is required as in analgesics or to facilitate the bioavailability of a poorly soluble compound (Fukami *et al*., 2006; Yasmin *et al*., 2020). Nimodipine was used as model drug. It is a calcium channel blocker used for reducing cerebral infraction and improving outcomes after SAH (Sub Arachnoid hemorrhage). It is a BCS II drug which leads to its limited dissolution thus results in poor bioavailability (13%). Oral bioavailability is reported to be about 9 hours (Zhao *et al*., 2014).

Fast dispersible tablets are usually manufactured by direct compression method. This method enables the tablet manufacturing using powder blend without initial granulation step. Development of tablet can be challenging due to several competing objectives. One of them is ensuring a consistent tablet weight. Powder blend should compress and compact to form robust and stable tablets (Solaiman *et al*., 2016).

Quality by Design (QbD) is one of the effective approach for the development of numerous products with definite objectives, which improved both process and product understanding with inadequate resources mainly cost, time and efforts (Bonthagarala *et al*., 2019). Designs of Experiments (DoE) are one of the essential components of QbD, as it facilitates in developing a relationship between variables and effects among various factors. Several scientists used effectively both QbD and DoE approaches in product development for obtaining efficient product performance (Charoo *et al*., 2011, Chappidi *et al*., 2019).

In 1955, Battista and Smith have discovered microcrystalline cellulose (MCC) (FMC, 2013). In 1964, avicel PH was introduced as direct compression tableting ingredients by FMC Corporation (Thoorens *et al*., 2014). It is self-disintegrating with reduced lubricant requirement having low coefficient of friction. MCC plastically deforms during compression and thus increases the area of interparticle bonding. MCC type 102 has lower median particle size which indicates it's easy flowing characteristics with narrow compressibility index and shear cell flow functions (FFc) values > 4. The plastic nature together with high surface area and low bulk density describes its distinctive binding properties (Yassin *et al*., 2015).

Disintegrants are used to establish rapid release features. Superdisintegrants are added in concentration between

*Corresponding author: e-mail: farya.zafar@edu.uok.pk

2 - 5% which influenced the disintegration of the tablets (Markl and Zeitler, 2017). The selection of disintegrants based on the compatibility of the compound and optimum disintegration for the system under development. The rate of hydration is very important in regulating the degree of disintegration in conventional tablet formulation. The ac-di-sol exhibits porous nature which enhance the diffusion of water in tablets, enhancing it's wicking and the rapid tablet disintegration property (Yasmin *et al*., 2020).

In the present study, dispersibility of tablet in water is enhanced which influences the therapeutic performance of the compound in the body. In this context, fast dispersible tablets were developed and optimized using QbD approach using central composite design (CCRD). The developed formulations contains varying concentrations of binder and super disintegrant i.e. avicel PH102 and crospovidone. Optimized formulations were manufactured by direct compression method. Formulations were tested by various quality tests. Release profiles were estimated by model dependent and independent methods. The SEM (scanning electron microscopy) study reported the surface characteristics of the formulation components.

MATERIALS AND METHODS

Nimodipine (Medisure Pharmaceutical Pvt.Ltd.), avicel PH 102 (BASF, Luderwigshafe, Germany), crospovidone (FMC Biopolymer. Philadelphia, USA) and aspartame (Lubon industry Co. Ltd., China), magnesium stearate (Jingjiang Chemical Co. Ltd., China).

Experimental design

Central composite design (CCD) successfully applied to analyze two factors at three levels statistically (Siddiqui *et al*., 2021). Nine fast dispersible Nimodipine tablet formulations (30mg) were designed and developed using Central Composite Design Expert (11.0 software) (Stat-Ease, Inc, Minneapolis, MN 55413, USA). Avicel PH 102 (35-60%) and crospovidone (1-5%) were selected as independent variables, whereas aspartame (1.7mg) as a sweetening agent and magnesium stearate as lubricant were added in fixed quantity as mentioned in table 1.

Precompression assessment

Bulk density of powder blends were assessed using a measuring cylinder. Initially the weight of cylinder was tare to zero and then some amount of powder blend was filled and reweighed. Bulk density (g/cm^3) was determined by the following formula:

$$P_{bulk} = \frac{Mass}{Bulk\ volume} \qquad \text{Eq.1}$$

Where ρbulk = bulk density. The initial volume of the blend is the bulk volume. Finally the cylinder was tapped 100 times and the decline in bed's volume was considered as tapped volume. Tapped density (g/cm^3) was determined by the following formula:

$$P_{tap} = \frac{Mass}{Tapped\ volume} \qquad \text{Eq.2}$$

Flow characteristics of powder blends were estimated by angle of repose (θ) and hausner's Ratio (HR) and carr's Index using the following equations (Bushra *et al*., 2018):

$$hausner's\ Ratio = \frac{P_{tapped}}{P_{bulk}} \qquad \text{Eq. 3}$$

$$\theta = \tan^{-1}\frac{2h}{D} \qquad \text{Eq. 4}$$

$$carr's\ Index = \frac{P_{tapped} - P_{bulk}}{P_{tapped}} \times 100 \qquad \text{Eq. 5}$$

So, θ = angle of repose, 'D'= diameter of the heap form and 'h'= height of heap.

Assessment of physicochemical parameters of fast dispersible nimodipine formulations

Nine formulations were compressed and weighed, their diameter, thickness and hardness assessments were measured with digital vernier caliper (Digital Vernier Caliper: Seiko brand) and hardness tester (OSK Fujiwara, Ogawa Seiki Co. Ltd., Tokyo, Japan). Percentage (%) friability was estimated using Roche type Friabilator (H. Jurgens Gmbh H and Co- Bremen, D2800, Germany).

Disintegration test of fast dispersible tablets was carried out in 100 mL of distilled water was maintained at 37˚C. Tablets disintegration time was determined in seconds. The assay and dissolution assessments were performed using acetate buffer pH 4.5 and 0.3% sodium dodecyl sulphate (SDS) (B.P. 2009) using UV-Spectrophotometer (UV-1800 Shimadzu Corporation Kyoto, Japan) at 317nm.

Determination of release behavior

Drug release behavior was also determined using 900ml of dissolution medium (acetate buffer pH 4.5 and 0.3% sodium dodecyl sulphate). Temperature was set at 35±2°C at 75rpm. Samples were taken at different time points i.e. 5min, 10 min, 15min, 20 min, 30min, 45min, 60min, 90min and 120min. Release kinetics estimation was carried out by DD Solver® (Add Ins program).

Release kinetics

Model-dependent method

Several kinetic models (Zhang *et al*., 2010) were used for the estimation of release behavior i.e. first order kinetics (Polli *et al*., 1997), higuchi kinetics (Yuksel *et al*., 2000), hixon crowell model (Siepmann and Siepmann, 2008) and weibull model (Berry and Likar, 2007).

$$(ln\,Q_t = ln\,Q_0 - k_i t) \qquad \text{Eq. 6}$$

$$Q_t = kt^{\frac{1}{2}} \quad \text{Eq.7}$$

$$Q_0^{\frac{1}{3}} - Q_t^{\frac{1}{3}} = K_{HC} \times t \quad \text{Eq. 8}$$

$$m = 1 - exp\left[-\frac{([t - Ti)]^{\beta}}{\alpha}\right] \quad \text{Eq. 9}$$

Where, Q_t = is the collective amount of drug release at time *t*, Q_o = is the initial concentration of drug and k_1, k, K_{HC} and are the release rate constants for the first-order, higuchi, hixon - crowell. For Weibull model m is the solution at time *t*. Models were estimated by DD-solver rate constant.

Also mean dissolution time (MDT) and dissolution efficiency (DE) were determined using following equations:

$$MDT = \frac{\left(\sum [n_{j=1}(\hat{t_j}\Delta M_j]\right)}{\sum n_{j=1}\Delta M_j} \quad \text{Eq.10}$$

$$D.E = \frac{\int_0^t y \times dt}{y100 \times t} \times 100 \quad \text{Eq.11}$$

Where, j = no of sample, n = no of dissolution sample times, $\hat{tj}$ is the time at the midpoint between t_j and t_{j-1}, ΔM_j is the additional amount of drug dissolved between t_j and t_{j-1} and y is the percentage drug dissolved at time *t*.

Model-dependent method

The difference and similarity factors were calculated using the following equations:

$$f_1 = \left[\frac{\sum_{t=1}^{n}(R_t - T_t)}{\sum_{t=1}^{n} R_t}\right] \times 100$$

Eq. 12

$$f_2 = 50 \times log\left\{\left[1 + \left(\frac{1}{N}\right)\sum (Ri - Ti)^2\right]^{-0.5}\right\} \times 100$$

Eq.13

Where, R_t and T_t are the amount of drug release at different time points from reference and test formulations respectively and n is the no of dissolution samples (Qureshi *et al*., 2017).

Scanning electron microscopic assessment (SEM)

SEM (JSM- 6380A, JEOL, Japan) was used in the present study to observe the SEM images (at magnification x550 - x7000) of nimodipine (API) as well as of API: disintegrant and API: binder. The powder samples were dried for 1hr at 40°C before SEM analysis. The analyzer consists of a column & stage. The function of stage to set image resolution while the purpose of column is to provide electron beam that strikes with powder sample to create images of varying resolutions and sizes.

Thermal gravimetric analysis and differential scanning calorimetry (TGA-DSC)

The thermal stability of nimodipine was determined by thermal analyzer (SDT 650 simultaneous TGA-DSC). In the sample holder four mg of sample was taken. Standard was taken in an empty aluminum reference holder. Analysis was carried out at a temperature range from 20-600ºC, the rate was found to be 10°C/min. In the active nitrogen atmosphere, the flow rate was 99.98 mL/min (Zeb-un-Nisa *et al*., 2021).

STATISTICAL ANALYSIS

Statistical assessment of the experimental analysis was performed to explored the interaction of binder and super disintegrant to establish the optimum quantity of excipients for the development of fast dispersible tablets. Based on fit summary and ANOVA, the responses were statistically analyzed using Design Expert version 11.0.0 software (Stat-Ease, Inc, Minneapolis, MN 55413, USA). The p value, F value and Adeq precision were determined. In graphical presentation, the effect of individual factor on each response is presented. RSM plots for % friability, disintegration test and hardness tests have been determined.

RESULTS

Fast dispersible nimodipine (30mg) tablets using QbD approach to assess the effect of various concentration of avicel PH 102 and crospovidone on three different responses using Design Expert ® (11.0). Composition of all formulations was expressed in table 1. Probability value and coded equations of selected responses were mentioned in table 2. Flow characteristics of all the powders were analyzed by various tests as mentioned in table 3. Quality evaluation tests were performed on all optimized formulation. Results indicated that quality attributes of all formulations were found to be in adequate limits as shown in table 4. In RSM plot it is found that % friability was found to be decreased as the amount of avicel PH 102 was increased as shown in fig. 1A. RSM plot for disintegration time is presented in fig. 1B, indicated that disintegration time is decreased as the concentration of crospovidone was increased. RSM plot for hardness was shown in fig. 1C, explained that the higher concentration of avicel PH 102 increases the hardness of fast dispersible nimodipine tablets. *In vitro* release behavior of different newly designed and developed nimodipine fast dispersible formulations were carried out in dissolution medium (fig. 2). Results of drug release kinetics were presented in table 5 (A) and mean dissolution time (MDT) and dissolution efficiency (DE) were shown in table 5 (B).

Table 1: Fast dispersible nimodipine tablets using QbD design approach

Formulations	Center Composite Design of the Formulation Variables		Composition of the Formulations					
	A:Avicel PH 102	B:Crospovidone	Avicel PH 102	Crospovidone	Aspartame	API	Magnesium Stearate	Final Weight
	%	%	% (mg)	% (mg)	% (mg)	%(mg)	% (mg)	mg
F1	47.5	0.171	47.5(163.06)	0.17(0.58)	0.85(2.91)	15(30)	1(3.43)	200
F2	29.822	3	29.82(146.22)	3(14.70)	0.85(4.16)	15(30)	1(4.90)	200
F3	60	1	60(162.29)	1(2.70)	0.85(2.29)	15(30)	1(2.70)	200
F4	35	5	35(142.17)	5(20.31)	0.85(3.45)	15(30)	1(4.06)	200
F5	47.5	3	47.5(154.25)	3(9.72)	0.85(2.76)	15(30)	1(3.24)	200
F6	60	5	60(152.58)	5(12.71)	0.85(2.16)	15(30)	1(2.54)	200
F7	65.177	3	65.177(158.22)	3(7.28)	0.85(2.06)	15(30)	1(2.42)	200
F8	35	1	35(157.199)	1(4.49)	0.85(3.81)	15(30)	1(4.49)	200
F9	47.5	5.828	47.5(146.34)	5.82(17.95)	0.85(2.61)	15(30)	1(3.08)	200

Table 2*:* Probability Value and Coded Equations of Selected Responses

Responses	*p* value
R_1 (Friability)	0.0129
R_2 (Disintegration)	0.0182
R_3 (Hardness)	0.0241
Coded Equations for Responses	
R_1 = +0.4889+0.0125 * A-0.0125 * B-0.0750 – AB	
R_2 = +17.56+1.03 * A - 4.77*B	
R_3 = +2.10-0.0479 * A + 0.0552 * B	

Table 3: Micromeretic properties of fast dispersible niomodipine tablets

FORMULATIONS	ANGLE OF REPOSE (θ)	HAUSER'S RATIO	CARR'S INDEX (%)
F1	32.99 ± 1.32	1.12 ± 0.005	11.52 ± 0.68
F2	33.45 ± 0.92	1.16 ± 0.005	14.33 ± 0.43
F3	33.39 ± 1.21	1.13 ± 0.085	12.05 ± 1.28
F4	37.64 ± 0.78	1.19 ± 0.005	17.28 ± 0.49
F5	34.07 ± 2.52	1.12 ± 0.015	11.29 ± 2.19
F6	38.65 ± 0.98	1.17 ± 0.005	17.35 ± 1.06
F7	32.54 ± 2.61	1.13 ± 0.050	12.37 ± 2.19
F8	33.38 ± 0.85	1.14 ± 0.020	13.27 ± 1.30
F9	31.83 ± 0.73	1.21 ± 0.01	13.68 ± 1.24

Table 4: Quality attributes of nine different fast dispersible nimodipine tablets.

QUALITY EVALUATIONS OF THE FAST DISPERSIBLE NIMODIINE (30mg) TABLETS								
		Weight Variation	Hardness Variation	Thickness Variation	Friability	Disintegration Test	Assay	Dissolution
	Limit	± 7.5	2-5 Kg	± 5	< 1 %	< 3 min	90-110 %	> 75 % at 45 min
	n (Tablets)	20	20	20	20	6	20	6
	Values	Mean ± SD	Mean ± SD	Mean ± SD	Value	Value	Value	Value
	Unit	Mg	kg	mm	%	Min	%	%
Formulations	F1	204.93 ± 3.29	4.051 ± 0.025	3.005 ± 0.045	0.65	31	96.677 ± 0.525	95.878 ± 0.793
	F2	204.61 ± 3.07	4.1 ± 0.536	2.969 ± 0.079	0.58	15	96.523 ± 0.580	95.875 ± 0.852
	F3	204.68 ± 4.37	4.085 ± 0.3901	2.941 ± 0.201	0.72	27	94.663 ± 0.814	94.010 ± 2.664
	F4	205 ± 3.02	4.146 ± 0.095	2.976 ± 0.067	0.59	9	97.247 ± 0.527	95.703 ± 0.528
	F5	206.02 ± 4.65	4.107 ± 0.145	3.028 ± 0.116	0.71	13	93.310 + 0.930	92.697 ± 1.751
	F6	204.45 ± 2.66	4.080 ± 0.041	2.958 ± 0.074	0.65	14	96.673 ± 0.416	95.727 ± 0.888
	F7	203.54 ± 4.08	4.009 ± 0.092	2.922 ± 0.099	0.64	18	94.580 ± 1.394	94.450 ± 0.686
	F8	205.20 ± 4.94	4.107 ± 0.057	2.961 ± 0.102	0.63	29	93.877 ± 0.867	93.980 ± 1.478
	F9	202.91 ± 1.61	4.034 ± 0.021	2.941 ± 0.064	0.58	16	97.093 ± 0.591	95.933 ± 0.628

Table 5 (A): Drug release kinetics of fast dispersible nimodipine tablets

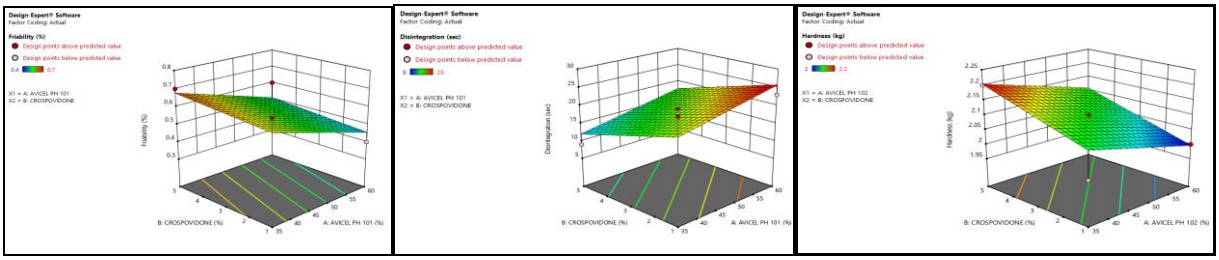
Formulations	First Order		Higuchi		Hixon Crowell		Weibull Model		
	r^2	$k_1(h^{-1})$	r^2	$k_H(h^{-1/2})$	r^2	$k_{HC}(h^{-1/3})$	r^2	B	A
Acetate Buffer pH 4.5, 0.3 % SDS									
F1	0.9412	0.029	0.7239	6.290	0.8939	0.005	0.9760	0.341	1.588
F2	0.9600	0.033	0.7340	6.644	0.9210	0.006	0.9874	0.379	1.812
F3	0.9584	0.034	0.7241	6.399	0.9228	0.006	0.9677	0.360	1.612
F4	0.9691	0.034	0.7535	6.476	0.9389	0.006	0.9636	0.360	1.606
F5	0.9922	0.036	0.7872	6.935	0.9769	0.006	0.9694	0.397	1.861
F6	0.9607	0.032	0.7348	6.484	0.9245	0.006	0.9723	0.361	1.671
F7	0.9585	0.034	0.6971	6.386	0.9201	0.006	0.9782	0.361	1.597
F8	0.9807	0.030	0.8368	6.953	0.9654	0.005	0.9676	0.377	1.839
F9	0.9803	0.041	0.7130	7.057	0.9684	0.008	0.9629	0.436	2.086

Table 5 (B): Mean dissolution time and dissolution efficiency of fast dispersible nimodipine formulations at acetate buffer PH 4.5 and 0.3% SDS

PARAMETERS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Mean Dissolution Time (MDT)	0.876	0.878	0.888	0.890	0.891	0.882	0.889	0.878	0.893
Dissolution Efficiency	10.576	11.461	10.862	11.512	11.708	10.793	10.454	12.883	11.040

Table 6: Model independent method of fast dispersible nimodipine formulations

Similarity factor and differential factor	Dissolution medium	F1	F2	F3	F5	F6	F7	F8	F9
f_1	Acetate buffer pH 4.5, 0.3 % SDS	1.53	1.98	0.22	0.92	1.18	0.24	2.44	0.99
f_2		88.01	81.94	98.51	83.53	91.21	97.55	74.09	74.96



(A) (B) (C)

Fig. 1: 3D Response Surface Plots of Fast Dispersible Nimodipine Formulations Showing effects of Independent Variables on (A) Friability, (B) Disintegration, (C) Hardness.

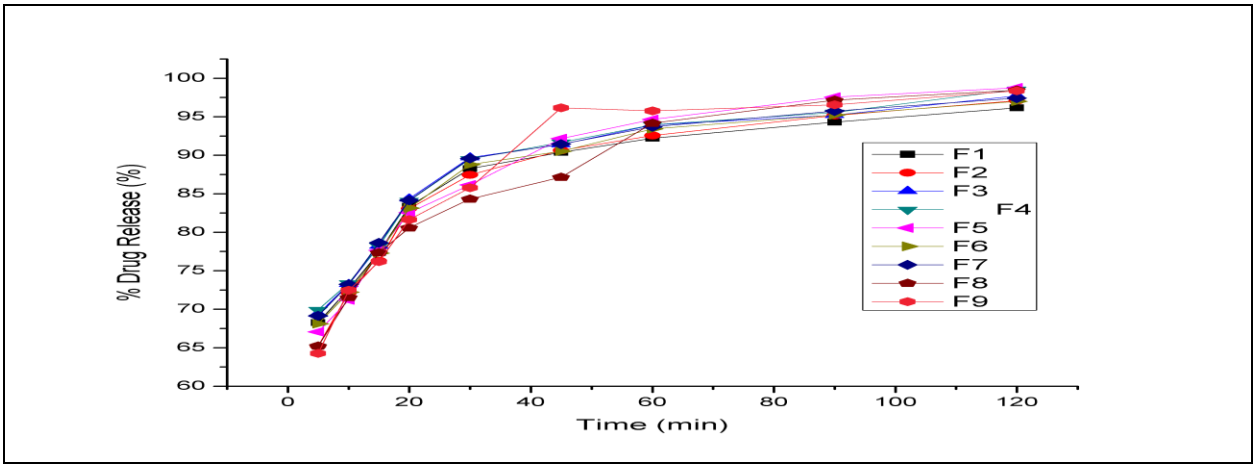


Fig. 2: Release profiles of fast dispersible nimodipine formulations at acetate buffer Ph 4.5 with 0.3 % SDS.

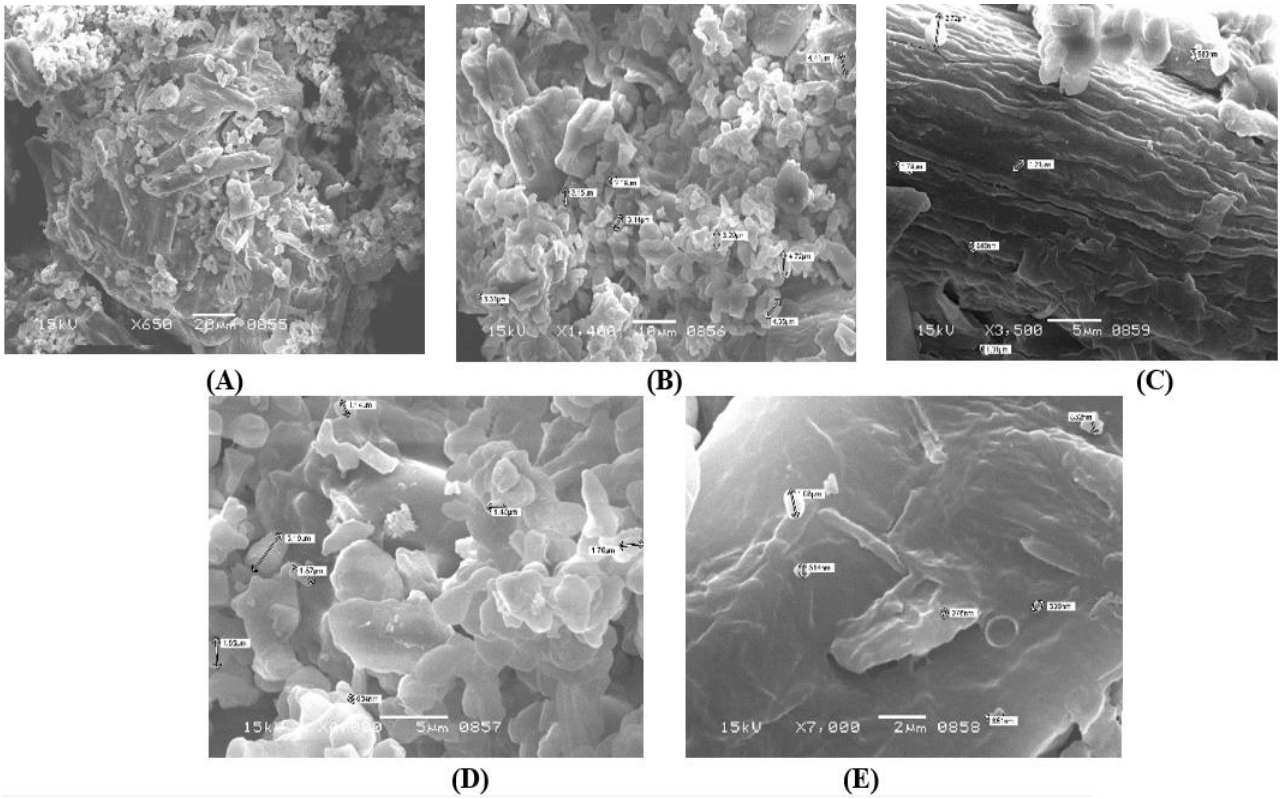


Fig. 3: SEM images of drug Nimodipine (A) at x650 (B) at x1400 (C) x3500 (D) x4000 (E) x7000

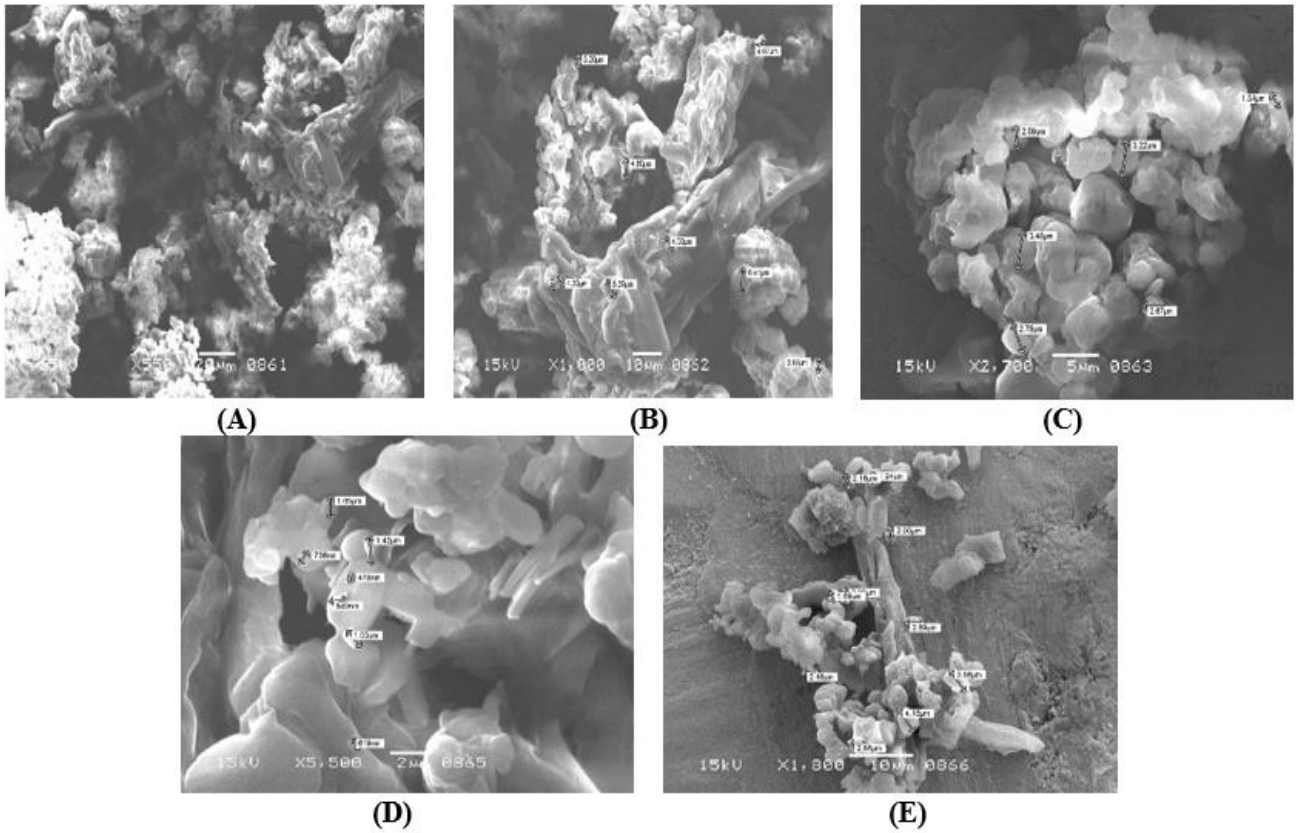


Fig. 4: SEM images of drug: disintegrant (A) at x550 (B) at x1000 (C) x1800 (D) x2700 (E) x5500.

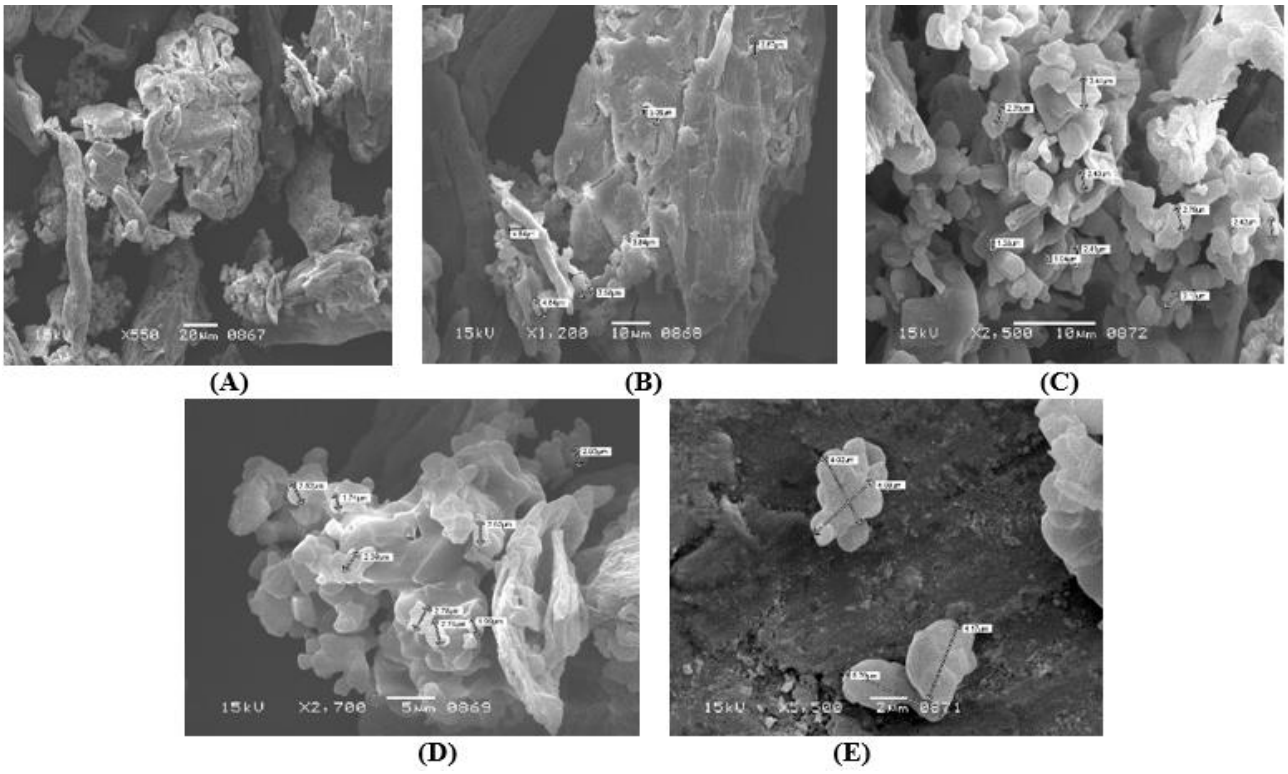


Fig. 5: SEM images of drug: binder (A) at x550 (B) at x1200 (C) x2500 (D) x2700 (E) x5500

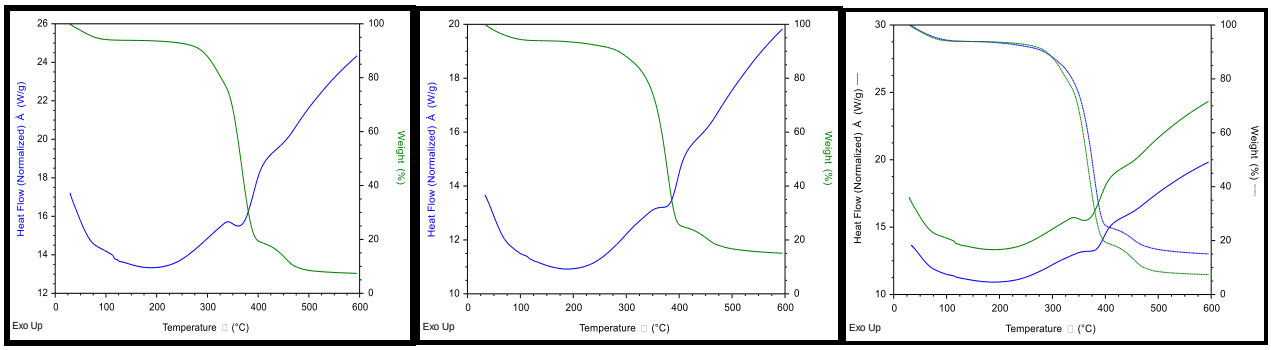


Fig. 6 (A): TGA-DSC of Nimodipine (API). (B): TGA-DSC of Optimized Formulation. (C): Overlay TGA-DSC Results of API and Optimized Formulation

Results of similarity and difference factor were mentioned in table 6. Scanning electron microscopic assessment was performed on API as shown in fig. 3A-3E, images of drug: disintegrant and drug: Binder combination were presented in fig. 4A-4E and 5A-5E respectively. Thermal gravimetric analysis and differential scanning calorimetry (TGA-DSC) assessment has been carried out to estimate the thermal degradation pattern of nimodipine (API) and nimodipine/formulation as shown in fig. 6 (A) and 6 (B) respectively. Fig. 6 (C) presented the overlay TGA-DSC results of API and optimized formulation.

DISCUSSION

Response surface methodology has been widely considered by scientists. CCRD was successfully applied for the optimization of nimodipine tablets. The rotatability of CCRD offered minimum number of runs for formulations. Hence extensively utilized for product optimization (Rehman *et al.*, 2018). In this study concentration of avicel PH 102 and crospovidone were varied at five different levels.

Hence avicel PH 102 (30-65%) and crospovidone (0.1-5.8%) were used for the formulation optimization. Aspartame was used as a sweetener to enhance the mouth feel. The shape of tablets was round. The influence of independent variables were observed on three different responses i.e. R_1 (Friability), R_2 (Disintegration) and R_3 (Hardness). The ANOVA summary of % friability indicated the F value was 22.72 and the *p* value was found to be < 0.05. The adequate precision was found to be

15.1643 presented indicates an adequate signal. For disintegration response, F value, *p* value and Adeq precision were found to be 8.41, < 0.05 and 6.9444 respectively specifying linear model was significant. For hardness response, F value, *p* value and Adeq precision were 7.39, <0.05 and 6.6426 respectively showing linear model was acceptable with adequate signal.

Essential flow behavior of powders minimizes the chance of inappropriate distribution of active compound in unit dosage form (Iqbal *et al*., 2020). Flow characteristics of all the powders were analyzed by using angle of repose, hauser's ratio and carr's index and their respective values were found to be 31.83±0.73-38.65±0.98º, 1.12±0.005-1.21±0.01 and 11.29±2.19-17.35±1.06% respectively showing better flow behavior of powder blends. After micromeritic assessment powder blends were compressed using single punch tablet machine.

Post compression analysis was carried out using various physico - chemical methods to determine the quality attributes of all the formulations. Weight variation of the formulations were performed and the results were found to be in range 202.91±1.61-206.02±4.65mg. Different quality parameters such as friability and hardness tests of tablet may affect the tablet disintegration time. All the formulations (F1-F9) showed adequate disintegration time ranging from 9-31 sec. Formulations having low levels of crospovidone resulted in rapid disintegration. Results of hardness and disintegration tests were influenced by the concentration of avicel PH 102 and crospovidone used in different formulation. It was reported that ac-di-sol gives reduced wetting time. Due to the highly porous structure of crospovidone, it improves the water diffusion into the compressed tablets which results in fast tablet deaggregation (Kumar, 2016). All the formulations showed adequate hardness and friability ranging from 4.009±0.092-4.146±0.095kg and 0.58-0.72%. High percentages of avicel PH 102 increase the hardness and disintegration time of tablets. Several scientists have reported that the tablets hardness and friability are significantly correlated with fast tablet disintegration (Zafar *et al*., 2015).

To estimate the drug release kinetics, multiple point dissolution study of different formulations was conducted. Using DD-solver the release constants and regression coefficients were determined. All the formulations followed weibull kinetic model with highest r^2 values found in the range from 0.9629-0.9874. The MDT and DE of all formulations were found to be in the range from 0.876-0.893 and 10.454%-12.883% respectively (table 5(B)). Also results of f_1 and f_2 indicated that reference and test formulations showed similar release behavior.

In the present study SEM study was performed. SEM employees a beam of electron for elaborated pictorial examination of morphological features including size, shape, surface characteristics, particles size and agglomeration. SEM images are attained at various magnifications to permit maximum resolution of fine particles as well as to take in higher number of particles (Zaheer *et al*., 2021). The results revealed that at x650 single drug particles were seen separately which showed irregular size, shape and rough surfaces. As the magnification increased at x1400 particle size of the drug ranged from 2.19-6.31µm. At x3500 a large aggregated particle was shown with highly folded rough surface. Few smaller spherical particles, 849nm-2.72µm, were seen. At x4000 agglomeration becomes more. At x7000 particles were around ranging from 376nm-1.08µm. Overall particles size of the drug ranged from 376nm- 6.31µm. In case of images of drug: disintegrant combination at x550 the results showed large aggregates of particles with no single particle visible. At x1000 aggregates of various sizes were seen. Particles, ranging from 3.20-6.41µm. At x1800 few small aggregates were seen attached to a rough surface. Particles in aggregates were ranging from 1.69-4.16µm. At x2700 particles of irregular sizes (1.54-3.46µm) and shapes were seen in a cluster. At x5500 particles were ranging from 478nm-1.42µm. Overall particles size of the drug: disintegrant were found to be in range of 478nm-6.41µm. In case of images of drug: binder combination the results at x550 illustrated more strongly bounded together. At x1200 few smaller particles (3.58-5.08µm) were seen attached to the cluster. At x2500 spherical particles non uniform in size, with 1.04-3.44µm. At x2700 particles were ranged from 1.74-2.78µm. At x5500 few small aggregates were seen adhered on a large rough surface. Aggregates vary in size (4.02-5.70µm). Drug: binder particle sizes were ranged from 1.04-5.70µm. SEM studies of compound were irregular, with crystalline appearance (Maria *et al*., 2017). The SEM studies of nanoparticles of nimodipine with tween 80 and stearic acid showed spherical particles with rough surfaces (Remya and Damodharan, 2020).

In this study, TGA-DSC was used to estimate the thermal degradation pattern of nimodipine (API) and nimodipine/ formulation. At 350°C (API) and 358°C (API/ formulation), a sharp melting point appeared indicating major weight loss. Decomposition was shown by heat flow curve through endothermic peak which was appeared at 29-395°C (API) and 34-250°C (API/ formulation) indicating that the material was initially crystalline. Samples of API and API/formulation were decomposed at a temperature above 395°C and 398°C respectively.

CONCLUSION

Fast dispersible nimodipine tablets were successfully developed by direct compression method. All the formulations have passed the quality assessments

parameters and results were found to be in adequate limits. Multi point dissolution studies revealed that all the formulations followed the weibull kinetic. Hence these optimized formulations could be considered for future pilot studies.

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