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Formulation and *In-Vitro* Evaluation of Taste Masked Fast Dissolving Tablet of Pregabalin Using Natural Superdisintegrant

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Keywords: Fast dissolving tablet, Natural super disintegrant, Taste masking, Response surface optimal design

ABSTRACT

Fast dissolving tablet is those which disintegrate rapidly within mouth and taken without consumption of water. The present work is concerned with the formulation and in-vitro evaluation of taste-masked pregabalin fast dissolving tablets using natural super disintegrant. Pregabalin is an anti-epileptic drug used in partial-onset of seizures and neuropathic pain. The objective of the present work was to improve the rapid onset of action of the drug. The fast dissolving tablets of Pregabalin were prepared using a direct compression method by using natural super disintegrant like dehydrated banana powder and *Ocimum sanctum* seed powder. Eudragit E-100 used as a taste masking agent in the ratio of (1:0.25), (1:0.5), and (1:0.75) of Drug: Eudragit. The optimum ratio (1:0.5) of drug& eudragit was selected based on the taste-masking effect by performing the sensory test. Total of fifteen batches was prepared as per standard experimental design protocol using response surface optimal design. All the pre-compression parameters are evaluated. Tablet containing 10% of dehydrated *Ocimum sanctum* seed powder as super disintegrant was found to be best which disintegrated within 15 sec. with 98.5% drug release at the end of 30 min. Also, hardness, friability, weight variation, drug content of prepared tablets were found to be in an acceptable limit.

INTRODUCTION

Rapidly dissolving or quick-dissolving dosage forms have acquired great importance in the pharmaceutical industry due to their unique properties and advantages. Of all the dosage forms administered orally, the tablet is one of the most preferred dosage forms. Pregabalin (PRE; S-(3)-amino methyl hexanoic acid) is a structural analog of γ -aminobutyric acid, which is used to treat refractory partial seizures, diabetic neuropathy, post-therapeutic neuralgia, and social anxiety disorders. [1, 2]

PRE is a highly soluble and highly permeable drug, categorized according to the biopharmaceutics classification system (BCS) as a class 1 compound. PRE has an oral bioavailability of more than 90% with an average elimination half-life of 6.3 h, and it is excreted unchanged in the urine. [2, 3]

In the present study, an attempt has been made to masked the taste of pregabalin and formulate the orally disintegrating tablets by direct compression method using dehydrated banana powder and *Ocimum sanctum* seed powder as the superdisintegrants for rapid dissolution of drug and absorption, which may produce the rapid onset of action**.**

MATERIALS AND METHOD

MATERIALS

Pregabalin was obtained as a gift sample from Wockhardt Ltd. The raw bananas and seeds of *Ocimum sanctum* seed powder were collected locally and from herbal drug store respectively. Eudragit E-100, Avicel pH 102, Magnesium stearate, talc, sucralose, mannitol were obtained from college laboratory.

METHOD

Preparation of dehydrated banana powder:

The bananas were purchased from a local market. Peel was removed and fruits were sliced. The sliced pulp was washed with distilled water to remove water-soluble contents.0.2%w/w methylparaben was added as a preservative. Sliced pulp was grounded in a domestic mixture and the obtained wet mass was dried in an oven at 45°C for 24hr to get constant weight. The resultant was passed through mesh size 80 and stored. [5,6]

Preparation of *Ocimum sanctum* seed powder: *Ocimum sanctum* seeds were blended and kept in contact with petroleum ether for 12 hr. The flask was kept on the electrical shaker for continuous shaking. The material was then filtered out and dried at room temp. For complete removal of petroleum ether. The seed powder then soaked in distilled water. After that swollen mass dried at 60°c and pass through the sieve. [7,8]

Preparation of taste-masked granules:

Drug and Eudragit E-100 were mixed in different ratios (1:0.25, 1:0.5, and 1:0.75) properly and granules were prepared by wet granulation method using starch paste as a binder. The granules were dried at 50ºC.[9,10]

Taste evaluation of granules:

A sensory taste is used for the evaluation of taste masking of prepared granules. The test was performed using 6 adult volunteers from whom informed consent was obtained. They rinsed their mouth cavities before and after tasting. The prepared granules were kept in a volunteer's mouth for 20sec and then split out. The taste score was set to a range of 0-3based on taste-masking (0-Good,1-Taste less,2-slightly bitter,3- bitter). Then based on scores, the best masked (1:0.5) granules were selected as optimized.[10]

Preparation of fast dissolving tablet:

Fast dissolving tablets were prepared using super disintegrants by the direct compression method. Different percentages of dehydrated banana powder and *Ocimum sanctum* seed powder were used. A total number of fifteen batches were prepared by using the design expert software. Accurately weighed optimized taste-masked granules were mixed with super disintegrants, mannitol, avicel pH102, sucralose, talc, magnesium stearate, and were compressed into tablets by direct compression. [11]

Formulation of taste-masked pregabalin FDTs:

Pregabalin fast dissolving tablets were formulated and optimized by three factors three-level by 2 levels response surface optimal design using design expert software (version 12). Two independent factors were numeric and these were concentration of super disintegrant and concentration of avicel and categoric factor i.e. type of super disintegrants.

Table No. 1: Independent factors and levels

Independent variables	Levels	
	-1	+1
Concentration of super disintegrants (%w/w)	2	10
Concentration of Avicel pH102(mg)	80	100
Type of super disintegrants (categoric factor)		

Table No. 2 Response surface optimal design for the formulation of FDTs of pregabalin

Sr. No.	Type of super disintegrants	Concentration of super-disintegrants (%)	Concentration of Avicel pH102(mg)
1	Banana	6	100
2	Banana	2	90
3	Ocimum	10	80
4	Banana	6	100
5	Banana	2	80
6	Banana	6	80
7	Ocimum	10	90
8	Ocimum	2	100
9	Banana	10	90
10	Ocimum	2	80
11	Ocimum	6	100
12	Ocimum	2	90
13	Ocimum	10	100
14	Banana	10	90
15	Ocimum	6	90
16	Ocimum	6	90
17	Banana	2	90
18	Banana	10	80
19	Ocimum	6	90

Table No. 3: Formulation table for FDTs of pregabalin using dehydrated banana powder

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7
Pregabalin+Eudragit granules(1:0.5)	75	75	75	75	75	75	75
DBP	12	4	4	12	20	4	20
Avicel pH102	100	90	80	90	80	90	80
Magnesium stearate	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2
Sucralose	4	4	4	4	4	4	4
Mannitol	5	23	43	15	17	23	27
Total	200	200	200	200	200	200	200

Table No. 4: Formulation table for FDTs of pregabalin using ocimum sanctum seed powder

Ingredient (mg)	F8	F9	F10	F11	F12	F13	F14	F15
Pregabalin+Eudragit granules(1:0.5)	75	75	75	75	75	75	75	75
ocimum santum seed powder	20	20	4	4	12	4	20	12
Avicel pH102	80	90	100	80	100	90	100	90
Magnesium stearate	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2
Sucralose	4	4	4	4	4	4	4	4
Mannitol	17	7	13	33	5	23	-	15
Total	200	200	200	200	200	200	200	200

Evaluation of pregabalin FDTs:

Precompression parameters: The uniformly mixed powders of all formulations were evaluated for:

Bulk density:

It is the ratio of the total mass of powder to the bulk volume of powder.it was measured by pouring the weighed powder into a measuring cylinder and volume was noted .it is expressed in gm/ml and determined by a formula.

Bulk density=mass/bulk volume

Tapped density: It is the ratio of the total mass of powder to the tapped volume of powder. Tapped volume was measured by tapping the powder to constant volume.

Tapped density=mass/tapped volume

Angle of Repose: The frictional forces in a loose powder can be measured by angle of repose θ It is used to find the flow properties of the powder and this is the maximum angle between the surface of the pile of powder and horizontal plane.

$$\theta = Tan^{-1}h/r$$

Carr's index= Carr's density is measured by using values of tapped density and bulk density.

Carr's index = tapped density-bulk density/tapped density*100

Hausner's Ratio: Hausner ratio is an indirect index of ease of powder flow.

Hausner's ratio =Tapped density/Bulk density

POST COMPRESSION PARAMETERS:

Thickness:

Randomly 10 tablets were taken from each batch and thickness was measured using a digital vernier caliper. And average thickness was determined in mm.

Weight variation test:

20 tablets were randomly selected form batch and their weight was calculated using digital balance and individually weighed. The tablets meet USP specifications if not more than 2 tablets outside the percentage limit and if no tablet differ by more than 2 times the percentage limit.

Hardness: hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of tablets was determined using Monsanto hardness tester. It was expressed in kg/cm^2. Five tablets of each batch were randomly picked and the hardness of each tablet was determined.

Friability: The friability of the tablet was determined using Roche friabilator.10tablets were randomly selected and their initial weight was noted. The friabilator was operated at 25rpm for 4 min. Again weigh tablet's weight. For conventional tablets, the percentage loss in friability should be less than 1% while friability value up to4% is acceptable for fats dissolving tablets or chewable tablets.

Wetting time: The wetting time of the dosage form is related to the contact angle. A lower wetting time implies quicker the disintegration time.

Procedure: Five circular tissue papers of 10cm diameter were placed in a petri dish of 10 cm diameter.10ml of water was added to the Petri dish. A tablet was carefully placed on the surface of tissue paper .time required for water to reach the upper surface of the tablet was noted as the wetting time.

In-vitro disintegration time:

Disintegration time is the time taken by the tablet to break into smaller particles. the test is carried out using the USP disintegration test apparatus. The phosphate buffer of 6.8 pH as a disintegration media, maintained at 37±2ºC.6 tablets was placed in each tube, and time for the disintegration of FDTs was calculated.[11]

In-vitro **dissolution test**: The in-vitro dissolution studies were carried out using the USP paddle apparatus at 100rpm in 900 ml of phosphate buffer pH 6.8 as a dissolution media, maintained at 37±5ºC.5ml of aliquots was withdrawn at a specified time interval, filtered through Whatman filter paper and assayed and assayed at 206nm. An equal volume of a fresh medium that was pre-warmed at 37ºC was replaced into dissolution media after each sampling to maintain the constant volume throughout the test.[11,12]

Stability study:

FDA and ICH specify the guidelines for stability testing of new drug products. The ICH guidelines have established long term stability testing to be done at 25º C/60% RH for 12

months. Accelerated stability testing should be done at 40º C/75%RH for 6 months and stability testing at intermediate storage conditions should be done at 30º C/65%RH.[13,14]

Drug -Excipient Compatibility Study:

Fourier Transform Infrared Spectroscopy (FTIR): FTIR spectrum pure drug and natural polymer i.e dehydrated banana powder and *Ocimum sanctum* seed powder were recorded. The sample was analyzed by the KBr method using FTIR spectroscopy. About 10mg of the formulation is mixed with dried KBr of equal weight. The mixture is properly ground using mortar and pestle. Then the powder was scanned over the frequency range.

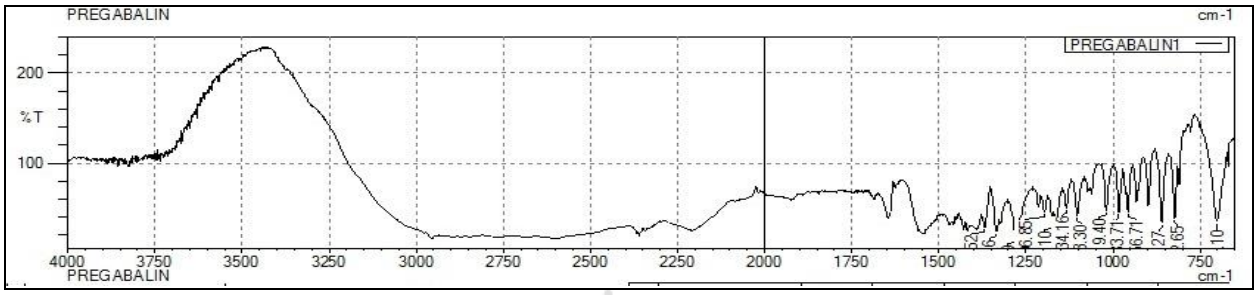

Figure No. 1: FTIR spectra of pregabalin

Functional group	**Wavenumber cm^{-1}**
CH- Out of plane stretch	701
CH out of the plane plane	822
C-H Stretch	1279
NH_2 scissoring	1691
C=O	1836
NH_2 stretching	3330

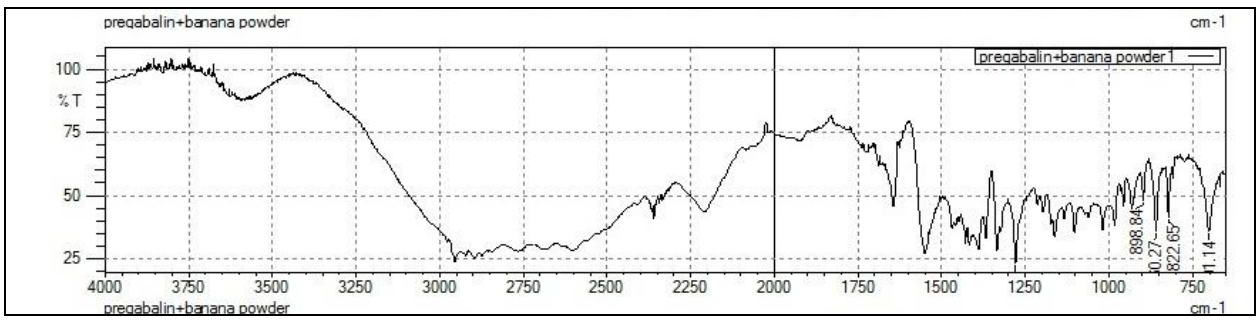

Figure No. 2: FTIR Spectra of mixture of pregabalin and dehydrated banana powder

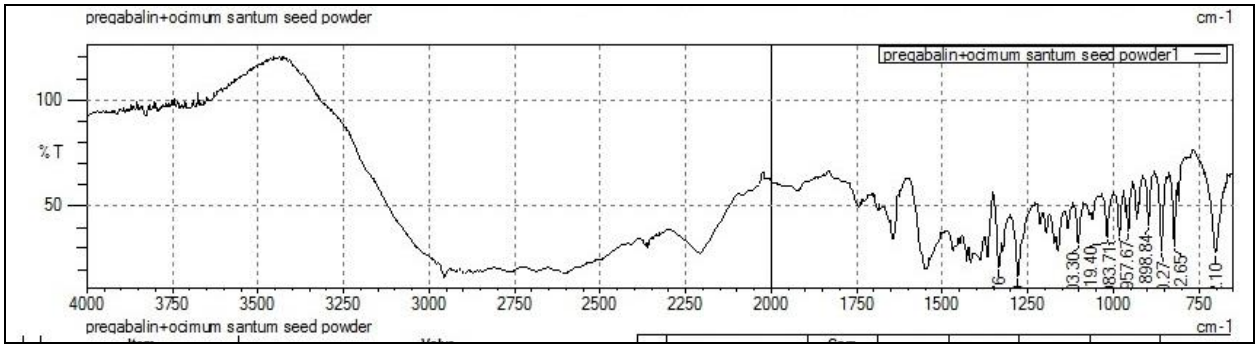

Figure No. 3: FTIR Spectra of mixture of pregabalin and Ocimum sanctum seed powder

The above peaks are considered as characteristic peaks of pregabalin. These peaks were not affected and prominently observed in IR spectra of drug and excipients. This indicates there is no interaction between drug and excipients.

RESULTS AND DISCUSSION

Table No. 5: Preformulation characteristics of pregabalin FDTs using dehydrated banana powder

Formulation	Bulk density	Tapped density	Hausner ratio	Compressibility index	Angle of repose
F1	0.28	0.34	1.21	12.53	26.27
F2	0.28	0.32	1.15	14.38	26.09
F3	0.26	0.33	1.17	12.01	24.12
F4	0.25	0.31	1.16	13.04	26.02
F5	0.29	0.42	1.19	13.63	27.12
F6	0.31	0.45	1.22	18.18	28.02
F7	0.29	0.41	1.19	19.04	24.1

Table No. 6: Preformulation characteristics of pregabalin FDTs using *Ocimum sanctum* seed powder

Formulation	Bulk density	Tapped density	Hausner ratio	Compressibility index	Angle of repose
F8	0.27	0.35	1.15	12.53	27.12
F9	0.28	0.33	1.17	12.01	26.01
F10	0.26	0.32	1.19	14.20	25.09
F11	0.28	0.36	1.23	13.38	26.12
F12	0.31	0.41	1.20	13.61	24.16
F13	0.31	0.41	1.18	19.01	25.42
F14	0.28	0.34	1.16	19.12	22.31
F15	0.27	0.35	1.17	20.21	24.21

Table No. 7: Post compression parameters of pregabalin FDTs using DBP

Formulation	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Weight (mg)	Drug content (%)
F1	3.6	0.53	15	10	200.2	98.99
F2	3.6	0.49	19	13	200.1	99.23
F3	3.7	0.48	15	11	200.6	98.79
F4	3.8	0.55	20	15	199.8	99.54
F5	3.9	0.57	15	11	200.1	99.16
F6	3.9	0.58	19	15	200.3	99.1
F7	3.8	0.56	16	11	200.2	98.84

Table No. 8: Post compression parameters of pregabalin FDTs using ocimum sanctum seed powder

Formulation	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Weight (mg)	Drug content (%)
F8	3.8	0.48	14	9	199.8	98.85
F9	3.85	0.57	15	9	200.3	99.15
F10	3.9	0.55	25	14	200.2	99.01
F11	4	0.56	27	15	200.1	98.52
F12	3.9	0.52	19	11	200.1	98.12
F13	4.1	0.55	29	18	200.5	98.52
F14	3.5	0.58	15	7	200.2	99.03
F15	3.7	0.58	18	9	200.1	98.6

OPTIMIZATION

After all evaluation and the comparison between both super disintegrants i.e *Ocimum sanctum* seed powder and dehydrated banana powder, the study reveals that *Ocimum sanctum* seed powder gives faster disintegration, effective hardness, and better dissolution and by using design expert software. From which 10% concentration of *Ocimum sanctum* seed powder and 90mg of avicel gives effective results.

EVALUATION OF OPTIMIZED BATCH

Response 1: disintegration time:

The **Model F-value** of 22.84 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case, A, C, AC are significant model terms.

Type of super disintegrant: *Ocimum sanctum* seed powder

Disintegration= +79.650-3.70486 *conc. of Ocimum -0.974138 *conc. of avicel+0.014063*conc. of Ocimum *conc. avicel +0.0678 conc. of ocimum^2 +0.004808 conc. of avicel

Equation states that as the concentration of *Ocimum sanctum* seed powder increases the tablets will disintegrate fastly and which helps for faster dissolution and absorption. As the concentration of super disintegrant increases, i.e from 2-10% tablet will disintegrate fastly.

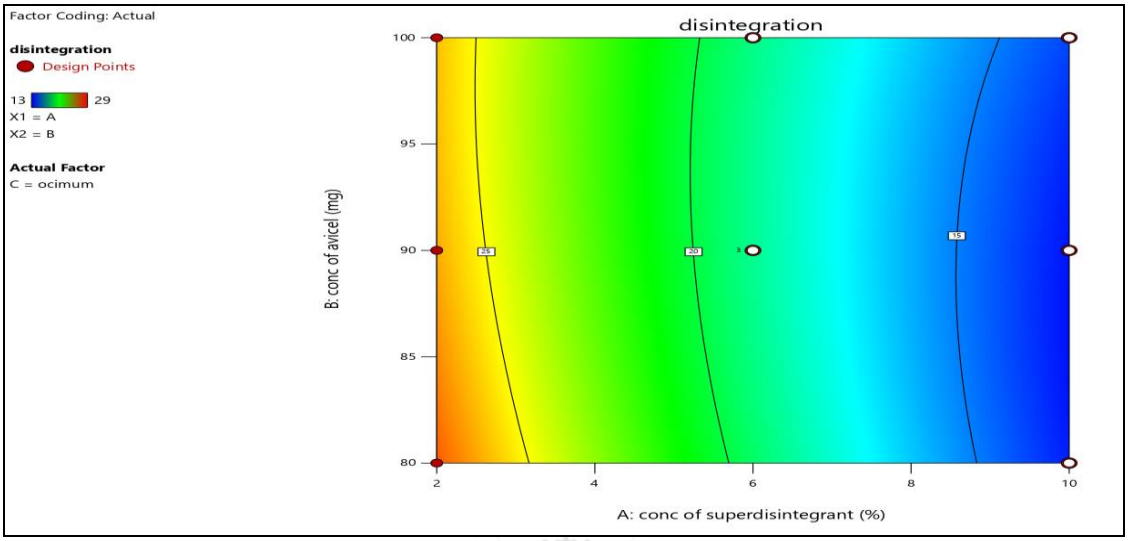

Figure No. 4: Contour Plot for Effect of Concentration of Superdisingrant and Concentration of avicel on Disintegration

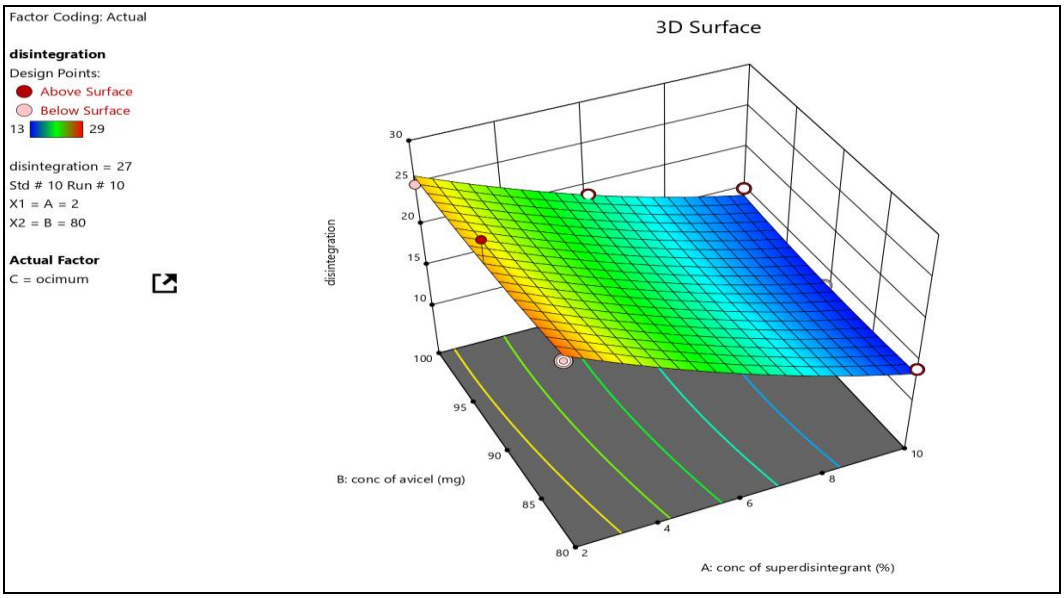

Figure No. 5: 3-D Graph for Effect of Concentration of Superdisingrant and Concentration of avicel on Disintegration

Response 2: Drug release

Type of super disintegrants: *Ocimum sanctum* seed powder

The **Model F-value** of 36.79 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case, A, B, C, AC, BC are significant model terms.

71.46+6.074 * conc. of Ocimum +3.46048 *conc. of avicel -0.05154 conc. of Ocimum *conc. of avicel- 0.018343 * conc. of avicel^2

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This study reveals that as the concentration of super disintegrant i.e *Ocimum sanctum* seed powder increases it disintegrate easily and get easily dissolve which shows higher drug release.

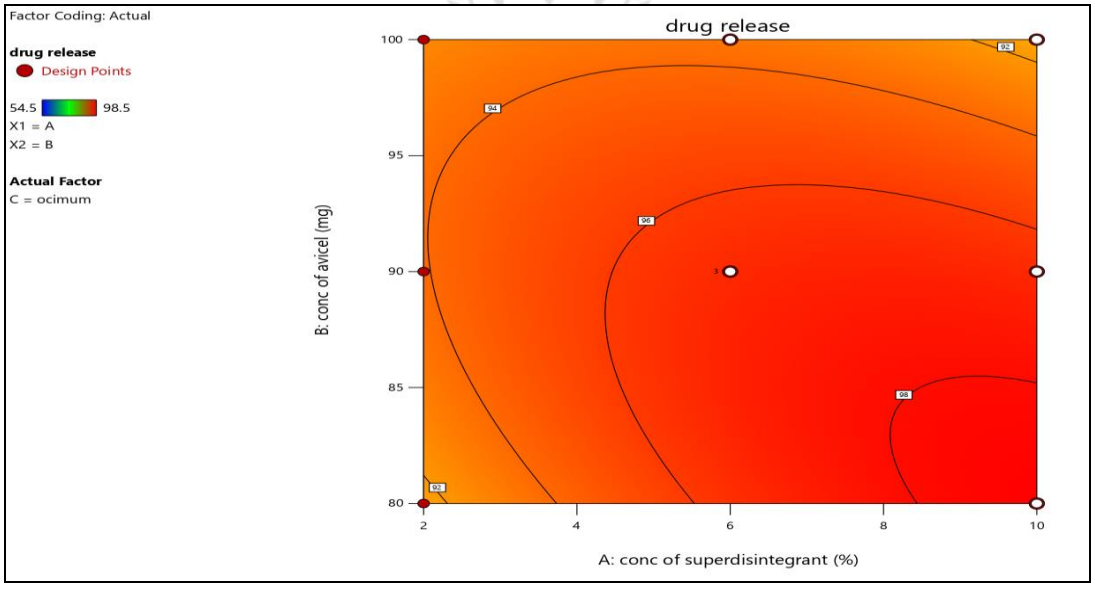

Figure No. 6: Contour plot for effect of concentration of super disintegrant and concentration of avicel on drug release

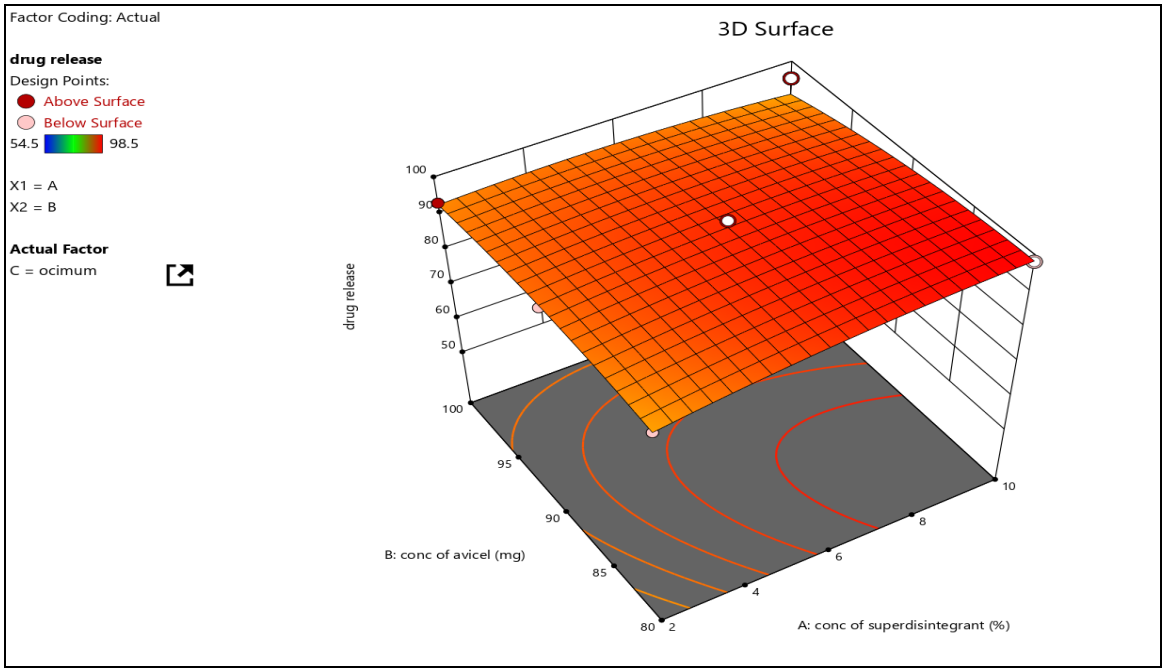

Figure No. 7: 3-D Graph For Effect Of Concentration Of Superdisintegrant And Effect Of Concentration Of avicel On Drug Release

Response 3:

Hardness:

Type of super disintegrants-*Ocimum sanctum* seed powder:

The **Model F-value** of 55.36 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case, A, B, C, AB, AC, BC are significant model terms.

Equation:+2.0623 + 0.3032 conc. of Ocimum +0.037 conc of avicel -0.003594 Conc. of ocimum*conc of avicel -0.000229*conc. of ocimum^2 -0.000188 Conc. of avicel^2.

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor.

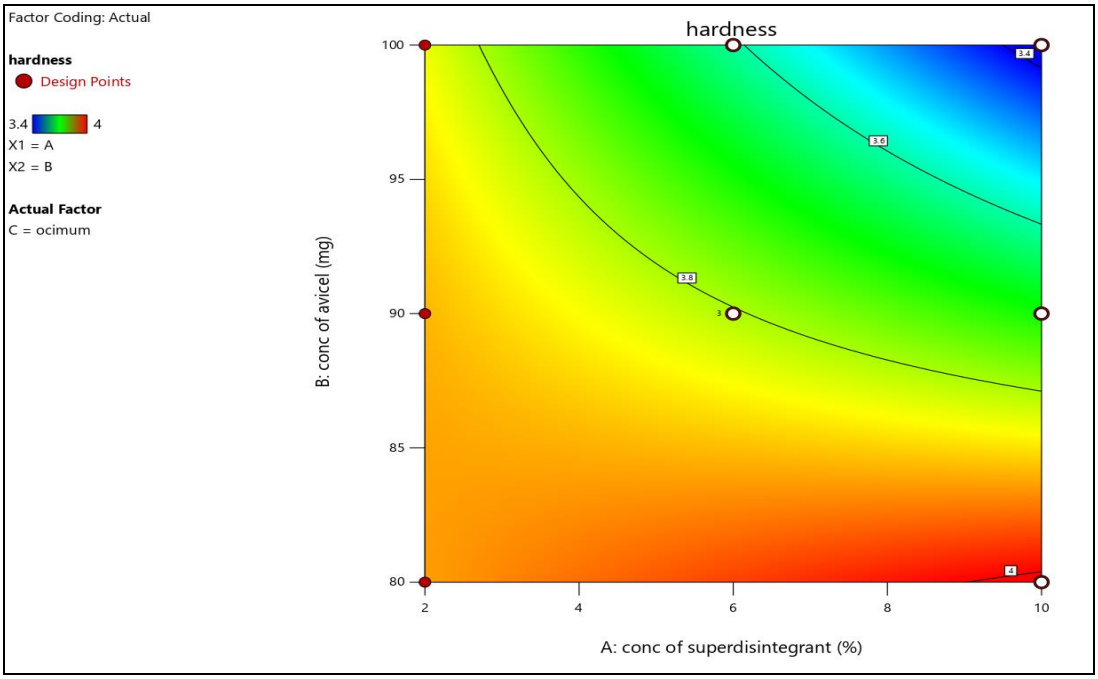

Figure No. 8: Contour Plot for Effect Of Concentration Of Superdisintegrant And Concentration Of avicel On Hardness

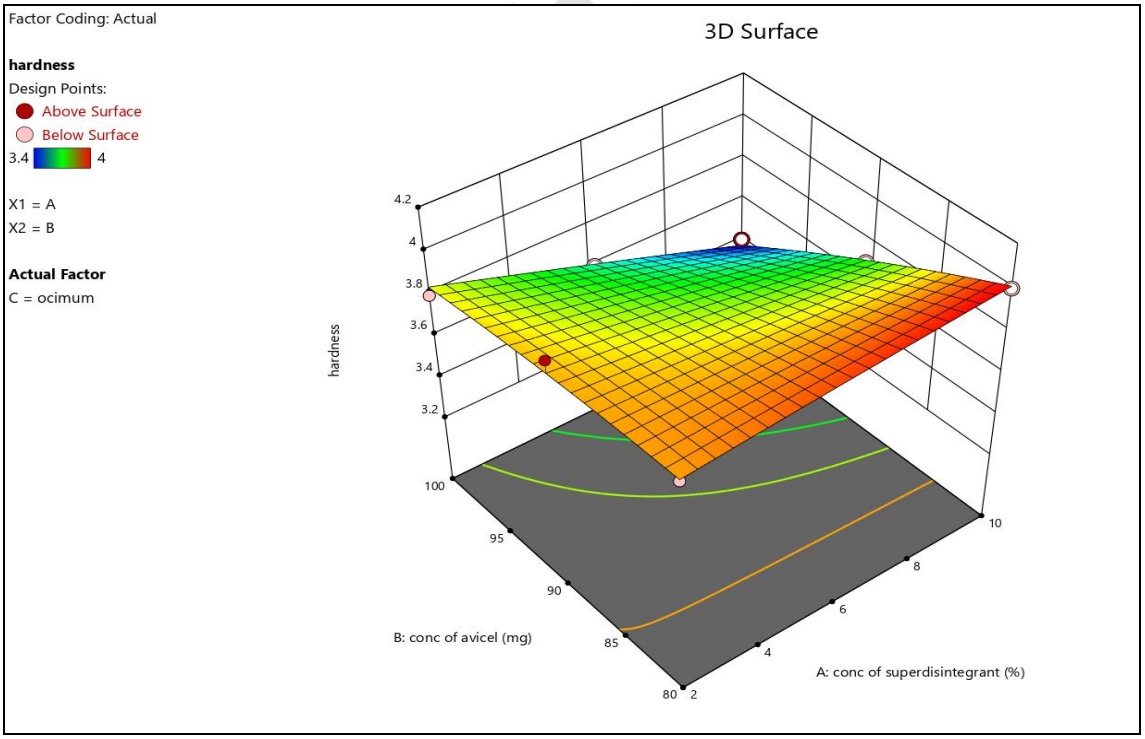

Figure No. 9: 3-D graph for effect of concentration super disintegrants and concentration of avicel hardness

Stability studies:

There was no significant change in physical and chemical properties of tablets of formulation F9 after 3 months. Parameters were quantified at various time interval were:

Table No. 9: Results of stability studies of optimized formulation F9

Sr. No.	Parameters	Initial	1 month	2 month	3 month
1	40ºC/75%RH % Drug release	98.5%	98.52%	98.2%	97.6%
2	Drug content	99.15	99.2	99.2	99.01
3	wetting time	9 sec	10sec	10sec	10sec
4	disintegration time	15sec	15sec	15sec	15sec
5	friability	0.57	0.57	0.58	0.59
6	Hardness	3.85kg/cm^3	3.84kg/cm^3	3.85kg/cm^3	3.85kg/cm^3
7	Thickness	3.92mm	3.92mm	3.91mm	3.91mm

CONCLUSION

This study discusses the formulation and evaluation of taste-masked fast dissolving tablets of pregabalin using natural super disintegrant. Design expert software (response surface optimal design) was used to optimized and respond to surface plots and contour plots were drawn, and optimum formulations were selected by feasibility. Polynomial mathematical model (Quadratic), generated for various response variables, were found to be statistically significant ($p < 0.05$). Formulation F9 (10% conc. of *Ocimum sanctum* seed powder; 90mg avicel) was selected by design expert software which exhibited disintegration time 15 sec, and in-vitro drug release 98.5% within 30 minutes.

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