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RESEARCH ARTICLE
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APPLICATION OF ANOVA STATISTICS AND DISSOLUTION DATA MODELING OF OPTIMIZED NIMODIPINE DISPERSIBLE TABLET AT VARIOUS CONCENTRATIONS OF CO-PROCESSED POLYMER (LUDIPRESS®) AND SUPER DISINTEGRANT BY DIRECT COMPRESSION METHOD.

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Abstract:
Objective: The study aims to formulate a fast dispersible tablet of Nimodipine using central composite rotatable Design technology using two independent variables such as ludipress (20-55%) and crospovidone (3-5%) hardness, disintegration and friability were dependent variables.

Method: Nine different formulations were designed each formulation of each powder blend was subjected to precompression testing such as tapped density, bulk density, angle of repose, Hausner's ratio, and cars index, and tablets were compressed by Direct compression method. Tablets were subjected to several compendial and non-compendial test

Results All nine formulations F1-F9 average weight was found to be 203.4±0.47-212.5±0.34 mg, Hardness was found to be within the limit 3.89±0.24-5.07±0.05kg. Tablet thickness and diameter were found to be in the range of 3.005±0.045 and 10.9±0.023. All test formulations F1-F9 disintegration was found to be within less than 3 minutes (8-20 seconds)

friability of all test formulation tablets was found to be within the limit of less than 1% (0.3-0.8%). Percentage Assay of all formulations was found to be in the range of 97.86±0.04-101.3±0.07. ANOVA statistics and p-value were determined for all three responses of the optimized formulations model F value for all dependent responses hardness, friability, and disintegration was found to be 9.16, 5.34, and 6.07. The p-values for all dependent responses were found to be 0.004, 0.004, and 0.005. Fit statistics adequate precision showed signal-to-noise ratio which was found to be 8.136, 5.651, and 6.027 value which indicated the navigation of the design space. r^2 value of all the responses was found to be 0.9 for hardness, 0.64 for friability, and 0.66 for disintegration which shows a significant correlation between dependent and independent variables. multiple point dissolution studies of all formulations F1-F9 were conducted at acetate buffer pH 4.5 and 0.3% sodium dodecyl sulfate (SDS). Samples were drawn at 5, 10, 15, 20, 30 and 45 minutes. Several kinetic models were applied to the dissolution data such as the First Order, Hixson Crowell, Higuchi, and Weibull models based on an r^2 value close to 0.9 all the tested formulations F1-F9 followed the First Order and Weibull model. Similarity *(f2)* and dissimilarity factors *(f1)* were also calculated by choosing F3 formulations as standard based on a high drug release of 97.89% at 45 minutes. All test formulations were found to be in the limit Similarity *(f2)* (3-4) and dissimilarity factors *(f1)* (69-79). **Conclusion**: Nine different Nimodipine dispersible tablets were easily formulated by direct compression method and all tested compressed tablets passed pharmacopeial and non-pharmacopeial tests. All test formulations disintegrated within the specified limit hence a combination of ludipress and crospovidone was found to be an effective excipient in the field of formulation and development.

Keywords: dissolution, ANOVA, superdisintegrant, ludipress

Introduction:

Tablets are one of the most suitable dosage forms in terms of Dose accuracy and stability point of view and their production cost is reduced (1) but the most common problem with this dosage form is dysphagia among young and elderly patients to overcome this problem fast dispersible tablets are formulated. As disintegration is the most crucial step for the dissolution of immediate release fast dispersible tablets in physiological fluid in a short period (2) this not only provides fast therapeutic activity but enhances the bioavailability of poorly soluble drugs (3). Excipients impart a very important role in the performance of Active Pharmaceutical ingredients such as disintegration and dissolution Excipients are considered inactive substances as they never interact with API function nor impart any physiological effect and remain stable in chemical as well as physical forms they are free from bacterial contaminants and produced pharmaceutical products of the required standard (4). Nowadays processed excipients are gaining too much importance as they involve the processing of two or more excipients to provide a synergistic effect (5). As direct compression method is the most widely used process for the manufacturing of pharmaceutical tablets due to less number of steps and proper die filling with proper tablet properties (6). This process requires an excipient of high good flow ability which could be achieved by improving commercial excipients or by developing co-processed excipients that are established at the sub-particle level and showed good flow ability and compatibility (7).ludipress is one of the most important co-processed excipient contained 93% lactose, 3.5% kollidon 30 and kollidon CL. Lactose acts as a Diluent, Kollidon 30 acts as a binder, and Kollidon CL acts as a disintegrant. Nimodipine is a centrally acting 1, 4 dihydropyridine calcium channel blocker to treat subarachnoid hemorrhage allowing the relaxation of vascular smooth muscle and minimizing vasospasm (8) it also minimizes the global cerebral infraction after subarachnoid hemorrhage (9). This drug is highly hydrophobic and can cross the blood-brain barrier and cerebrospinal fluid as well (10). The poor water solubility of the chemicals imparts a significant challenge in the development of Pharmaceutical products Biopharmaceutical classification system helps in classifying the drug according to the solubility and permeability of the drug (11). Nimodipine belongs to the BCS class II drug which shows its poor aqueous solubility and high Lipophilicity log

P = 3.41 (12). Several techniques were utilized to enhance the solubility of Nimodipine such as nanoparticle technology (13), Complexation with cyclodextrin (14), solid dispersion (15), self-micro emulsification (16), and the use of super disintegrant (17). Superdisintegrant gives rapid disintegration as well as dissolution due to their incorporated effect of swelling and water absorption it enhances the wettability of the tablets (18). The aim of the study is to formulate a fast dispersible tablets and enhances the disintegration time of Nimodipine by using various concentration of ludipress (20-70%) and superdisintegrants crospovidone (1-5%) by using CCRD technology. On the values fit summary, ANOVA and multiple correlation coefficient appropriate model were selected.

MATERIAL AND METHOD

Nimodipine (Medisure Pharmaceutical Pvt.Ltd.), Crospovidone (FMC Biopolymer. Philadelphia, USA), Ludipress (BASF, Lud-wigshafen, Germany) and Aspartame (Lubon industry Co. Ltd., China), Magnesium Stearate (Jingjiang Chemical Co. Ltd., China).

Central Composite Rotatable Design

Nine different formulations were prepared by using ludipress (20-55%), and crospovidone (3-5%) by using CCRD Technique as an independent variable at five different levels whereas Hardness, Disintegration, and Friability were dependent variables. Magnesium stearate was used as (1%) and Aspartame as(2%) in all formulations. The quantity of the Active Drug Nimodipine was constant at 30 mg as shown in Table 1.

Table 1: **Formulation of fast Dispersible Nimodipine tablets with Ludipress and Crospovidone**

Formulations	Center Composite Design of the Formulation Variables		Composition of the Formulations					
	A:LUDIPRESS	B:Crospovidone	ludipress	Crospovidone	Aspartame	API	Magnesium Stearate	Final Weight
	%	%	% (mg)	% (mg)	% (mg)	%(mg)	% (mg)	mg
F1	55	5	148.4127	13.49206	5.396825	30	2.698413	200
F2	20	5	121.4286	30.35714	12.14286	30	6.071429	200
F3	37.5	5.82843	137.6045	21.38715	7.338906	30	3.669453	200
F4	37.5	0.171573	156.7434	0.717145	8.359647	30	4.179824	200
F5	62.2487	3	155.0547	7.47267	4.98178	30	2.49089	200
F6	20	1	141.6667	7.083333	14.16667	30	7.083333	200
F7	55	1	158.4746	2.881356	5.762712	30	2.881356	200
F8	12.7513	3	115.6038	27.19811	18.13208	30	9.066038	200
F9	37.5	3	146.5517	11.72414	7.816092	30	3.908046	200

Precompression Analysis

First, weigh the measuring cylinder and tare its weight now add 20 gm of the powder blend note its volume, and reweigh it. Bulk density (g/cm^3) was determined by the following formula:

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

Where ρbulk = bulk density. Bulk powder is then tapped 100 times note its volume and reweigh it. Tapped density (g/cm^3) was determined by the following formula:

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

angle of repose (θ) Hausner's Ratio (HR) and Carr's Index estimated the flow characteristics of the powder according to USP by using the following equations

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

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

$$Carr'sIndex = \frac{P_{tapped} - P_{bulk}}{P_{tapped}} \times 100 \qquad Eq.5$$

So, θ = angle of repose, 'D'= diameter of the heap form, and 'h'= height of the heap. (14, 19).

Post compression Analysis

Nine different powder blends were weighed individually and tablets were compared by a single punch tableting machine (19, 20)

Weight variation:

Twenty tablets were randomly selected from nine formulations and weighed individually and their average weight was calculated with ±7.5% deviation and Standard deviation calculated using Microsoft Excel 2010 (21, 22).

Hardness

A digital hardness tester apparatus was used to determine the hardness. Randomly 20 tablets from nine formulations were taken individually were subjected to (OSK Fujiwara, Ogawa Seiki Co. Ltd., Tokyo, Japan), and their average hardness was calculated with ±5% deviation and Standard deviation calculated using Microsoft Excel 2010.

Diameter and Thickness

(Digital Vernier Caliper: Seiko brand) were used to determine the diameter and thickness of optimized tablets. Randomly 20 tablets from nine formulations were taken individually and their average diameter was calculated with ±5% deviation and Standard deviation calculated using Microsoft Excel 2010.

Friability

Roche type Friabilitor (H. Jurgens Gmbh H and Co- Bremen, D2800, Germany) was used to determine the friability of tablets Randomly 20 tablets from nine formulations were taken individually and their initial weight was noted now placed 20 tablets in the friabilitor which rotates at 25 rpm for 4 minutes and their final weight calculated. Friability is calculated by the following equation

$\%F = (1-W/W0) \times 100\ \%$

Friability of tablets <1% is thought out as satisfactory

Disintegration

6 tablets were selected randomly from every nine formulations and were kept in a disintegration apparatus basket assembly which was immersed in 1000 ml distilled water and the temperature was maintained at 37centigrade. According to USP time for the disintegration of the fast dispersible tablet should be less than 3-5

Assay

An assay of the optimized formulation was carried out in acetate buffer pH 4.5 and 0.3% sodium dodecyl sulfate (SDS) and absorbance of the tablets was noted at π_{max} 317 nm.

Dissolution

Tests were performed using acetate buffer pH 4.5 and 0.3% sodium dodecyl sulphate (SDS) as medium placing one tablet in 900 ml of the medium. 10 ml of sample were collected at different time points such as 5min, 10 min, 15min, 20 min, 30min, and 45min each time replace the same amount of freshly prepared medium and analyze the sample using UV-Spectrophotometer (UV-1800 Shimadzu Corporation Kyoto, Japan) at 317nm.

Determination of release behavior

Release kinetics of multiple point dissolution studies of optimized formulations were carried out by DD Solver® (Add-Ins program).

R*elease kinetics*

Model-dependent method

It involves the first order, Higuchi model, Hixon Crowell cube root law, and Weibull model

First order reveals that the drug release is directly proportional to the concentration of the drug and is represented by

$(\ln Q_t = \ln Q_0 - k_i t)$ *Eq. 6*

Higuchi kinetics involves the diffusibility of the drug indicated by the

$Q_t = \mathrm{kt}^{\frac{1}{2}}$ *Eq.7*

Hixon Crowell cube root law explains the change in the particle size of the drug during the dissolution of the drug indicated by the equation

$\mathrm{Q}_0^{1/3} - \mathrm{Q}_\mathrm{t}^{\frac{1}{3}} = \mathrm{K_{HC}} \times \mathrm{t}$ *Eq. 8*

Weibull model explains all kinetic curves of the release of the drug

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

Model-independent method

The difference and similarity factors with test and reference formulation were calculated using the following equations: it helps to determine how much similarity and dissimilarity exists between Reference and test formulation.

$f_1 = \left[\frac{\sum_{t=1}^{n}(R_t - T_t)}{\sum_{t=1}^{n} R_t}\right] \times 100$ *Eq. 10*

$f_2 = 50 \times log\left\{\left[1 + \left(\frac{1}{N}\right)\sum(Ri - Ti)^2\right]^{-0.5}\right\} \times 100$ *Eq.11*

Where, R_t and T_t is for reference and test formulations respectively and n is the no of dissolution samples

The value for *f1* should be between 0 to 10 and *f2* should be between 50 -100.

Table 2: Micromeritics evaluation of fast dispersible nimodipine 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 3: Quality attributes of nine different fast-dispersible nimodipine tablets.

Formulations	Weight Variation	Hardness Variation	Thickness Variation	Disintegration Test	Friability	Assay
Limit	± 7.5	2-5 Kg	± 5	< 3 min	< 1 %	90-110 %
n (Tablets)	20	20	20	6	20	20
Values	Mean ± SD	Mean ± SD	Mean ± SD	Value	Value	Value
Unit	mg	kg	mm	Seconds	%	%
F1	204.6±0.09	4.62±0.05	3.005 ± 0.045	8	0.4	99.83±0.01
F2	210.8±0.56	3.98±0.12	2.969 ± 0.079	20	0.6	100.6±0.81
F3	203.4±0.47	4.78±0.06	2.941 ± 0.201	25	0.7	99.76±0.5
F4	211.5±0.34	4.89±0.78	2.976 ± 0.067	250	0.6	97.86±0.04
F5	201.9±0.04	5.23±0.15	3.028 ± 0.116	42	0.3	97.66±0.06
F6	203.5±0.16	3.69±0.24	2.958 ± 0.074	120	0.7	101.2±0.05
F7	208.5±0.98	4.98±0.34	2.922 ± 0.099	98	0.5	99.9±0.23
F8	212.5±0.34	3.76±0.12	2.961 ± 0.102	35	0.8	100.6±0.06
F9	207.6±0.96	3.78±0.16	2.941 ± 0.064	22	0.8	101.3±0.07

Table 4: multiple point dissolution studies of fast dispersible nimodipine tablets acetate buffer pH 4.5 and 0.3% sodium dodecyl sulfate (SDS)

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	35.97	37.76	40.65	37.89	35.43	39.87	45.6	46.91	44.73
10	56.5	58.76	55.6	50.92	54.65	57.89	59.78	59.9	57.89
15	67.8	65.6	69.8	66.4	68.9	65.87	69.9	68.75	68.78
20	79.4	77.56	74.65	73.45	75.6	72.67	76.6	78.56	78.95
30	88.9	87.89	89.45	80.67	85.6	83.66	87.9	85.78	87.65
45	96.3	93.67	97.89	93.2	90.56	92.45	94.7	93.6	94.56

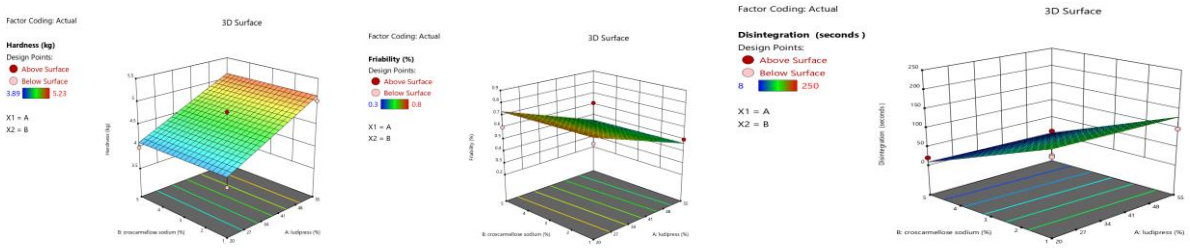
Table 5: Drug release kinetics of fast-dispersible nimodipine tablets

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	α	β
Acetate Buffer pH 4.5, 0.3 % SDS									
F1	0.9917	0.080	0.8979	16.078	0.9452	0.022	0.9984	9.608	0.898
F2	0.9618	0.079	0.8569	15.847	0.8804	0.022	0.9927	7.632	0.805
F3	0.9605	0.081	0.9062	16.140	0.8919	0.022	0.9856	7.800	0.823
F4	0.9346	0.070	0.9043	15.188	0.8277	0.019	0.9890	7.526	0.762
F5	0.9630	0.075	0.8436	15.467	0.8741	0.021	0.9942	7.978	0.804
F6	0.8984	0.075	0.8379	15.446	0.7554	0.020	0.9955	6.137	0.707
F7	0.8869	0.086	0.7405	16.168	0.7404	0.023	0.9928	5.294	0.695
F8	0.8404	0.086	0.6656	16.077	0.6615	0.023	0.9914	4.786	0.656
F9	0.9133	0.085	0.7748	16.136	0.7920	0.023	0.9910	5.797	0.725

Table 6: similarity *(f2)* and dissimilarity factor *(f1)* of Nimodipine Formulations with reference formulation F3

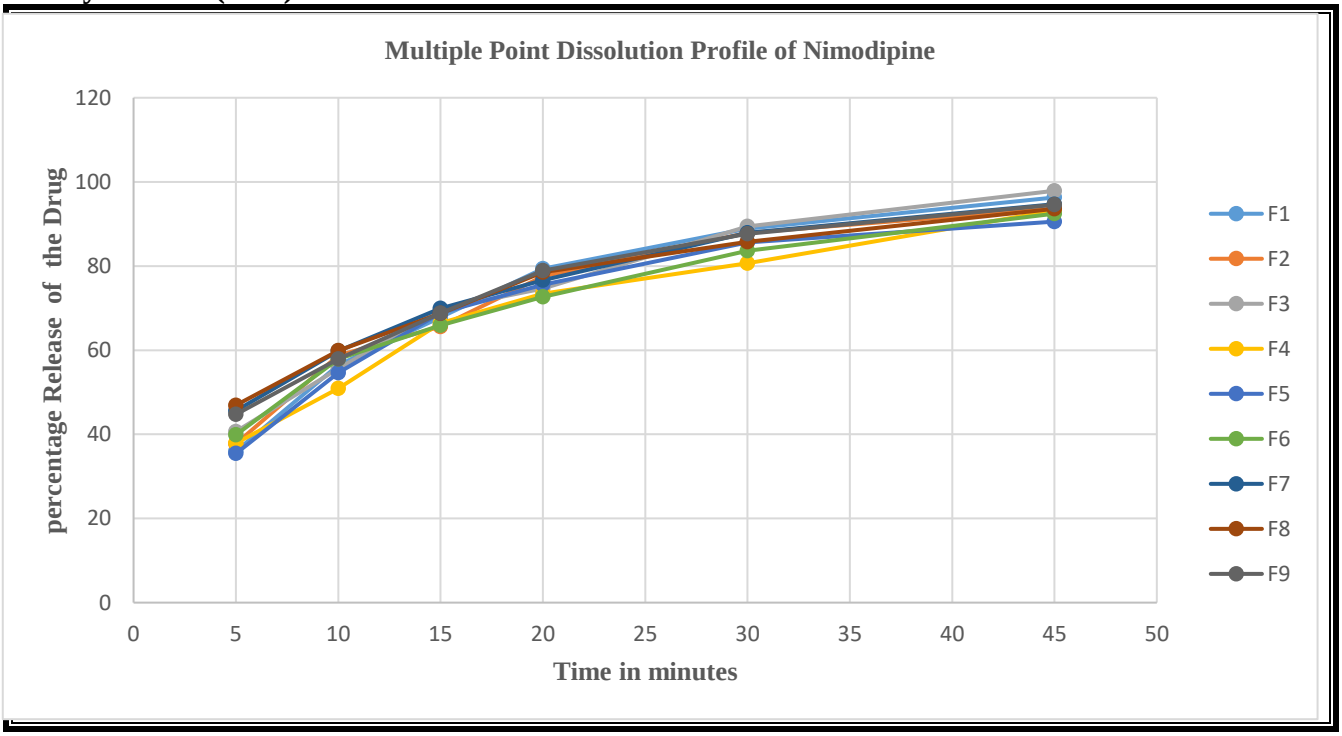
Similarity*(f2)* and dissimilarity factor *(f1)* at acetate buffer pH 4.5, 0.3 % SDS	F2	F3	F4	F5	F6	F7	F8	F9
f1	3	3	6	5	5	5	5	3
f2	86	79	69	72	72	71	69	75

Fig:1 Response surface 3D representation of Nimodipine on different responses Hardness, Friability, and Disintegration



(A) (B) (C)

Fig 2: Multiple Point Dissolution of Nimodipine at acetate buffer pH 4.5 and 0.3% sodium dodecyl sulfate (SDS)



RSM Plot and ANOVA Summary

The ANOVA summary for the first response fig1 (A) Hardness model F value is 9.16 which implies that the model is significant, the p-value was found to be 0.048 and the Adequate precision value was found to be 8.316 which shows this model can be used to navigate the design space as the concentration of ludipress is increased and crospovidone is decreased there is an increase in hardness. The second response friability fig 1(B) F Value is 5.34 which indicates that the model is significant, the probability was found to be 0.0466 and the Adequate precision value was found to be 5.651 which indicates an adequate signal as the friability is decreased when the concentration of the ludipress is increased. A third response was disintegration fig1(C) F Value is 6.07 which indicates that the model is significant, the probability was found to be 0.0500 and the adequate precision value was found to be 6.027 which indicates an adequate signal last two models were found to be linear as the concentration of super disintegrant increases there is a decrease in the disintegration time of the optimized formulations. The coded equations for all three responses are as follows A Ludipress and B croscarmellose sodium

Hardness

$+3.78+0.3693*A-0.0282*B-0.1625*AB+0.1594*A^2$
$+0.4777*B^2$

Friability
+0.6000-0.1348*A-0.0073*B

Disintegration
+68.89-3.01*A-63.52*B

Discussion:

The rate of availability of the drug in the body and its dissolution characteristics will depend upon the selection of proper excipients (23). The study investigated the change in the disintegration time of Nimodipine fast dispersible tablets by varying the Ludipress concentrations (20-55%) along with the concentration of crospovidone (1-5%). As the ludipress is composed of lactose monohydrate (96.5%) and kollidon 30 (3.5%). According to the study as the concentration of ludipress increases with increased concentration of crospovidone then reduced disintegration time was observed in the study with weight variation, and friability within the limit. The quality-by-design approach is the best way to develop certain formulations which helps identify the factors and their level to provide the best-optimized formulation reduces the cost and increases the production efficiency of the pharmaceutical product (24). Quality by design approach was successfully applied in the formulation and development of lornoxicam tablets by Direct compression method (25). All pharmacopeial and non-pharmacopeial tests were performed which were found to be within the limit as shown in Table 3. The value for all the dependent responses was found to be less than 0.005 which means the design models are significant and the adequate precision value of all three responses was greater than 4 which indicates an adequate signal. The model F value was found to be in the range of 5.34-9.16 which indicated models are significant. r^2 value of all the responses were found to be in the range of 0.9-0.66 which shows a co relation between independent and dependent variables. Multiple point Dissolution studies were conducted using acetate buffer pH 4.5 and 0.3% sodium dodecyl sulfate as dissolution medium and the data were subjected to the DD solver an add-in program in Excel. For the determination of the bioavailability of Nimodipine, studies were carried out in acetate buffer and sodium dodecyl sulfate dissolution medium (26). Model-dependent approaches and independent approaches were performed to carry out the kinetic parameters and similarity and dissimilarity index of nimodipine (27). In this study kinetic evaluation was done by selecting the best optimized formulation f1 based on less disintegration time. All the results were found to be within the limit. Kinetic evaluation studies reveal that an r^2 value of 0.9 shows that all the optimized formulations were found to follow first-order kinetics and the Weibull model as shown in Table 5.

Author's contribution

Conceptualization, Hira Akhtar; Data curation, Saira Shahnaz and Imran Ahmed; Formal analysis, Rabia Humayoon, and Amna Shaikh; Investigation, Rabia Humayoon, and Hina Furqan; Methodology, Muhammad Ali and Shoaib Nawaz; Resources, Syed Zohaib Hussain, Hidayat Ullah, and Muhammad Faizan Raza Alwani; Software, Syed Zohaib Hussain, Syed Muhammad Yaseen and Raahim Ali; Supervision, Khwaja Zafar; Validation, Syed Muhammad Yaseen; Visualization, Hira Akhtar, Rukhsar Islam and Raahim Ali; Writing – original draft, Hira Akhtar; Writing – review & editing, Khwaja Zafar.

Conflict of interest

Authors declare no conflict of interest

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