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EFFECT OF CO-PROCESSED SUPERDISINTIGRANT ON NIMODIPINE ORODISPERSIBLE TABLETS USING 2^3 FACTORIAL DESIGN APPROACH

Sagar Kothawade[1]*, Shubham Biyani[2], Chetan Harne[1], Rutuja Wakure[1], Udhhav Bagul[1] and Surendra Gattani[2]

[1]STES, Sinhgad Institute of Pharmacy, Narhe, Pune (MH), 411041, India.
[2]School of Pharmacy S.R.T.M University, Nanded (MH), 431606, India.

***Corresponding Author: Sagar Kothawade**

STES, Sinhgad Institute of Pharmacy, Narhe, Pune (MH), 411041, India.

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ABSTRACT

In present research work, Orodispersible tablets of Nimodipine drug were formulated by using direct compression method. Nimodipine is belonging to BCS class-II, therefore the solubility of Nimodipine was enhanced by complex with Beta-Cyclodextrins. The drug-excipient's compatibility was carried out by using FTIR spectrometry. The four preliminary trial of formulation were taken with three different superdisintegrants Viz. Sodium starch glycolate, Crospovidone and co-processed sodium starch glycolate with crospovidone. The prepared batches were evaluated for weight variation, hardness, thickness, mechanical strength, wetting ability, disintegration time and *in-vitro* drug release. The batch A4 Containing co-processed superdisintegrants 5 mg, mannitol 30 mg and MCC 61 mg has shown disintegration time of 21 seconds along with 100% drug release within 45 min. Among all preliminary trials batches the Batch A4 was selected for optimization by using 2^3 factorial design. The software generated 10 formulations were developed and evaluated for nature and concentration of superdisintegrants in tablets with respective to disintegration time, wetting time and *in-vitro* drug release. Optimised batch F4 was further subjected for stability studies & kinetic studies and found to be stable and followed first order release kinetics model.

KEYWORD: Nimodipine, Beta-cyclodextrins complex, Superdisintegrants, Factorial Design, Kinetic Study, 2^3 factorial design.

INTRODUCTION

Oral delivery is regarded as the safe, most convenient and most economical method of drug delivery system having the highest patient compliance. Fast dissolving tablets have received ever increasing demand during the last decade and the field has become a rapidly growing area in the Pharmaceutical industry. These are novel dosage forms which will rapidly disintegrate or dissolve in the saliva.[1]

United States Food and drug administration (FDA) defined fast dissolving tablet (FDT) as "A solid dosage form containing medicinal substance or active ingredient which disintegrate rapidly usually within a matter of seconds".[2] A variety of improved methods for delivering drugs have been developed with the aim of improving bioavailability, convenience and patient compliance. Some tablets are formulate to dissolve in saliva within a few seconds, and so called fast-dissolving tablets.[3]

Orodispersible tablets (ODT) are dosage forms for oral administration which, when placed in the mouth, rapidly disintegrate or dissolve and can be swallowed in the form of a liquid. ODTs have several advantages over conventional tablets like ease of administration for paediatrics, geriatrics, mentally ill, and uncooperative patients; quick disintegration and dissolution of the dosage form; overcome unacceptable taste of the drugs, when suitably taste masked; can be designed to leave minimal or no residue in the mouth after administration and provide a pleasant mouth feel.[4]

Nimodipine is a chemically dihydropyridine and calcium channel blocker originally developed for the treatment of high blood pressure. Nimodipine inhibits calcium ion transfer into these cells and thus inhibits contractions of vascular smooth muscle. However, Nimodipine is practically insoluble in water and this poor water solubility seems to be a problem for its bio-availability and gastrointestinal side effects.

Cyclodextrins are crystalline homogeneous non-hygroscopic substances, which have a torus like macro ring shape, built up from glucopyranose units. They are cyclic oligosaccharides, which are produced by enzymatic degradation of starch by a glucoasyltransferase most commonly derived from Bacillus macerans and have been recognized as useful pharmaceutical excipients. Complexation with cyclodextrins has been reported to enhance the solubility,

dissolution rate and bioavailability of poorly soluble drugs. Especially, HPß-CD is widely used in the pharmaceutical field owing to its high aqueous solubility, ability to stabilize the drug molecule and capable to mask the bad taste and odour.[5]

MATERIALS AND METHODS

Materials

Nimodipine was gifted from Aurobindo Pharma, Hyderabad. ß-Cyclodextrin, All other chemicals were used analytical grade.

Methods

Standard Calibration curve of Nimodipine

100 mg of pure Nimodipine was dissolved in 10 ml of 6.8 pH phosphate buffer and volume was made up to 100 ml with the 6.8 pH phosphate buffer (1000 µg/ml). 10 ml of the above solution was diluted up to 100 ml with 6.8 pH phosphate buffer (100 µg/ml). Further diluted to obtain series of Nimodipine solution in the concentration range 2, 4, 6, 8, 10 µg/ml. The absorbance was measured by using UV-Visible spectrophotometer (Jasco307) in the range 200-400 nm (Figure 1).

Drug excipients compatibility studies

Fourier transforms infrared spectroscopy (FTIR)

The FTIR absorption spectra of the pure Nimodipine, Physical mixture containing drug-Beta cyclodextrin complex and other excipients and physical mixture containing drug-beta cyclodextrin complex etc. were recorded in the range of 4000-400cm^{-1} by KBr disc method using FTIR spectrophotometer (Jasco FT/IR-4100).[6-7]

Formulation of Co-process Superdisintigrants

The Co-process superdisintigrant were prepared by solvent evaporation technique in which the complex of Sodium Starch Glycolate with crospovidone was in the ratio of 1:1.

Formulation development of Orodispersible tablets

Nimodipine and ß-cyclodextrin (1:1) inclusion complex was mixed manually in mortal pestles with different super disintegrants like crospovidone, sodium starch glycolate and co-processed sodium starch glycolate and crospovidone (As shown in table 1). Individually Mannitol and MCC102 was added as diluent and mixed for 10 minutes. The blend was lubricated with magnesium stearate for 3-5 minutes and aerosil was added as glidant[8]. The mixed blend was then compressed into tablets by direct compression method using 4 mm punches on a 12 station tablet punching machine.

Evaluation of Orodispersible tablets

Physicochemical parameters

The prepared Orodispersible tablets were evaluated for their physicochemical parameters like weight variation, hardness, thickness, friability and drug content.

In-vitro disintegration time

The disintegration test was performed using an USP disintegration apparatus, with distilled water at 37±0.5˚C. The time required to obtain complete disintegration of six tablets were recorded and average disintegration time was reported.[9]

Wetting time

A piece of tissue paper folded twice was kept in a petridish (Internal diameter 5.5cm) containing 10 ml of purified water. The tablet was placed on the tissue paper and allowed to wet completely. The time required for complete wetting of the tablet was then recorded.

Hardness and Friability

Hardness of disintegrating tablets were tested using Electrolab digital tablet hardness tester and friability by using Roche friability test apparatus.[10]

In-vitro drug release study

The drug release rate from Orodispersible tablets was studied using the USP type II dissolution test apparatus. The dissolution test was performed using 900 ml of phosphate buffer (pH 6.8) as the dissolution medium at 50 rpm and 37 ± 0.5˚C. 5 ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. The samples were analyzed spectrophotometrically at 250 nm.[11]

Stability Study

The Stability study of the optimised formulation was carried out storage conditions as per ICH guidelines. The tablets are wrapped in aluminium foil and place in accelerated stability condition at 40±2 °C and 75 ± 5 %. At the end of study, samples were analysed for the physical evaluation and in *vitro* dissolution etc.[12-13]

RESULTS AND DISCUSSION

Calibration curve of Nimodipine

Nimodipine solution showed maximum absorption at wavelength 255 nm in 6.8 pH phosphate buffer. Standard curve was plotted by taking absorption of diluted stock solutions (2, 4, 6, 8 and 10 µg/ml) at wavelength 255 nm. This graph was used for estimation of drug release in the formulated Nimodipine tablets.

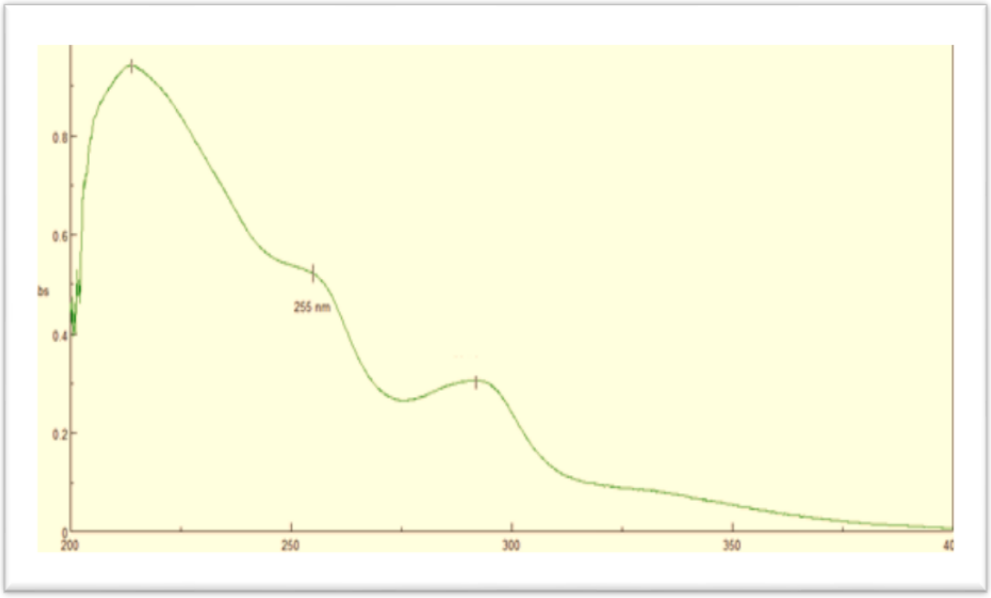

Figure 1: UV spectrum of Nimodipine.

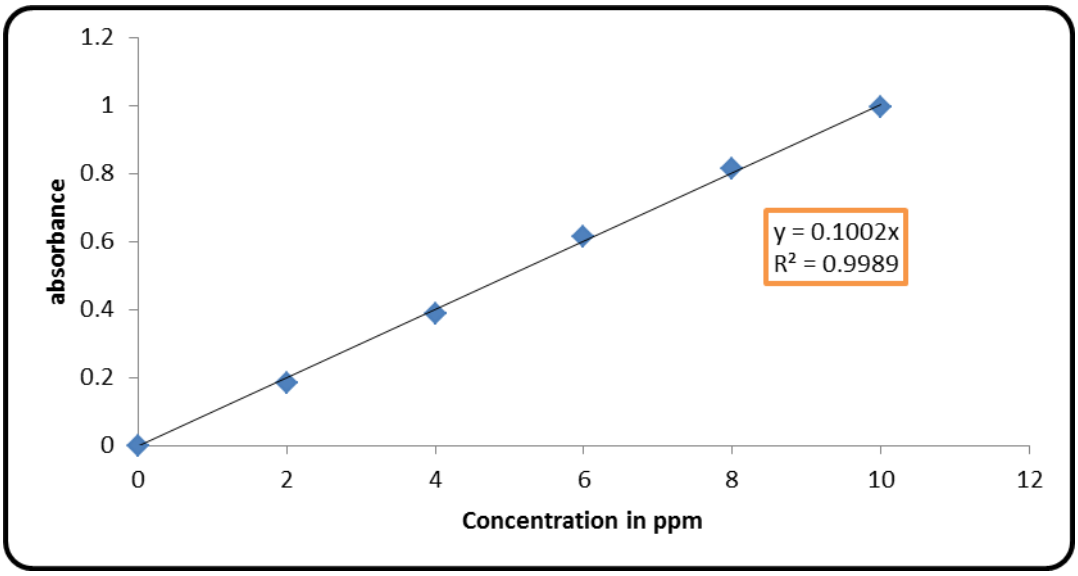

Figure 2: Calibration curve of Nimodipine in 6.8 pH phosphate buffer.

Drug Excipients Compatibility study

Fourier transforms infrared spectroscopy (FTIR)

FTIR spectra of Nimodipine (As shown in figure 3), Nimodipine- Beta Cyclodextrin (As shown in figure 4), and Nimodipine-Beta Cyclodextrin with all excipients (As shown in figure 5), were taken and compared (As shown in table.1) In FTIR study revealed that there was no known chemical interaction of drug with superdisintegrants and other ingredients.

IR spectrum of pure Nimodipine, Nimodipine- Beta Cyclodextrin and Nimodipine-Beta Cyclodextrin with all excipients was recorded and it was found in accordance with the reported peaks. It is shown in below figure (Figure 3, 4 and 5 respectively). The IR spectra of Nimodipine comply with its chemical structure and show peaks for principal groups. The structural assignments for the characteristics absorption bands are listed in following table no.1.

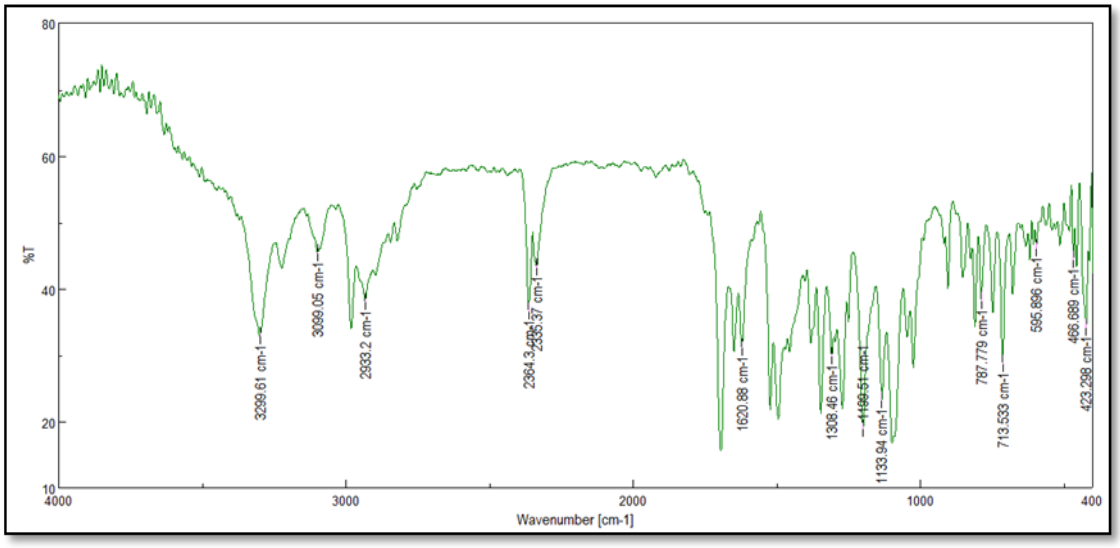

Figure 3: FTIR Spectrum of Nimodipine.

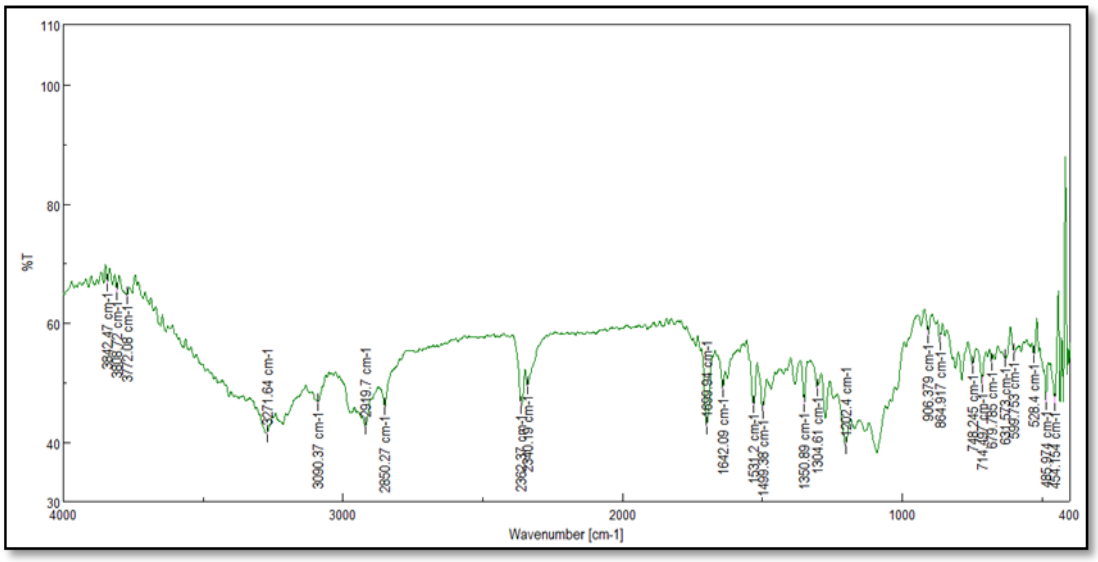

Figure 4: FTIR Spectrum of Nimodipine + Beta cyclodextrins complex.

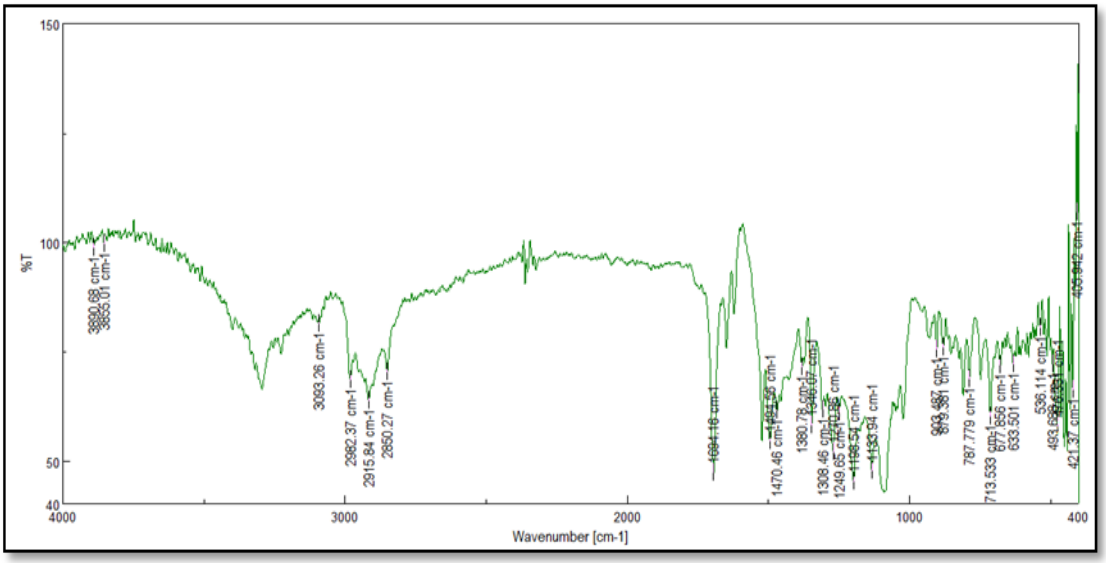

Figure 5: FTIR Spectrum of Physical mixture of Nimodipine-Beta Cyclodextrin complex and All Excipients.

Table 1: Comparative FTIR Study.

Functional group	Nimodipine	Nimodipine- Beta Cyclodextrin	Nimodipine-Beta Cyclodextrin with all excipients
N=H Stretching	3299.61 cm^{-1}	3271.0 cm^{-1}	3093.26 cm^{-1}
O-H Stretching	3099.05 cm^{-1}	3090.27 cm^{-1}	2962.37 cm^{-1}
C=N Stretching	1620.88 cm^{-1}	1642.09 cm^{-1}	1694.16 cm^{-1}
C-H Bending	1133.94 cm^{-1}	1102.4 cm^{-1}	1133.0 cm^{-1}

Formulation of Preliminary Batches

Table 2: Preliminary trail batch Nimodipine tablets.

Sr. No	Ingredients	A1	A2	A3	A4
1	API+ ß-CD HP (Complex)	100	100	100	100
2	Mannitol	60	60	60	30
3	MCC-102	31	31	31	61
4	Crospovidone	5.75	-	-	-
5	SSG	-	5.75	-	-
6	Co-process (SSG+CP)	-	-	5.75	5.0
7	Aerosil	0.75	0.75	0.75	1.5
8	Magnesium Stearate	2.5	2.5	2.5	2.5
	Total	200	200	200	200

Evaluation of Preliminary Batches

Physicochemical parameters of tablets

Weight variation: Average weight of orodispersible tablets of Nimodipine was 196 ±2 to 203 ±2 mg (As shown in table 3).

Hardness: The hardness of all prepared tablets was in the range of 4.5 to 6.5 (As shown in table 3).

Thickness: Thickness ranged between 3.1 and 3.2 mm with SD values of 0.24 to 1.08 (As shown in table 3).

Friability: It was found to be less than 1% in optimised formulation.

Drug content: The twenty tablets were weighted and crushed to obtained powder; the portion equivalent to 30 mg of Nimodipine was dissolved in 100 ml of 6.8 pH phosphate buffer, filter to obtained clear solution. Above solution diluted suitably and drug content estimated by UV visible spectroscopically.

Table 3: Evaluation preliminary trail batches.

Batches No	Avg. Weight (mg) SD (n=3)	Thickness (mm) SD (n=3)	Hardness (kpa) SD (n=3)	Disintegration time (sec) SD (n=6)	Wetting time (sec) SD (n=3)	Friability (%) SD (n=3)	Drug Content (%)
A1	198±2	3.1 ±0.2	6.5 ±1.5	109 ±5	35 ±3	1.6 ±0.10	98.17± 0.56
A2	196 ±2	3.1 ±0.2	6.5 ±1.5	75±5	23 ±3	0.88 ±0.10	99.1± 0.76
A3	203 ±2	3.1 ±0.2	6.5 ±1.5	20±5	29 ±3	0.94 ±0.10	98.93± 0.42
A4	199 ±2	3.1 ±0.2	6.5 ±1.5	21 ±5	09 ±3	0.33 ±0.10	99.23± 0.42

Table 4: *In- Vitro* drug release from preliminary trial batches (A1 to A4).

Time Min.	*In- Vitro* % drug Release			
	A1	**A2**	**A3**	**A4**
0	0	0	0	0
5	29	40	39	39
10	42	51	46	48
15	62	62	59	68
20	78	76	69	88
30	85	81	86	95
45	93	97	100	100

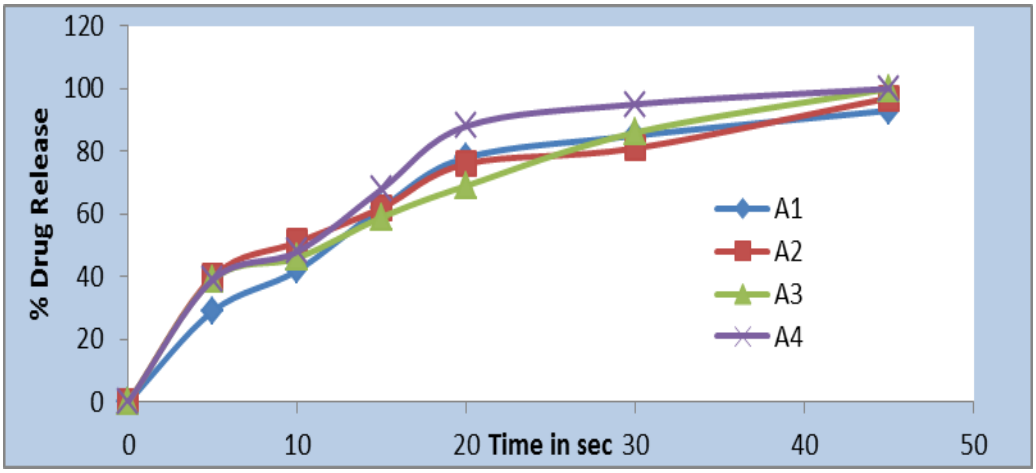

Figure 6: *In- Vitro* drug release from preliminary trial batches (A1 to A4).

Table 5: Absolute values of level and variables.

Sr. no	Variables	Level			
	Independent Variables	**Coded**	**-1**	**0**	**+1**
1	Mannitol (mg/tab)	X1	15	30	45
2	Co-process Superdisintigrant (mg/tab)	X2	2.5	5.0	7.5
Dependent Variables			**Acceptable Ranges**		
3	% Friability	Y1	NMT 1%		
4	Disintegration Time	Y2	NMT 60 Seconds		
5	Wetting Time	Y3	NMT 10 Seconds		

Table 6: Optimization batches by using factorial design.

Sr. no	Ingredients	Qty. (mg/tab)									
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
1	**API+ ß-CD HP**	100	100	100	100	100	100	100	100	100	100
2	**Mannitol**	15	45	45	30	30	15	15	30	45	30
3	**MCC-102**	78.5	43.5	48.5	58.5	61	78.5	76	63.5	46	61
4	**Co-processed (SSG+CP)**	2.5	7.5	2.5	7.5	5.0	2.5	5.0	2.5	5.0	5.0
5	**Aerosil**	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
6	**Magnesium Stearate**	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total		200	200	200	200	200	200	200	200	200	200

Table 7: Evaluations of optimisation formulation.

Batch No	Avg. Weight (mg) SD (n=3)	Thickness (mm) SD (n=3)	Hardness (kpa) SD (n=3)	Disintegration time (sec) SD (n=6)	Wetting time (sec) SD (n=3)	Friability (%) SD (n=3)	Drug Content (%)
F1	200±2	3.1 ±0.2	5.5 ±1.5	28 ±4	11 ±3	0.52 ±0.10	98.19± 0.66
F2	198 ±2	3.1 ±0.2	5.5 ±1.5	19 ±4	12 ±3	0.38 ±0.10	99.23± 0.49
F3	196 ±2	3.1 ±0.2	5.4 ±1.5	48 ±4	23 ±3	0.54 ±0.10	99.93± 0.42
F4	199 ±2	3.1 ±0.2	4.5 ±1.5	19 ±4	09 ±3	0.83 ±0.10	98.73± 0.51
F5	205 ±2	3.1 ±0.2	4.5 ±1.5	22 ±4	09 ±3	0.42 ±0.10	99.43± 0.44
F6	196 ±2	3.1 ±0.2	5.8 ±1.5	48 ±4	22±3	0.52 ±0.10	99.18± 0.51
F7	198 ±2	3.1 ±0.2	5.9 ±1.5	48 ±4	26 ±3	0.39 ±0.10	98.73± 0.51
F8	196 ±2	3.1 ±0.2	4.6 ±1.5	56±4	26 ±3	0.34 ±0.10	99.13± 0.69
F9	203±2	3.1 ±0.2	4.9 ±1.5	22 ±4	09 ±3	0.59 ±0.10	98.88± 0.32
F10	193 ±2	3.1 ±0.2	4.9 ±1.5	19±4	09 ±3	0.43 ±0.10	98.95± 0.31

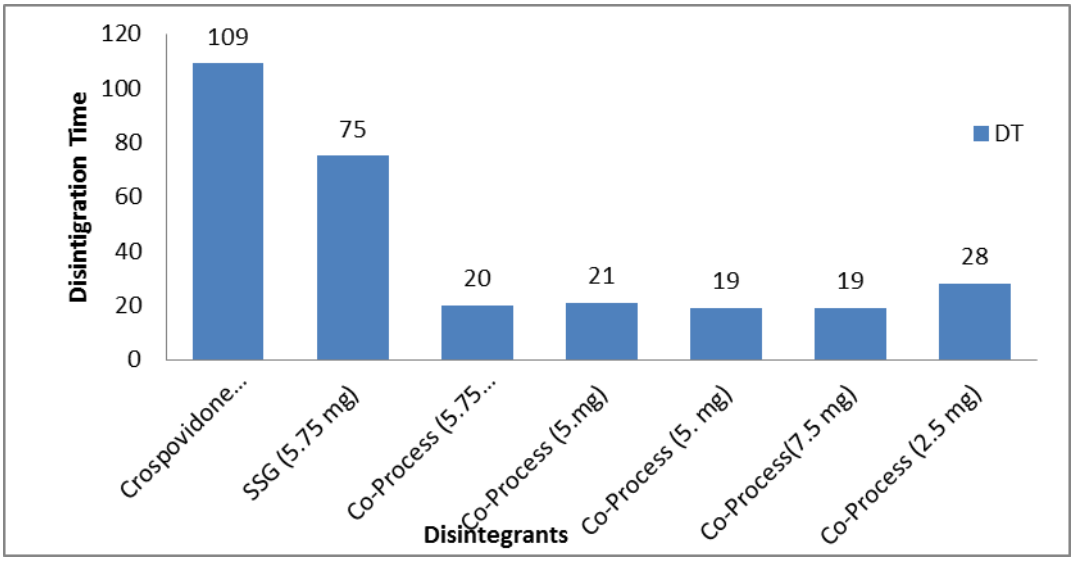

Figure 7: Effect of different disintegrant on disintegration time.

Table 8: *In- Vitro* drug release from factorial batches.

Time (min)	*In- Vitro* % drug Release									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
0	0	0	0	**0**	0	0	0	0	0	0
5	10	40	23	**28**	35	10	33	12	40	32
10	26	55	38	**36**	44	26	46	26	53	40
15	35	69	46	**54**	56	35	53	43	68	56
20	45	76	55	**69**	68	45	66	63	76	68
30	59	86	67	**77**	88	59	79	79	84	73
45	69	100	88	**100**	100	69	88	99	95	100

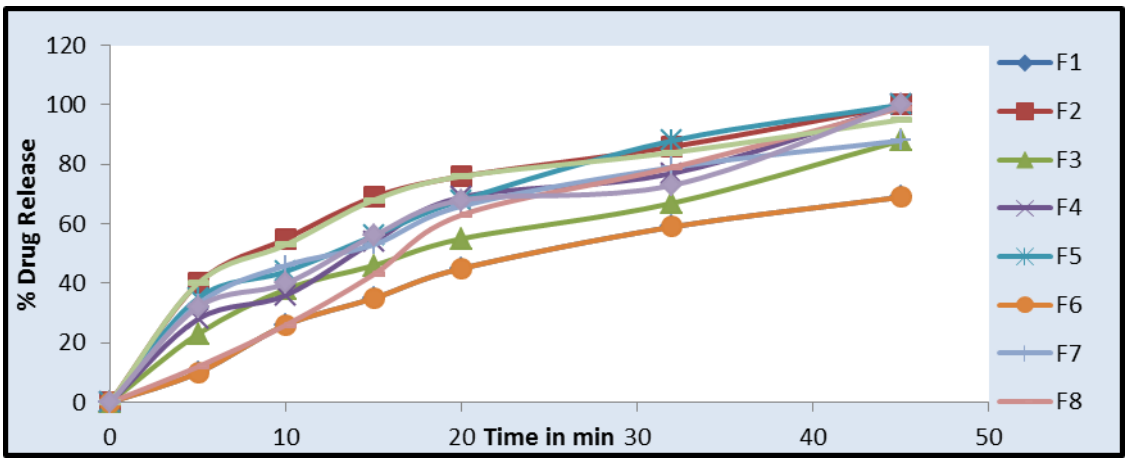

Figure 8: *In- Vitro* % drug release from factorial batches.

Optimization Response

In 2^3 full factorial design, the dependable variables of formulation batches F1 to F10 such as disintegration time. 15-65 seconds, friability in 0.27-0.83 % and wetting time in 9-20 seconds showed a wide variation. The obtained data from DOE batches showed that the dependent variables i.e. disintegration time and wetting time were strongly independent on the selected dependant variables. The factorial equations can be used to draw conclusion after considering the magnitude of coefficient and mathematical sign it carries positive or negative. The analysis of variance (ANOVA) was performed to identify insignificant/significant factors. The surface plot, which denotes the combined effects of independent variables on dependent variables.

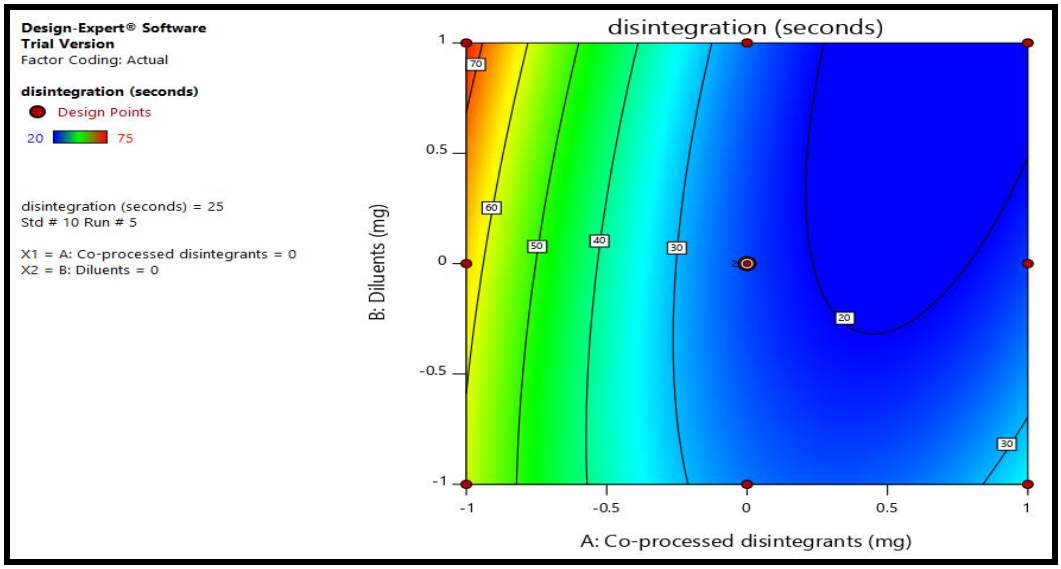

Figure 9: Contour plot for disintegration time.

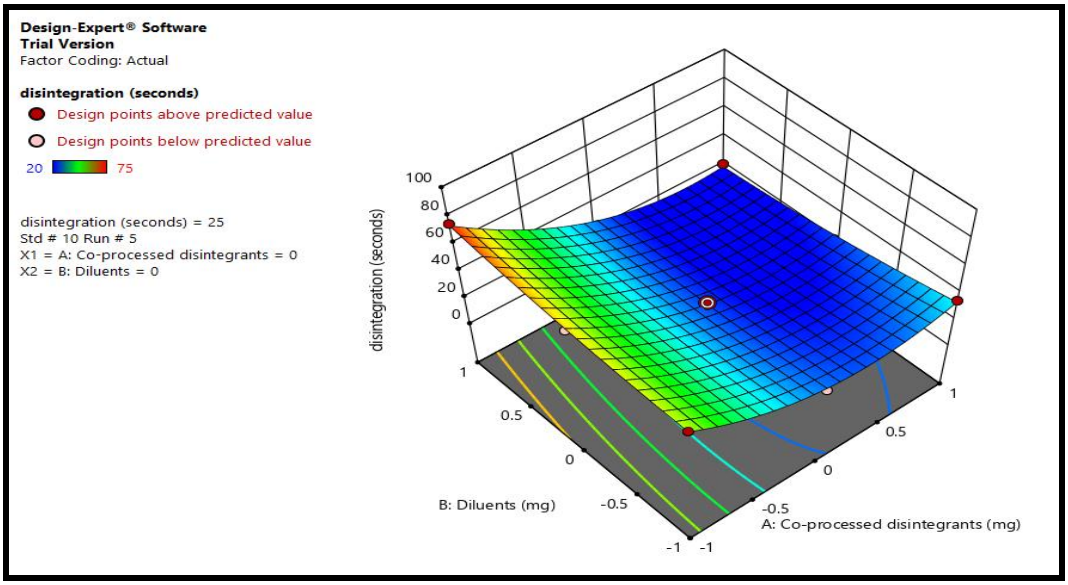

Figure 10: 3D surface responses for disintegration time.

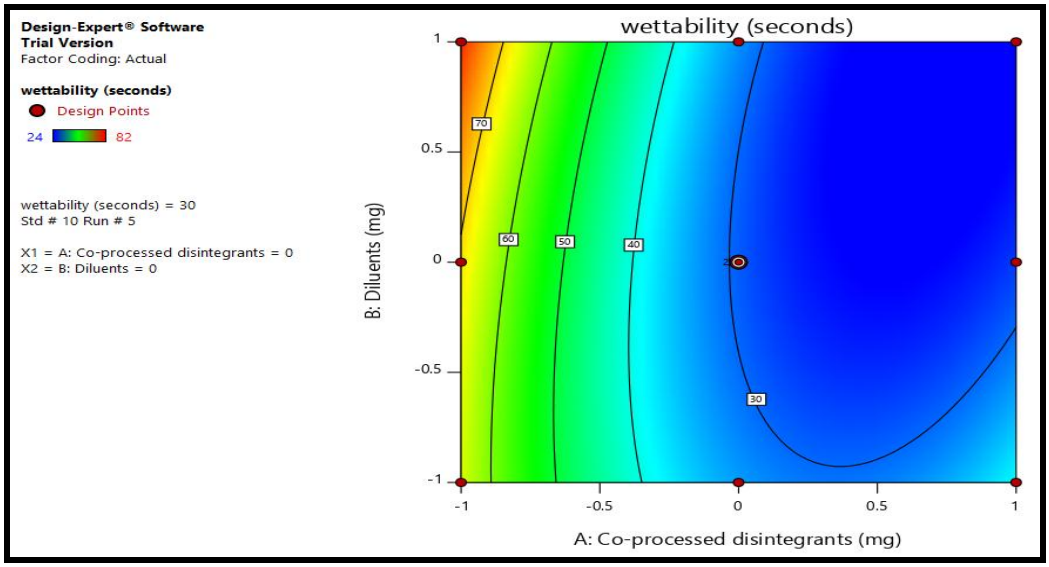

Figure 11: Contour plot for wetting time.

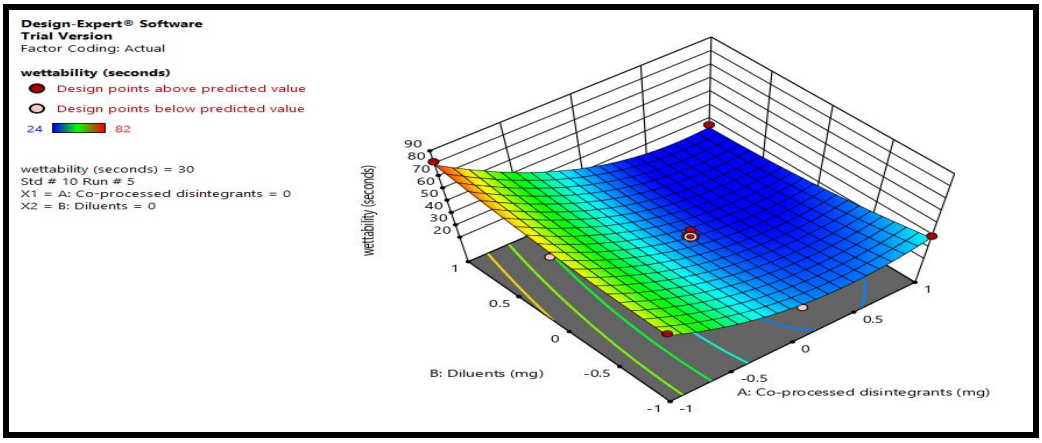

Figure 12: 3D surface responses for wetting time.

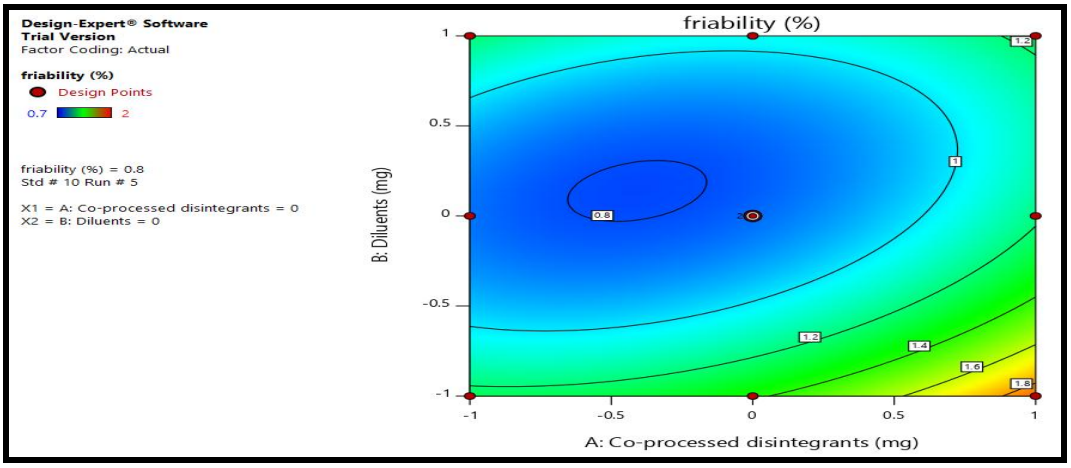

Figure 13: Contour plot for friability.

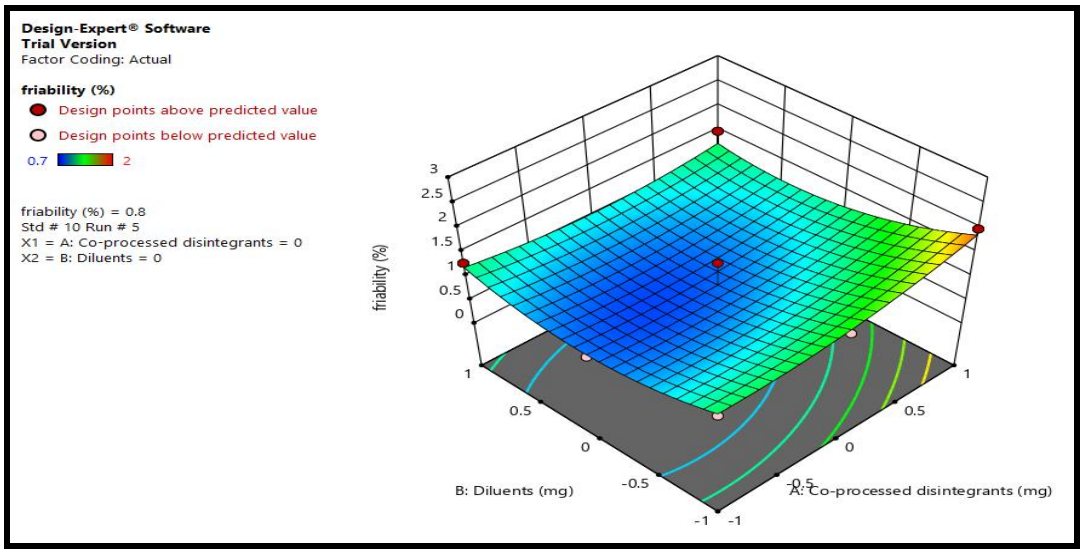

Figure 14: 3D surface responses for friability.

Data analysis: Kinetic Data / Model fitting

The dissolution release data of the optimized formulation F4 was reported and was processed into graphs (Figure 15, 16, 17 and 18) to understand the linear relationship, i.e., kinetic principles. The data were processed for regression analysis using MS - Excel statistical functions. The parameters and equations were given in the is indicated that the release kinetics of the drug followed first order model of kinetics release from optimized formulation.

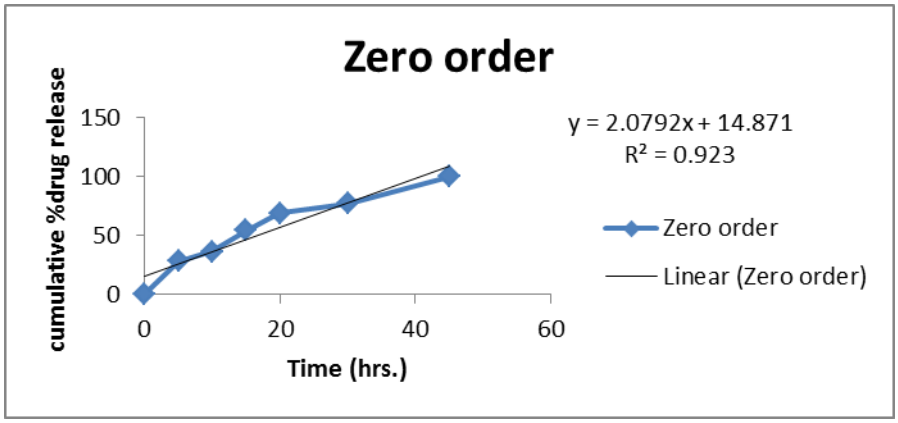

Figure 15: Zero order kinetics Study.

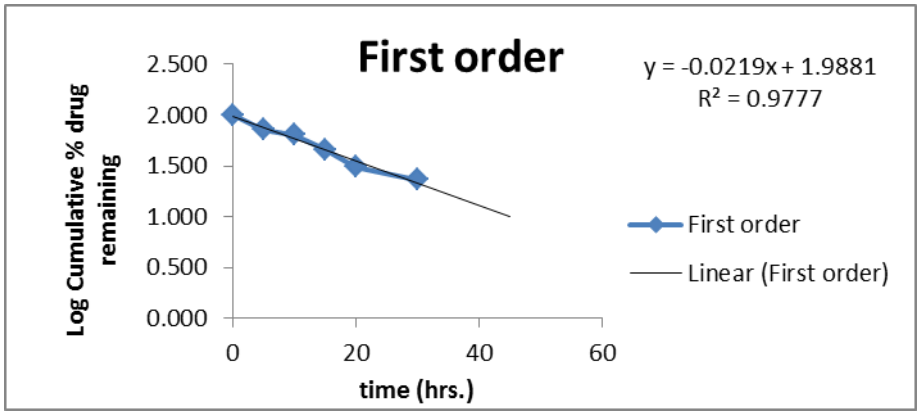

Figure 16: First order kinetics Study.

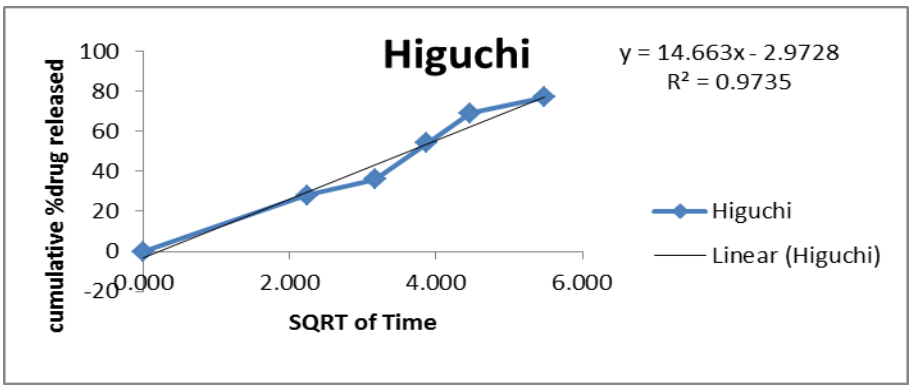

Figure 17: Higuchi model for kinetic study.

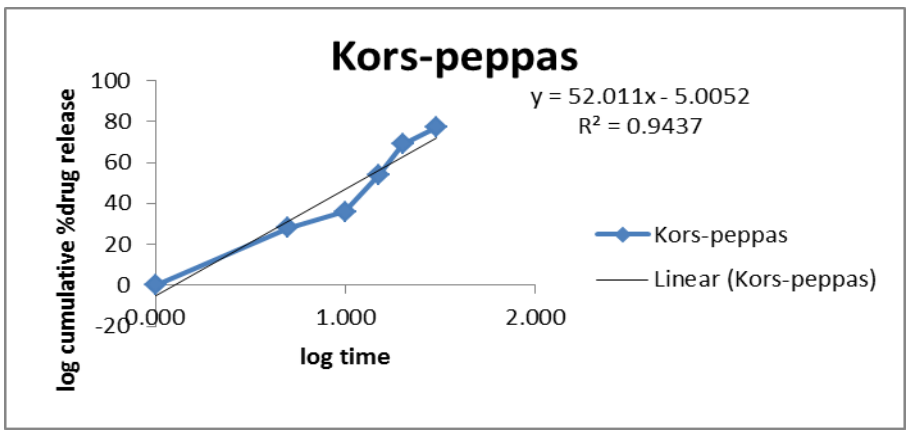

Figure 18: Kors-peppas model for kinetic study.

Stability study

The optimized formulations batch F4 stored at 40 ± 2 °C / 75 ± 5 % was found to be stable. After storage at 40 ± 2 °C / 75 ± 5 %, no shape deformation in the tablets was found. The cumulative percentage drug release was nearly similar before and after storage. Therefore, it is clear that drug was thermally stable at 40 ± 2°C as well as not affected by high humidity at 75 ± 5 %. Considering the in *vitro* drug release behaviour of optimized formulation of Nimodipine tablet initially and after 6 month, it was found that there was no much more variation in the *in vitro* drug release behaviour of tablets**.**

Table 9: Evaluations of optimised batch (F4) after stability study.

Batch No	Avg. Weight (mg)	Thickness (mm)	Hardness (kpa)	Disintegration Time (sec)	Wetting time (sec)	Friability (%)	Drug content (%)
F4	200±2	3.1 ±4	5.5 ±1.5	18 ±2	09 ±4	0.59	99.23 ±0.25

CONCLUSION

The objective of present investigation has been achieved by preparing Nimodipine Orodispersible tablets. The combination of super disintegrants at 2.5% w/w concentrations gives good results for *in vitro* tests. To improve the solubility of Nimodipine complex with Beta-Cyclodextrin and the disintegrating ability of Superdisintegrants by formation of co-processed superdisintigrant, this shows the greater disintegrating ability than single excipient effect. The results of a 2^3 factorial design evaluated that the concentration of super disintegrating agent are significantly effect on the dependant variables.

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CONFLICT OF INTEREST: The authors declare no conflict of interest.

REFERENCES

1. Rao N, Sudhan M, Development and evaluation of nimodpine fast dissolving tablets prepared with a complex by direct compression method, American Journal of pharmatech research, 2011; 1(2): 84-93.
2. Shahabaz S, Soujanya C, Kumar M, Formulation and evaluation of oral disintegrating tablets of nimodipine, World journal of pharmacy and pharmaceutical sciences, 2017; 7(1): 926-946.
3. Mandadi S, Yerragunta V, Tarkash U, Formulation and evaluation of Atorvastating calcium sustained release tablets, International journal of pharmacy, 2016; 6(3): 125-132.
4. Shirsand S, Raman G, Novel co-processed superdisintegrants in the design of fast dissolving tablets, International journal of pharma an bio sciences, 2010; 1(1): 8_15.
5. Laddha U, Zilpelwar V, Orodispersible tablet: a novel approach for better patient compliance, International journal of pharma tech research, 2015; 8(6): 56-64.
6. Amareshwar S, Swati A, Prashanthi Y, Vishwanadham Y, Sreekanth d and Vivekamda B, Development and invitro characterization of probencid rapidly disintegrating tablets by using different co-processed super disintegrants, WJPPS, 2017; 6(12): 76-86.
7. Kapse N, Bharti V, Birajdar A, Munde A, Panchal P, Co-processed superdisintegrants: Novel technique for design ordispersible tablets, Journal of innovations in pharmaceutical and biological sciences, 2015; 2(4): 541-555.
8. Parfati N, Citra K, Charles R, Geovanny V, Preparation and evaluation of atenolol B-Cyclodextrin orally disintegrating tablets using co-processed crospovidone sodium starch glycolate, International journal of applied pharmaceutics, 2018; 10(5): 230-243.
9. Bagul US, Gujar K, Patel N, Aphale S, Dhat S, Formulation and evaluation of sublimed fast melt tablets of Levocetirizine Dihydrochloride, International Journal of pharmaceutical Science, 2010; 2: 76-80
10. Raymond CR, Handbook of Pharmaceutical Excipients APHA Publishers, 8th Edition 2017.
11. Kokare CR, Tagalpallewar AA, Argad PS, Bagul US, Bachav RK, Nanjwade BK, Formulation, evaluation and optimization of Asenapine maleate fast Orodispersible film, Journal of Pharmaceutical Sciences and Pharmacology, 2015; 2: 194-207.
12. ain D, Gupta RN, Shrivastav S, Formulation and evaluation of Orodispersible tablet of omeprazole, International Journal of Current Pharmaceutical Research, 2016; 8: 48-51.
13. Biyani S, Moon R, Gattani S, Kothawade S, Formulation and evaluation of cevimeline hydrochloride orally dissolving film for sjograne syndrome by optimal design, World journal of pharmaceutical and medical research, 2019; 5(8): 166-178.
14. Saleh AR, Ganmal A, Propatenone HCl fast dissolving tablets containing subliming agent prepared by direct compression method, Saudi pharmaceutical Journal, 2017; 25: 1086-1092.