International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 17, Issue 1, 2025

Original Article

DESIGN, OPTIMIZATION (2^3FACTORIAL DESIGN), AND EVALUATION OF CARVEDILOL FAST DISSOLVING TABLETS BY EMPLOYING SOURSOP STARCH AS A NEW NATURAL SUPERDISINTEGRANT

VASUDEVA REDDY MATTA[1], SANTOSH KUMAR RADA[1]*

[1]Department of Pharmaceutics GITAM School of Pharmacy, GITAM (Deemed to be University), Rushikonda, Visakhapatnam, Andhra Pradesh-530045, India

*Corresponding author: Santosh Kumar Rada; *Email: srada@gitam.edu

Received: 16 Sep 2024, Revised and Accepted: 05 Nov 2024

ABSTRACT

Objective: The study objective is to focus on the isolation of the Soursop Starch (SSS) from the fruit pulp of *Annona muratica* (Soursop) used as a natural super disintegrating agent in the carvedilol formulation of Fast-Dissolving Tablets (FDTs) using (2^3) factorial design.

Methods: The SSS was isolated from the fruits of *Annona muratica* (Annonaceae family) by using sedimentation and centrifugation techniques. The physicochemical properties of the SSS were assessed. A direct compression method was employed to prepare Carvedilol Fast-Dissolving Tablets (C-FDTs). The factorial design was adopted at two levels (0 and 5 %) of superdisintegrant, and the dependent variables are SSS, psyllium husk, and Sodium Starch Glycolate (SSG). The Critical Quality Attributes (CQA) were measured for all eight formulations, including Disintegration Time (DT), Wetting Time (WT), % Drug Dissolved in 10 Min (PD10) and dissolution efficiency. The finished C-FDTs were evaluated for different test parameters like drug content, water absorption ratio, weight variation, hardness, dissolution, dissolution efficiency at 10 min, and stability studies for optimized formulation.

Results: The isolated SSS was found to be insoluble in water and other inorganic solvents, and its swelling index, viscosity, bulk density, and tapped density were found to be satisfactory. The critical quality attributes like DT (22±1.38 sec), WT (24±0.58 sec), and PD10 (99.05±0.21 %) were found to be satisfactory for the optimized formulation (F2). The dissolution efficiency (F2) at a 10 min time point was found to be 44 times higher than that of the F1 formulation.

Conclusion: C-FDTs were successfully designed and optimized by employing the SSS as a natural superdisintegrant which exhibited a better % of the drug release in 10 min with good DT, dissolution efficiency, and all other FDT characteristics.

Keywords: Superdisintegrant, Soursop starch, Carvedilol, Fast dissolving tablets, Factorial design, Natural, Disintegration time

DOI: https://dx.doi.org/10.22159/ijap.2025v17i1.52687 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

The drug delivery systems emphasize the quick availability of active moiety at the site of action with minimal side effects. In this context, one of the best delivery systems is FDTs [1]. The FDTs are known for patient compliance and good bioavailability. As per the United States Food and Drug Administration (US FDA), Oral Disintegration Tablets (ODT-known as FDTs) disintegrate in seconds once administered orally on the tongue [2]. This formulation (FDTs) will not need any extra water for intake through the oral route and also avoids swallowing the dosage form as such (this helps for the patient's dysphagia). This helps for patients such as paediatric, geriatric, and bedridden [1, 3].

The key ingredient in the formulation of FDT(s) is superdisintegrant [4]. There are numerous types of superdisintegrants on the market, including natural and synthetic [5]. Still, it has always been difficult to develop a new superdisintegrant that is compatible with the drug for rapid disintegration [6]. In this study, we have isolated the starch from the pulp of soursop fruit (*Annona muratica*.) This new soursop starch is natural, biocompatible and biodegradable; it has fewer processing steps, is cost-effective, and is being developed as a superdisintegrant to improve the solubility as well as dissolution of carvedilol. Carvedilol is a Biopharmaceutics Classification System (BCS) class II antihypertensive drug [7]. This drug is the first-line treatment for severe hypertensive crises. It exists as a white to half-white powder. The US FDA approved dosage ranges from 6.25 mg to 100 mg per day based on clinical conditions [8]. Dose titration shall be performed as per the requirement. The development of FDTs for this drug is important to increase compliance by patients, both the elderly and paediatric populations, who have difficulties swallowing solid oral medication [9].

Carvedilol was used to formulate the FDTs by employing the new superdisintegrant (SSS). The optimization design adopted in this study is a 2^3 factorial design. The three factors are SSS (A), psyllium husk (B), and SSG (C) at two levels of 0% and 5 %. The interaction of each independent variable (A, B, C) and the combination of variables have been established [10]. The product CQAs that were evaluated with this Design are DT, WT, PD10 and dissolution efficiency at 10 min, and the results indicative that a new natural superdisintegrant (SSS) shall be used for the formulation of FDTs for the BCS class-II molecules.

MATERIALS AND METHODS

Materials

The drug substance (carvedilol) and other excipients, like SSG, Microcrystalline Cellulose (MCC) Lactose Monohydrate, Talc, and Magnesium Stearate were the gift samples from M/s. DRL Limited Hyd. Soursop Starch was isolated in the lab. Psyllium husk acquired from Organic India Pvt Ltd. Hyd. Sodium sulphite, procured from M/s. Deepak nitrite Hyderabad and Amarnath die, sodium hydroxide was procured from yarrow chemicals Maharashtra.

Methods

Isolation of SSS

The ripened, bruised soursop fruits were selected for the soursop starch isolation. These fruits were cleaned, and the peel and seeds were removed from the fruit. The pulps are collected in the stainless steel vessel, quickly cleaned with sodium sulphite solution, and dried at 50 C in an oven. Ball Mill is used to grind the dried chips to powder form. For two hours, the powder's known weight was immersed in purified water at a 1:5 (powder: water) ratio, and then this solution was sieved through a muslin cloth. Wash water was used to clean the residue till it was completely clean. After centrifugation of the starch milk for thirty minutes at 5000 RPM, the

supernatant was poured off. After being separated in a solution of 0.3% NaOH (w/v), the resultant sediment of starch, which includes a thin layer of yellow mucus, was repeatedly rinsed with the same solution till the clean white starch appeared as a centrifuge. Cleaned white starch was dried, and the clean water had a neutral litmus colour. It was dried and kept in a sealed container [11, 12].

Physicochemical characteristics of the isolated SSS

The physicochemical properties such as identification, solubility, bulk density, tapped density, loss on drying, acidity/alkalinity, viscosity, swelling index, compressibility index, particle size distribution and Scanning Electron Microscopy (SEM) were evaluated for the newly isolated naturally occurring biodegradable and biocompatible superdisintegrant.

Identification

The isolated SSS was subjected to mix with the 0.2 % iodine solution. The blue colour indicates that the isolated SSS has the amylose and amylopectin groups.

Solubility

SSS was subjected to standard solubility testing using the saturation solubility technique and discovered to be not soluble in both aqueous and non-aqueous media.

Bulk density

A specified quantity of SSS was weighted and poured into the cylinder for measuring purposes to determine bulk density with the help of the formula density=mass/volume.

Tapped density

The specified quantity was weighed and filled into the cylinder for measurement and subjected to a standard tapping process till there was NO significant change in the volume of the material. By using the formula density = mass/volume, tapped density was determined.

Loss on drying

A specified quantity of SSS was placed in halogen moisture loss on drying apparatus and subjected to drying at 105 °C, and the weight difference divided by initial weight yielded the loss on drying [13].

Acidity/Alkalinity (pH)

A small amount of SSS was added to the distilled water, and a litmus paper test was performed on the solution.

Viscosity

2 % w/v solution of SSS was prepared, and a standard Brookfield viscometer method was used to measure the viscosity of the solution [14].

Swelling index

A specified quantity of SSS was taken into two graded test tubes. One was added with light paraffin, and the second one was added with distilled water. These dispersions were sediment for 12 h, and SI was calculated using the formula below.

$$\text{Swelling Index}(\%)=\frac{\text{Volume of sediment in water-volume of sediment in light liquid paraffin}}{\text{Volume of sediment in light paraffin}}\times 100$$

Compressibility index

Both bulk density and tapped density are required to calculate the CI. The formula to determine CI is as follows:

$$\text{Compressibility index} = \frac{\text{Vo} - \text{V}}{\text{V}} * 100$$

Where Vo= Tapped density V=Bulk density.

Particle size distribution

A specified quantity of SSS was poured into the sieve shaker setup by keeping the sieves in ascending order #20, #40, #60, #80, and #100. The retains on each sieve were measured and reported as cumulative particle size distribution [14].

SEM

The external structure and shape of SSS were then examined with a scanning electron microscope (DSM 940 apparatus Carl Zeiss, Oberkochen, Germany) [15].

Preparation of C-FDTs

The most convenient and industrial feasible tablet manufacturing methods are direct compression methods followed by dry granulation, wet granulation, top spray granulation, and other complex granulations like centrifugal coating granulation.

Hence, we have opted for the direct compression process for the preparation of C-FDTs. The précised ingredients in every preparation are provided below (table 1). The drug and excipients were dispensed as per the formulae. Carvedilol, MCC, Lactose Monohydrate, and selected superdisintegrant were sifted through #60 mesh. Talc and magnesium stearate were sieved through # 80 mesh. The #60 mesh sieved materials were blended in the bag for a couple of minutes, and then the # 80 mesh sieved materials were added and blended for another couple of minutes to get the uniform blend. An eight-station rotary compression machine with 6 mm round plain punches [16] was used to compress the final blend into tablets.

Evaluation methods of C-FDTs

The compressed tablets are evaluated for their weight fluctuation, thickness, hardness, friability, DT, WT, the ratio of water absorption, drug content, dissolution, and efficiency of dissolution at a 10 min time point. The detailed process of these evaluations is provided below.

Weight variation

We use the analytical balance to determine the weight fluctuation. Randomly selected, ten tablets were ingested, and the weight of each tablet was noted.

Table 1: C-FDTs formulae

Ingredient (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
Carvedilol	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Soursop Starch	---	5	---	5	---	5	---	5
Psyllium Husk	---	---	5	5	---	---	5	5
Sodium Starch Glycolate	---	---	---	---	5	5	5	5
MCC	50	50	50	50	50	50	50	50
Lactose monohydrate	33.5	28.5	28.5	23.5	28.5	23.5	23.5	18.5
Talc	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100

Thickness

With the use of Vernier-Callipers, the tablet's thickness was determined and noted. Ten pills were chosen at random, and their thickness was measured and noted.

Hardness

The force required to deform the tablet/pill is the measure of its hardness. Hardness is a destructive test. Hardness is an output of compression activity that can impact the quality of the product. Ten

pills/tablets are chosen randomly and subjected to a hardness test by use of a Monsanto Hardness Tester (MHT). The tablet was kept horizontally on the MHT, and force was applied from the other side to deform the tablet. This measured force (Kg/cm^2) is the hardness of the tablet.

Friability

Friability is the parameter that will explain how the tablet withholds its shape and morphology. As per the standard procedure, "Roche friabilator" was used here. As per the guidance, ten tablets or 6.5 g (whichever is close) weight of tablets should be subjected to friability testing. In this study, about 6.5 g (approx. 66 tablets) of tablets were taken into consideration. These tablets were loaded into the friability and subjected to 100 rotations (25 RPM for 4 min), and the pills/tablets were collected after being weighed and de-dusted in the friability [17]. The % difference in the weight to that of the initial weight is the friability. Friability is calculated using the formula below.

$$\text{Friability} = \frac{\text{Initail weight} - \text{Final Weight}}{\text{Initial weight}} * 100$$

Duration of DT

As per the USP recommendation, 1000 ml of 6.8pH phosphate buffer was taken in the disintegration apparatus (6 stations). After the temperature reached about 37±0.5 °C, tablets were placed into the apparatus. The test was run till there was no mass left on the disintegration mesh (#40), and the time was recorded as disintegration time [18].

WT

To determine the tablet WT, we used the Petri dish method. The Whatman filter paper was cut into the petri dish size. In a plain petri dish, 2 mm water was poured, and a die soluble in water was included in it. Then, a filter paper was placed to wet it completely. The tablet/pill was positioned on the wetted filtration material, and time was counted till the tablet/pill got fully wet [19].

Water absorption ratio (R)

The test was performed by using the Petri dish method, and saturated tissue paper was used for the study. Six millilitres of water is poured into a petri dish, and the filter paper is placed over it and saturated with water. Then, one tablet was weighed and positioned over the filter paper. After the tablet had been fully soaked, it was removed and weighed again. Wetting ratio of absorption was calculated with the following equation:

$$R = \frac{Wa - Wb}{Wb} * 100$$

Where Wa = weight of the pill upon absorption of water, Wb= weight of the pill before absorption of water.

Drug content

Ten tablets were measured and crushed into a blend. From this similar blend, 10 mg carvedilol was weighed and moved into the conical cylinder and further diluted by using the pH 6.8 buffer solution. The absorbance was calculated at 242 nm by using Ultraviolet spectrometry and recorded [7].

***In vitro* dissolution rate studies**

Dissolution was performed by using the USP type-II dissolution apparatus (paddle-ElectrolabTDT-08L). The dissolution media was 900 ml of pH 6.8 buffer, rotations were 50 rpm and the dissolution conditions were 37±0.5 °C. The dissolution time points are 2, 4, 6, 8, 10, 15, 20, 25, 30, 45 and 60 min. Dissolution was performed on six tablets. Six tablets were placed in each of the dissolution vessels, and the dissolution was started. Dissolution samples (5 ml) were collected at specified time intervals and analysed for the active content on the UV spectrometer at 242 nm. The dissolution media was replaced after every sampling point.

The dissolution efficiency at 10 min intervals

Based on the generated dissolution information, the efficiency of dissolution at the 10 min was measured using the following formula.

$$\text{Dissolution Efficiency} = \frac{A}{(B * t)}$$

Where A is the Area under the dissolution curve till the time point "t";

B is the 100 % dissolution value

"t" is the time point of the dissolution test.

Optimization

Factorial design (2^3) was adopted in this study. The two levels are 0 and 5 % concentration of the superdisintegrant, and three independent variables are superdisintegrants SSS (A), psyllium husk (B), and SSG (C). The factorial design was as follows:

Table 2: A transformed matrix design for analysis of responses of C-FDTs

Design	A	B	C
1	0	0	0
2	0	0	5
3	0	5	0
4	0	5	5
5	5	0	0
6	5	0	5
7	5	5	0
8	5	5	5

These designs were formulated (F1-F8) and assessed for all the predefined critical quality attributes (CQAs). These inputs were further incorporated into the Design of Expert (DOE) software to know the impact of individual and interaction effects of each superdisintegrant used in this study. The surface plots of response and contour charts were assessed for the result of each superdisintegrant at a concentration of 0 to 5%.

Stability studies

According to regulations, an optimum composition of carvedilol rapidly dissolving tablets requires accelerated testing by simply storing them in HDPE containers for 180 d at a temperature of 40±2 °C and 75±5°RH [20]. These samples have been examined for modifications in physical change and drug release properties during storage for 180 d [21].

RESULTS AND DISCUSSION

The isolated SSS was found to be a fine powder with the below physicochemical properties (table 3).

The isolated SSS emerged to be insoluble in both water and non-water-based solvents, indicating that this will aid in improving the solvent-wicking effect. The weak acidity pH indicates that it is physiologically compatible with the saliva, and the swelling index of 74 indicates that it will be used as a superdisintegrant by swelling the mass around SSS. The moisture absorption is good enough to use in pharmaceutical formulations. The bulk density tapped density and other properties are promising that the isolated SSS has excellent flow properties.

Drug–excipients compatibility studies

The spectrum of carvedilol (fig. 1) shows a strong absorbance band around 3339.76 cm-1 because of N-H expanding. C-H expanding is

responsible for 2834.28 cm^{-1}, C=O expanding for 1606.66 cm^{-1}, C=C aromatic for 1500.24 cm^{-1}, C-O-C symmetric expanding at1284.53 cm^{-1}. The same peaks were also identified in the FTIR spectra of a pure medication with SSS (fig. 2): (-NH) 3340.01, (-CH)2834.62, (C=O) 1606.71, (-C=C)1500.32, (C-O-C) 1284.50, and ($C=CH_2$) 670.86. The FTIR chromatograms (fig. 1, fig. 2) of the pure drug and 1:1 ratio of the pure drug along with the isolated SSS (a new superdisintegrant) revealed that there is NO interaction between carvedilol and the new superdisintegrant SSS. The compatibility studies revealed that the proposed excipient is compatible with the formulation of tablets. The SEM of the SSS supports its spherical nature, as illustrated in fig. 3.

Table 3: The physicochemical properties of SSS

Character	Remarks
Solubility	Not soluble in both organic and aqueous solvents like Alcohol, Dichloromethane, Chloroform, Acetone and Petroleum ether
Viscosity (2% solution)	32.0
pH (1% aqueous dispersion)*	6.13±0.04
Swelling index	74%
Moisture absorption	4.6%
Particle size	90% Retains on #100 (150µm)
Bulk Density	0.498g/cc
Tapped density	0.515g/cc
Angle of repose	26.86
Compressibility index	9.12%

*n=3, Mean±SD

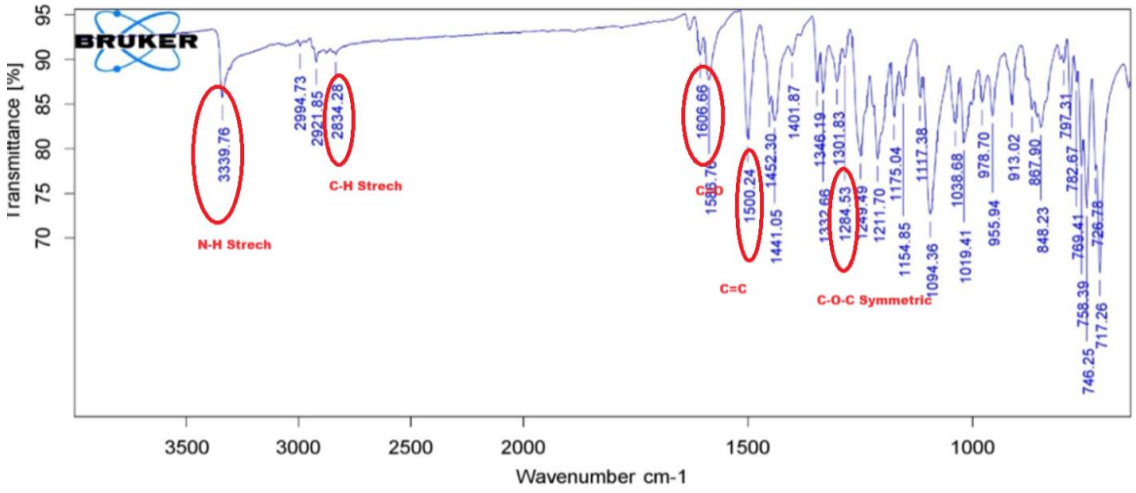

Fig. 1: Carvedilol FTIR spectrum

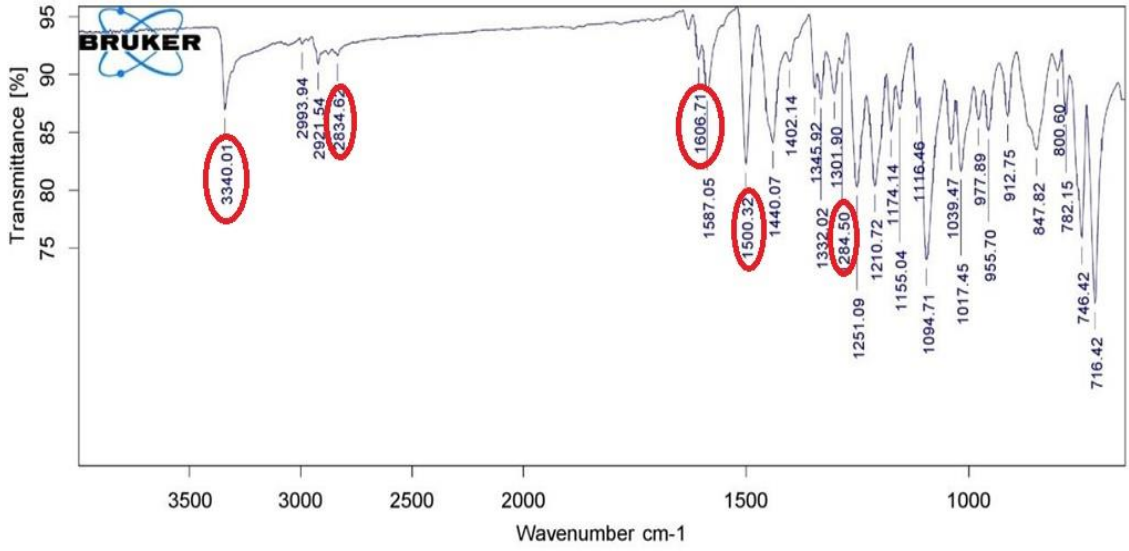

Fig. 2: FT-IR spectra of carvedilol with SSS

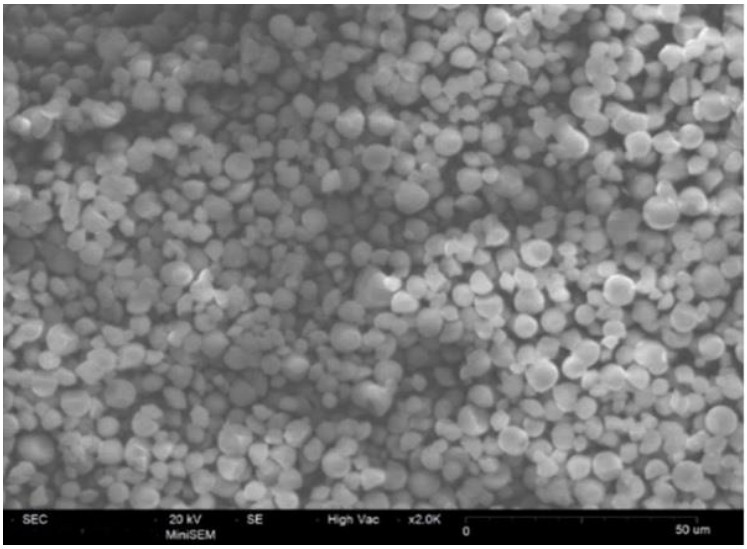

Fig. 3: SEM of the SSS

Tablet evaluation (s)

Weight variation

The weights of 10 tablets for each formulation are provided in table 4. The USP allowable weight variation for 100 mg tablet weight is±10 % (90-100 mg). All the formulation weights are well within the±5 % range. The results are indicative that the prepared tablets were consistent in weight with allowable weight variation (table 4) ranging from 98.77±1.95 to. 102.35±2.03 these results are in line with the a. Kusuma *et al.* [22].

Thickness

The thickness for ten tablets was measured by using the vernier callipers, and the results were found to be well within the limit of 3.39± 0.12 to 3.52± 0.12. Results are provided in table 4.

Hardness

The tablet's hardness was discovered to be 3.8±0.93 to 4.4±0.65 kg/cm^2. This hardness for the 6 mm tablet is found to be good enough to withstand while handling. Data is provided below in table 4.

Table 4: Weight variation, hardness, thickness, and friability of F1-F8

S. No.	Weight variation (mg/tab)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
F1	99.11±1.90	4.1±0.65	3.48± 0.13	0.11±0.030
F2	100.59±1.49	4.0±0.78	3.51± 0.12	0.25±0.074
F3	98.77±1.95	3.9± 0.26	3.51± 0.09	0.10±0.076
F4	101.53±1.72	3.8±0.93	3.39± 0.12	0.14±0.097
F5	101.03±2.27	4.1±0.87	3.41± 0.10	0.12±0.085
F6	99.04±2.32	4.4±0.65	3.50± 0.11	0.13±0.036
F7	102.35±2.03	3.9±1.00	3.45± 0.11	0.16±0.023
F8	99.14±2.01	4.0±0.75	3.52± 0.12	0.15±0.191

Data are given as mean±SD, n=3

Friability

As per USP, the recommended friability range for the tablet dosage forms is Not More Than (NMT 1.0 %). Each formulation was tested three times for friability: The friability data (0.10±0.076 to 0.25±0.074) is indicative that the prepared tablets have good strength during further manufacturing unit operations like packing. The friability data is provided in table 4, and these findings are consistent with other FDT researcher inputs [23].

Drug content

The drug composition of pills is measured and reported in table 5. As per the USP, the drug content of the formulations should be 90-110 % of the labelled claim. The formulations F1-F8 were well, having the drug content well within this limit. So, it is clear that the tablets have a sufficient amount of carvedilol for use. These results are in line with the research by A Kusuma *et al.* [24].

WT and water absorption ratio

The WT for FDTs should be as little as possible. The shorter WT indicates that the formulation will be hydrolytically fast and processed fast to get the active moiety into the molecular level for its defined therapeutic action. The WT(s) observed are provided in table 5, and the order of WT increases is F2<F6<F4<F5<F7<F8<F3<F1. The best formula had a WT of 24±0.87 sec, which was similar to the Jyotsana Madan *et al.* [25], who reported a WT of 32.66±1.87 seconds for tablets. The ability of the pill/tablet to absorb water and dissolve quickly is known as the water absorption ratio. The data is provided in table 5, and it is F8>F6>F2>F4>F7>F5>F3>F1. The water absorption ratio of F2 was 87±0.58% was higher than that of tablets (74.48%) manufactured by Kalpesh Gaur A., [26].

DT

Disintegration/degradation was performed on six tablets, and data was reported in table 6. The DT findings suggest that the decreasing order of DT of the formulations is F1>F3>F8>F7>F5>F4>F2>F6. The commercial superdisintegrant SSG was found to have less disintegration time, followed by the new natural superdisintegrant. The DT of F2 was found to be 22±1.38 sec, which was shorter than that of tablets (47±02 sec) manufactured by Nani Parfati *et al.* [27].

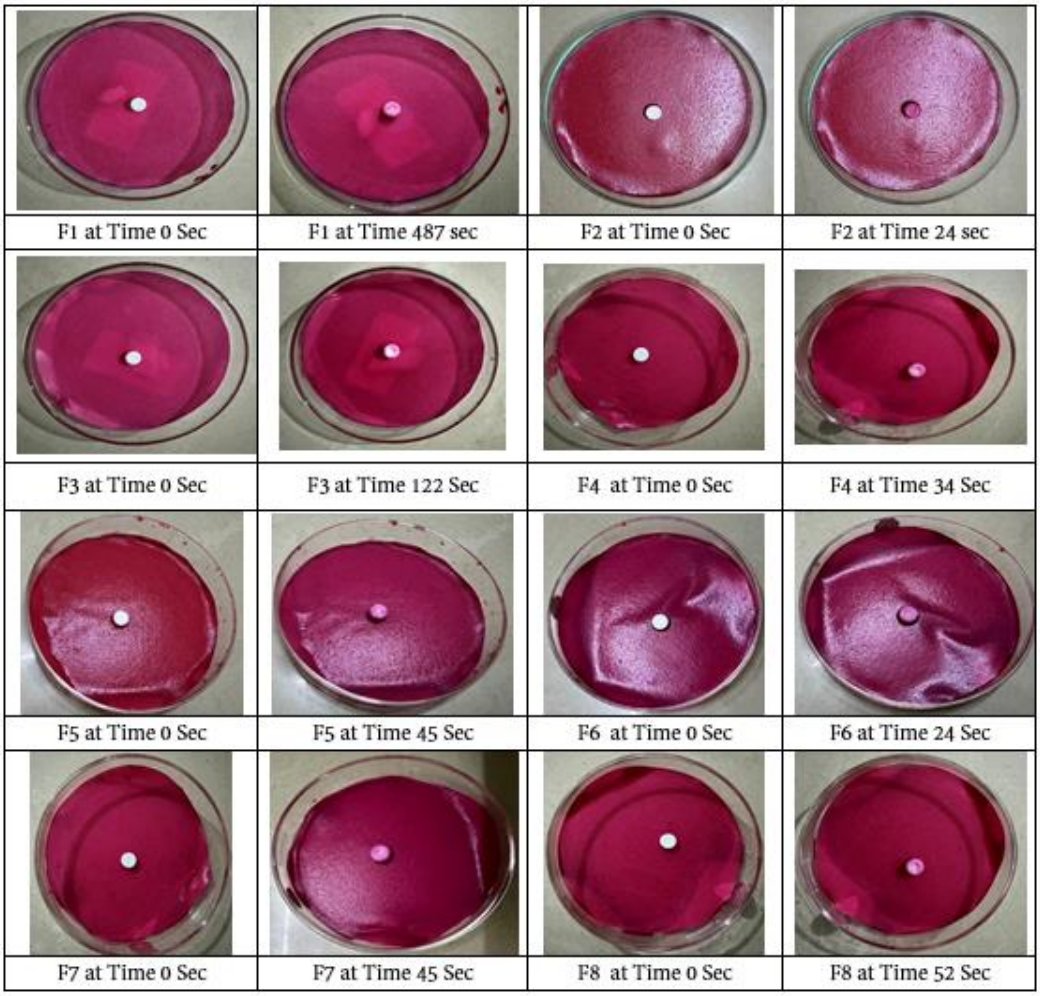

Fig. 4: Wetting time of C-FDTs

Table 5: Drug content, WT, water absorption ratio and DT of F1-F8 is provided below

S. No.	Drug content (mg/tab)	WT (sec)	Water Absorption ratio (%)	DT(Sec)
F1	98.21±1.29	487±2.65	13± 1.51	575± 10.88
F2	98.59±0.48	24±0.58	87± 0.58	22±1.38
F3	96.77±0.78	122±3.06	48± 2.15	120±3.61
F4	98.53±0.82	34±1.53	84± 2.97	24±1.03
F5	98.03±0.95	49±2.08	73± 2.27	55±1.94
F6	98.05±0.28	24±2.65	88± 0.99	20±0.82
F7	96.85±0.83	45±1.00	73± 1.78	58±1.87
F8	98.19±0.85	52±2.65	93± 0.50	59±2.16

Data are given as mean±SD, n=3

***In vitro* dissolution and dissolution efficiency at 10 min**

The *in vitro* dissolution investigations carried out under guidelines specified in the materials and techniques are given in table 6. By using the dissolution efficiency formula, dissolution efficiency at 10 min it was calculated and provided in table 6. From the dissolution data, it is clear that formulation 2 (releasing 99 % in 10 min) has a more rapid release than any other formulation. The dissolution efficiency at 10 min is indicative that formulation 2 (F2) is 44 times more efficient than the base formulation (F1).

Table 6: Dissolution and dissolution efficiency of all the formulations

Formulations	F1	F2	F3	F4	F5	F6	F7	F8
PD10 (%)*	3.40±1.39	99.05± 0.21	37.30±0.65	88.57± 1.45	64.80± 1.15	86.90±2.66	88.85±1.65	93.42±1.99
$	0.0126	0.5571	0.0888	0.4227	0.2410	0.5449	0.4260	0.4682
$$	-	44	7	34	19	43	34	37

Data are given as mean±SD, n=3. $: Dissolution Efficiency at 10 min. $$: No of folds' increase in Dissolution Efficiency

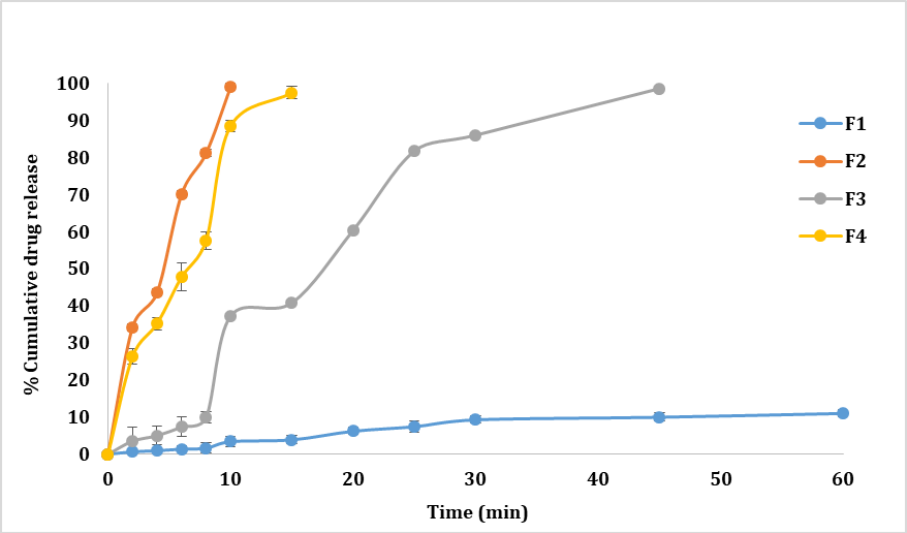

Fig. 5: C-FDTs dissolution profiles (F1 – F4). Data are given as mean±SD, n=3. Error bars indicate SD values

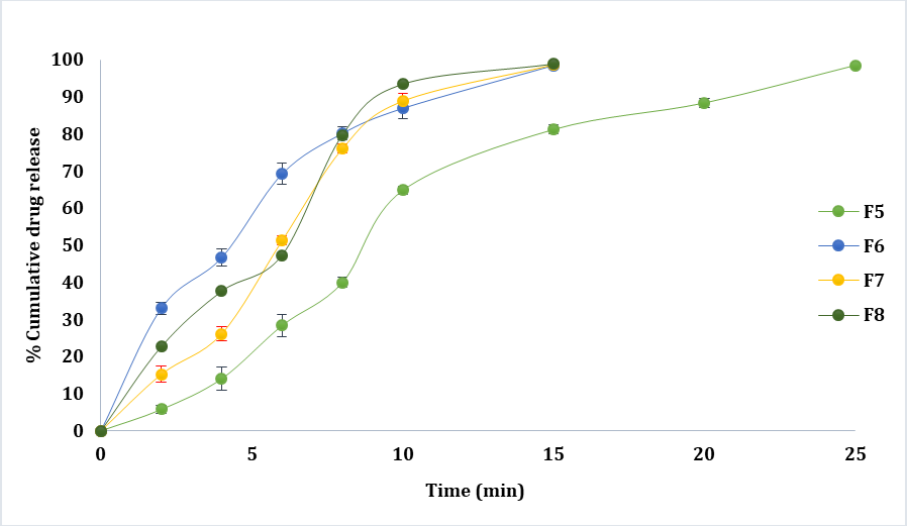

Fig. 6: C-FDTs dissolution profiles (F5 – F8). Data are given as mean±SD, n=3. Error bars indicate SD values

Factorial design

The adopted full factorial Design experimental data was run on the experiment's Design (DOE) software to understand the impact of each independent superdisintegrant and the interaction of each other at the level of 0 and 5 % were evaluated. WT, DT, PD10 and dissolution efficiency at 10 min intervals are the four CQAs that were chosen for the investigation. The independent variables were named SSS (A), psyllium husk (B) and SSG (C). The polynomial equations were written as equations no 1, 2, 3 and 4

$$\mathbf{WT} = 104.625 - 71.125\,A - 41.375\,B - 62.125\,C + 50.875\,AB + 66.625\,AC + 47.375\,BC - 42.875\,ABC \text{ -----Equation 1}$$

$$\mathbf{DT} = 116.625 - 85.375\,A - 51.375\,B - 68.625\,C + 61.625\,AB + 76.875\,AC + 61.875\,BC - 52.625\,ABC \text{ -----Equation 2}$$

$$\mathbf{PD10} = 70.2863 + 21.6987\,A + 6.74875\,B + 13.2063\,C - 7.73875\,AB - 15.0312\,AC + 0.89375\,BC + 3.35625\,ABC \text{ -----Equation 3}$$

$$\mathbf{Dissolution\ efficiency\ at\ 10\ min} = 0.345163 + 0.153062\,A + 0.0062625\,B + 0.0748625\,C - 0.0590375\,AB - 0.0665375\,AC + 0.0208125\,BC - 0.0063875ABC \text{ -----Equation 4}$$

The factorial design employed here is 2^3 designs. The model was run with the measured values of WT, DT, PD10 and dissolution efficiency. Based on the experimental results, the model has given the interaction effect for each superdisintegrant and also for the combination of disintegrants. The positive and negative impact indicates how the CQA is moving with the individual and combination inputs of independent variables. Using Design Expert 7.11 software, surface response curves and contour plots were created after the equation was generated. The effect of independent superdisintegrants SSS (A), psyllium husk (B), and SSG (C) is shown in table 7.

The contour charts and response surface charts are made considering the formulation results and provided in the below fig. from fig. 7-18. These fig. indicate that the concentration of superdisintegrants on WT, DT, PD10 and dissolution efficiency is 4-5 %. The F1-F8 formulations were studied for DT, WT, % drug release and dissolution efficiency. The factorial design plots are as follows:

DT and WT

Response and contour plots demonstrate that when the concentrations of SSS (A), psyllium husk (B), and SSG (C) increase, the DT and WT of FDTs decrease. The main, as well as interacting results from independent factors (A, B, C, AB, AC, BC, and ABC) on

the DT and WT were clarified further by the use of 3D response surface plots and contour plots. The interaction of A and B on DT and WT are depicted in fig. 7 and fig. 10. Fig. 8 and fig. 11 illustrate how A and C affect DT and WT. The interaction of B and C on DT and WT were depicted in fig. 9 and 12. The contour plots are linear; the concentration of SSS was inversely proportional to the DT and WT, which indicates that as the proportion of SSS increases, the DT and WT of FDTs decrease.

Table 7: Interactions between superdisintegrants and their effect on WT, DT, Cumulative % drug dissolved in 10 min and dissolution efficiency in 10 min

Superdisintegrants' Interactions	Effect on			
	WT	DT	Cumulative % drug dissolved in 10 min	Dissolution efficiency in 10 min
A	+	+	+	+
AB	-	-	-	+
AC	-	-	-	-
B	+	+	+	+
BC	-	-	+	+
C	+	+	+	-
ABC	+	+	+	+

"+" indicates positive effect means less WT, less DT, high dissolution at 10 min and good dissolution efficiency, "-" Indicates that there is NO favorable impact, like more WT, more DT, less dissolution at a 10 min time point, and low dissolution efficiency.

The cumulative percentage of drug dissolved in ten minutes and dissolution efficiency at 10 min

The results of SSS (A), psyllium husk (B), and SSG (C), along with their interaction with PD10 and dissolution efficiency at 10 min, were tabulated in table 7. The interaction of A and B on dissolution and dissolution efficiency are depicted in fig. 13 and fig. 16. Fig. 14 and fig. 17 illustrate how A and C affect dissolution and dissolution efficiency. The interaction of B and C on dissolution and dissolution efficiency were depicted in fig. 15 and 18. The contour plots were linear. It demonstrates that when the concentrations of SSS (A), psyllium husk (B), and SSG (C) rise, they correspondingly increase the PD10 and dissolution efficiency at 10 min of FDTs.

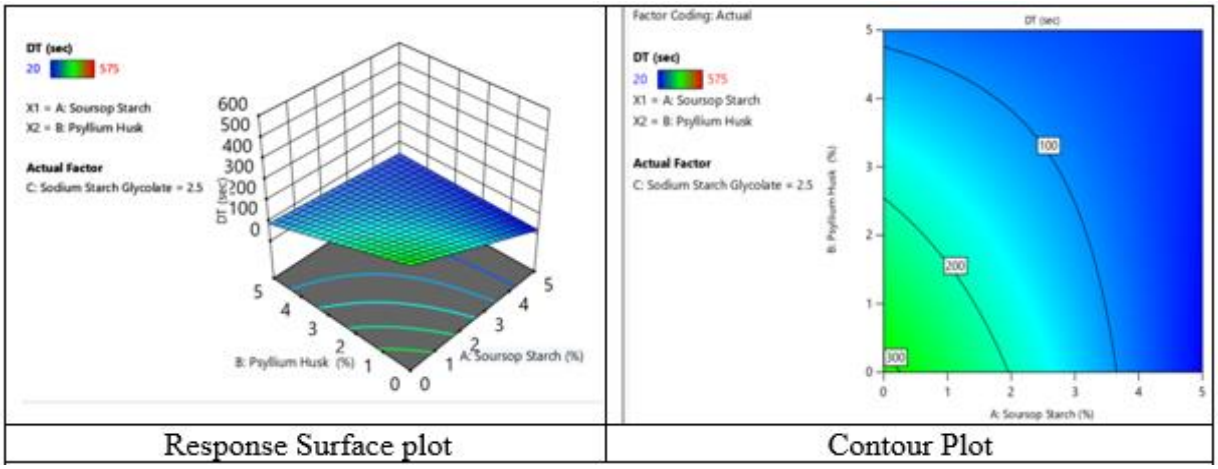

Fig. 7: Effect of A and B on DT

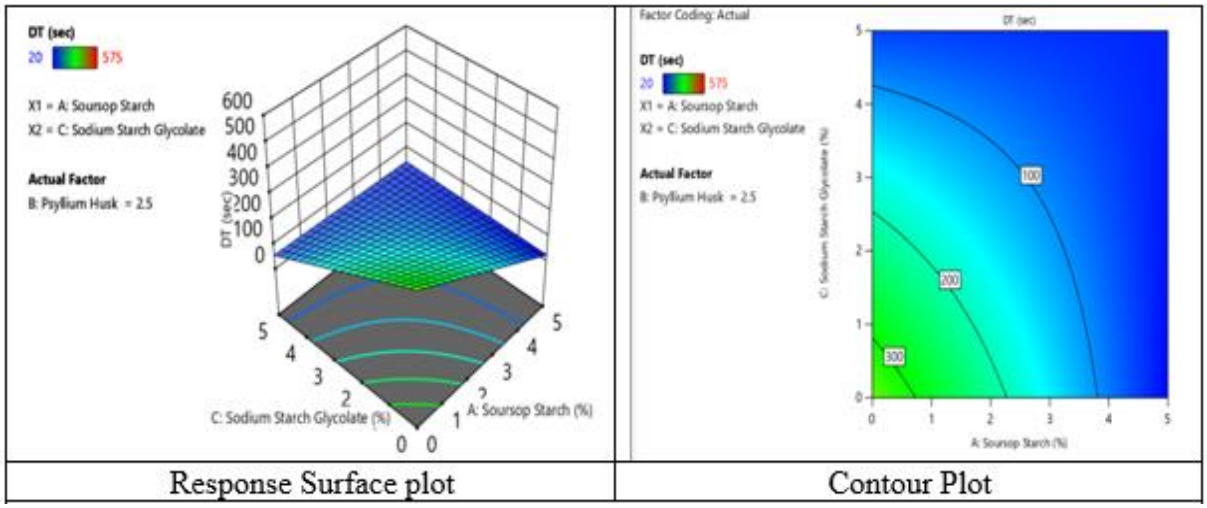

Fig. 8: Effect of A and C on DT

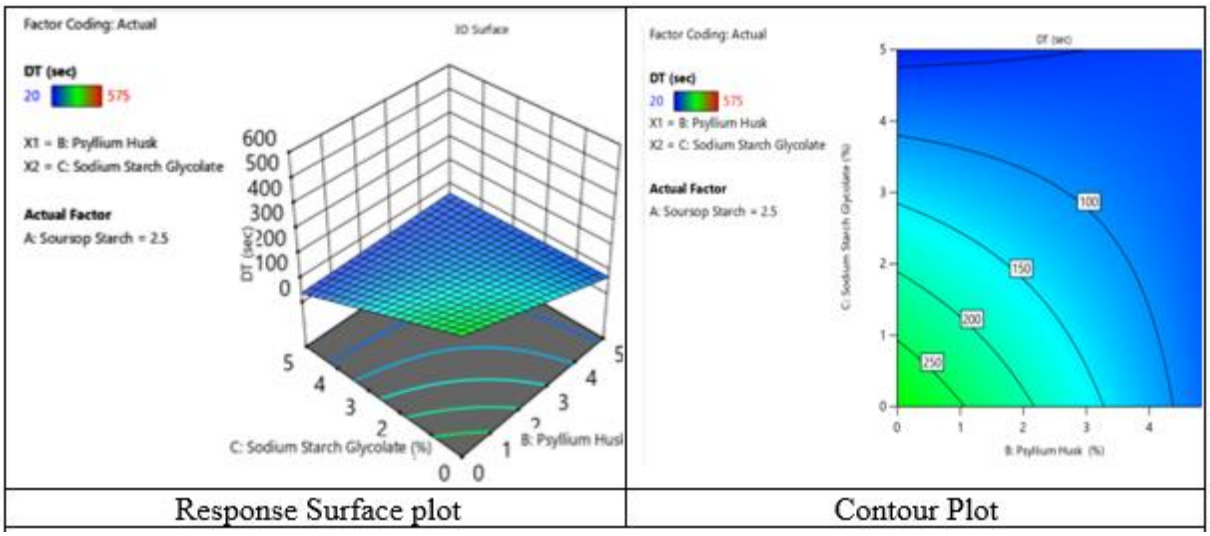

Fig. 9: Effect of B and C on DT

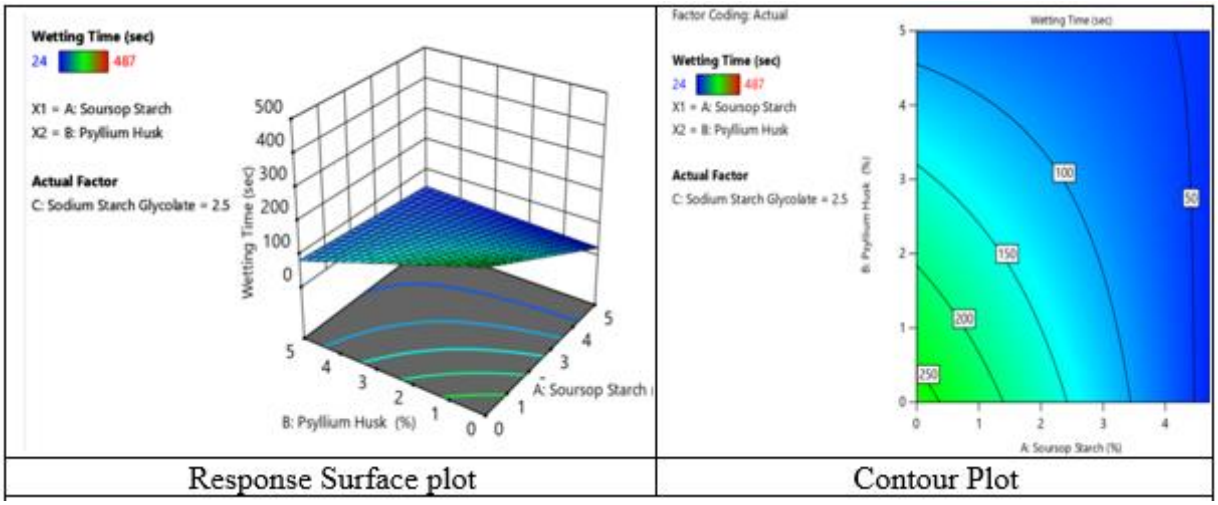

Fig. 10: Effect of A and B on WT

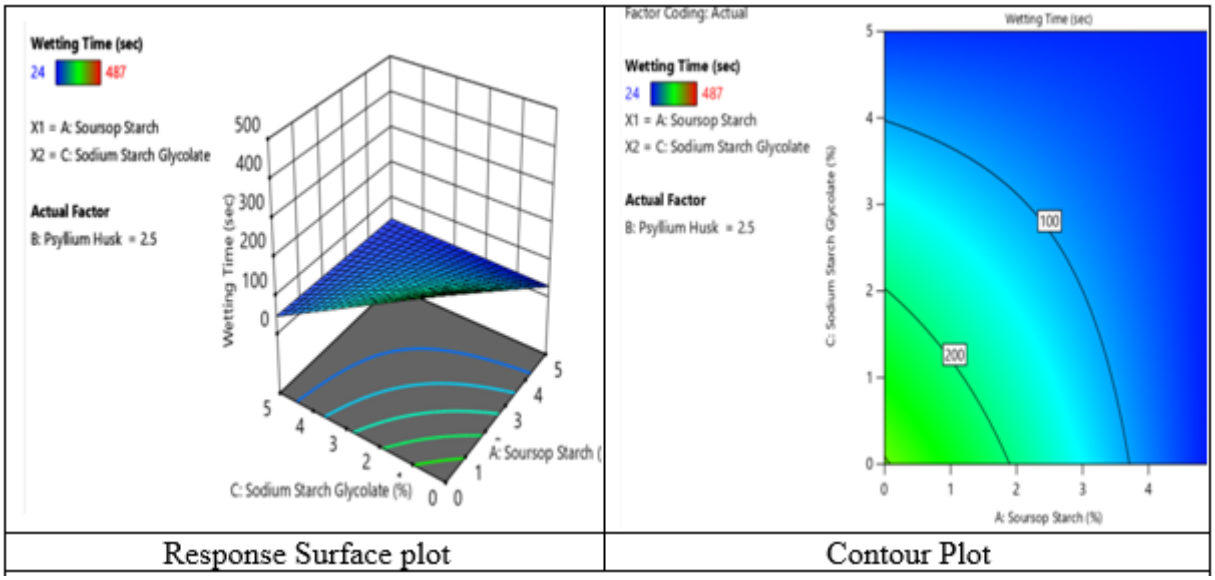

Fig. 11: Effect of A and C on WT

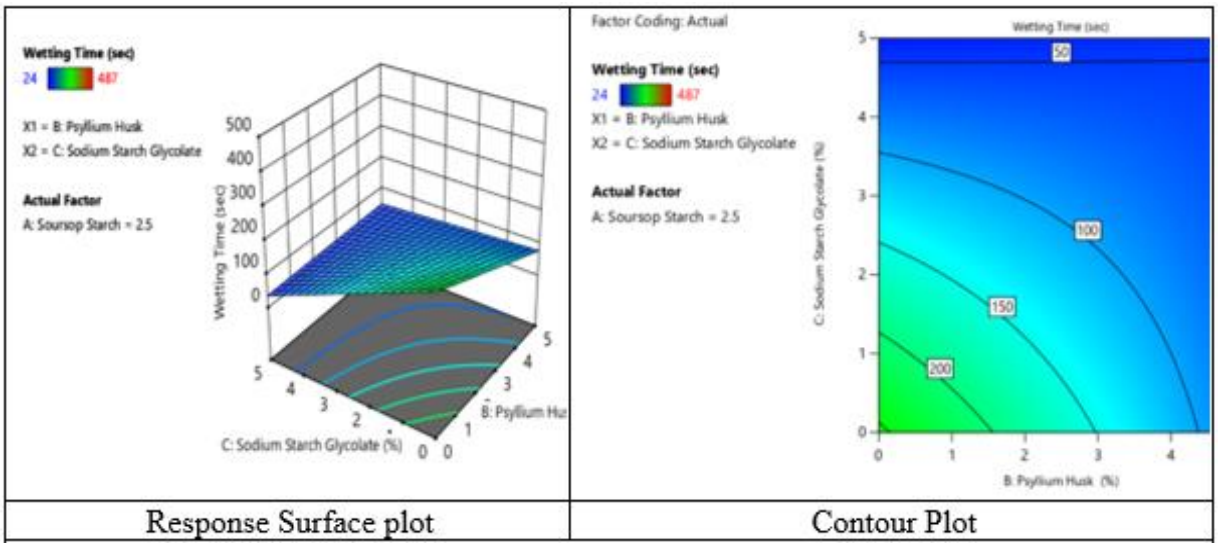

Fig. 12: Effect of B and C on WT

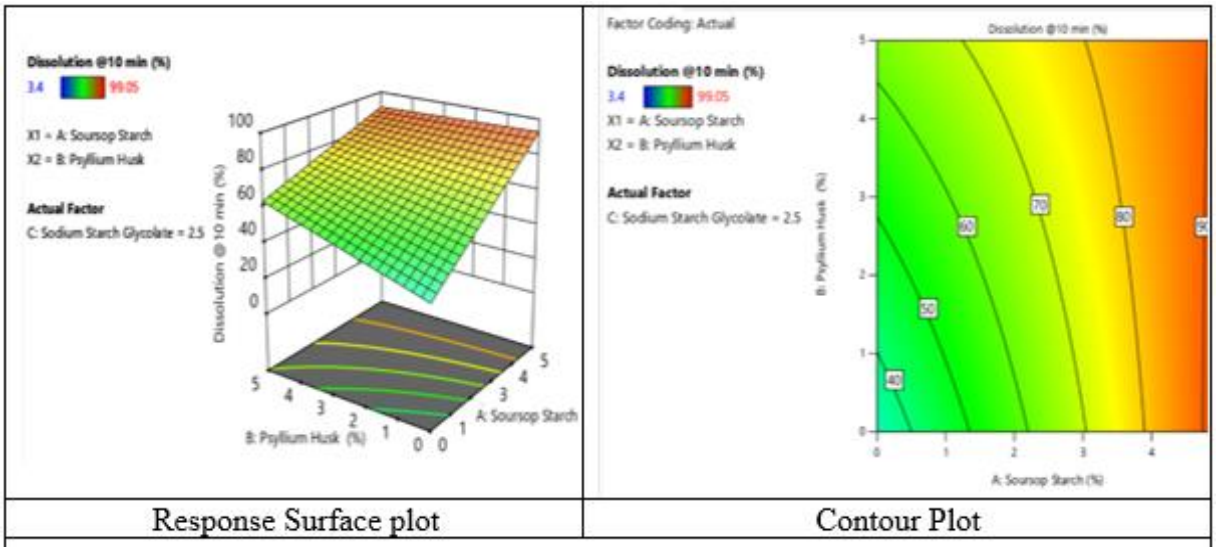

Fig. 13: Effect of A and B on dissolution

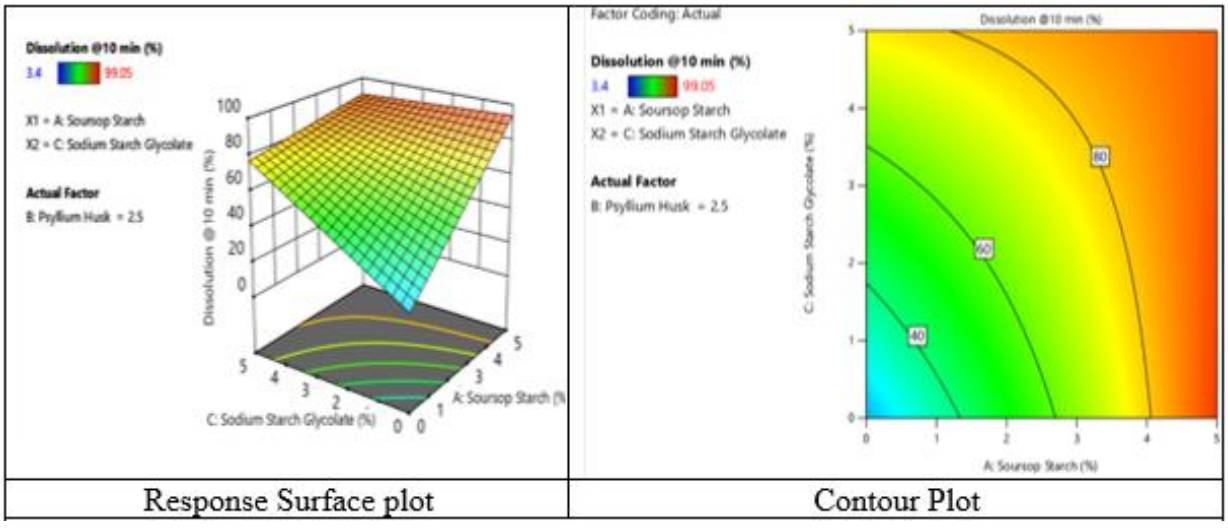

Fig. 14: Effect of A and C on dissolution

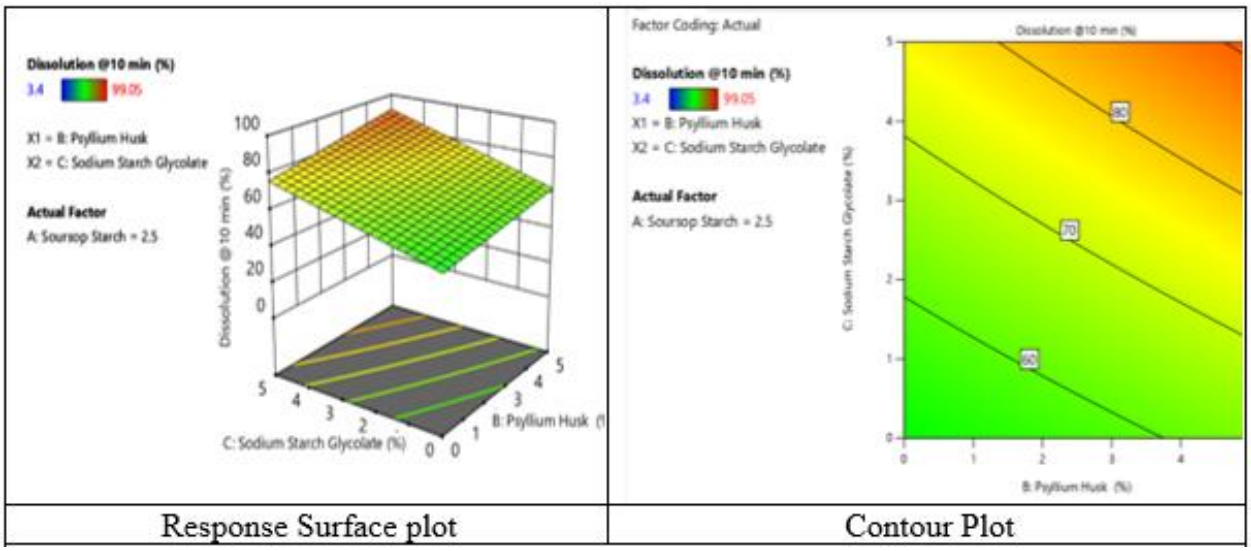

Fig. 15: Effect of B and C on dissolution

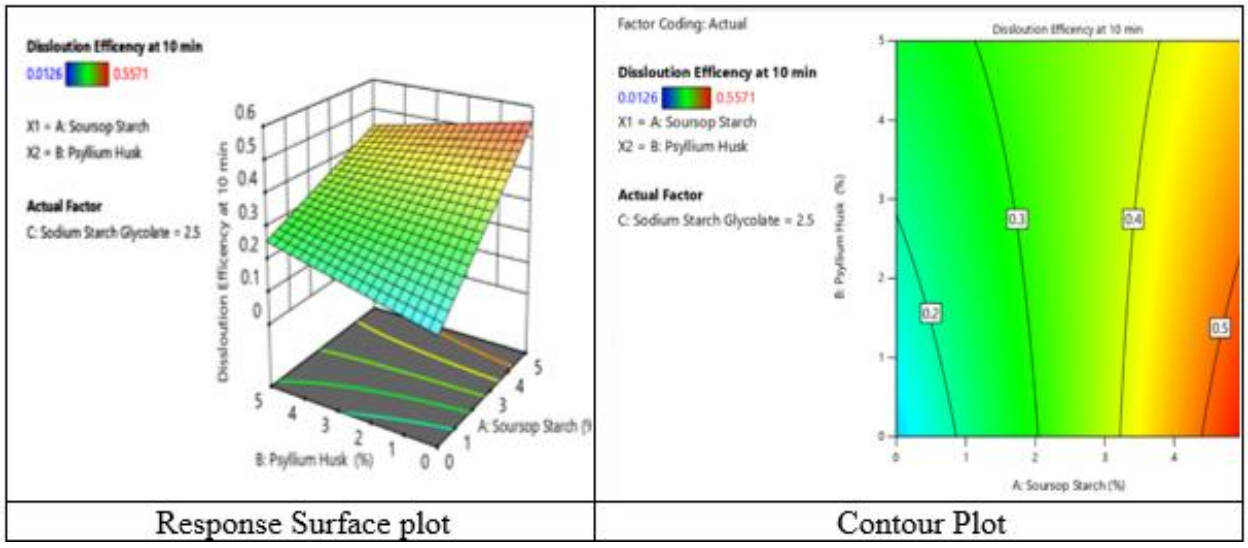

Fig. 16: Effect of A and B on dissolution efficiency

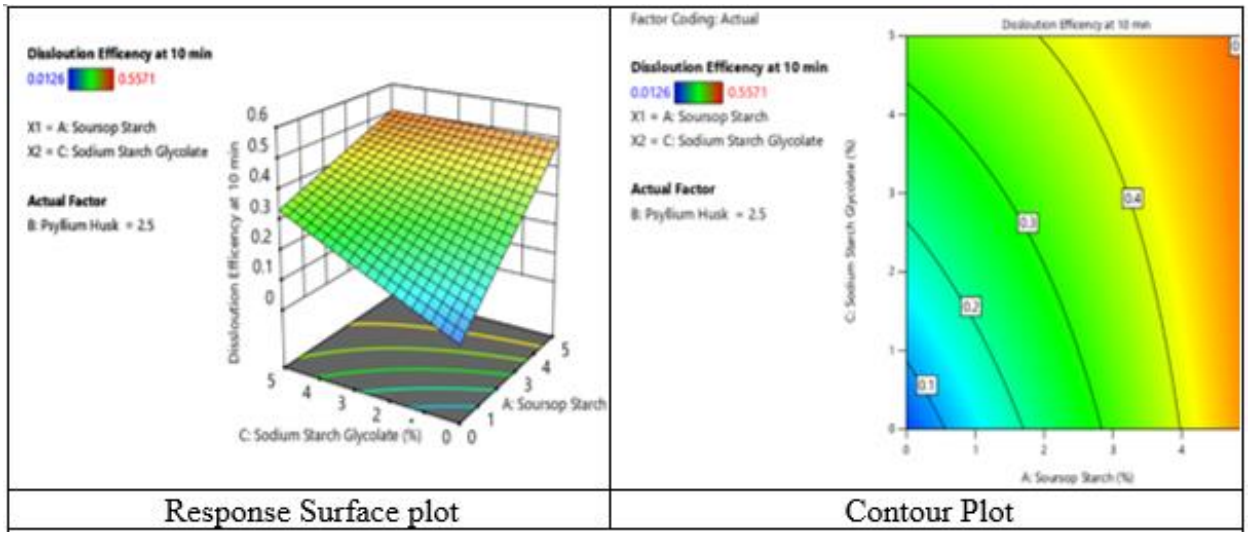

Fig. 17: Effect of A and C on dissolution efficiency

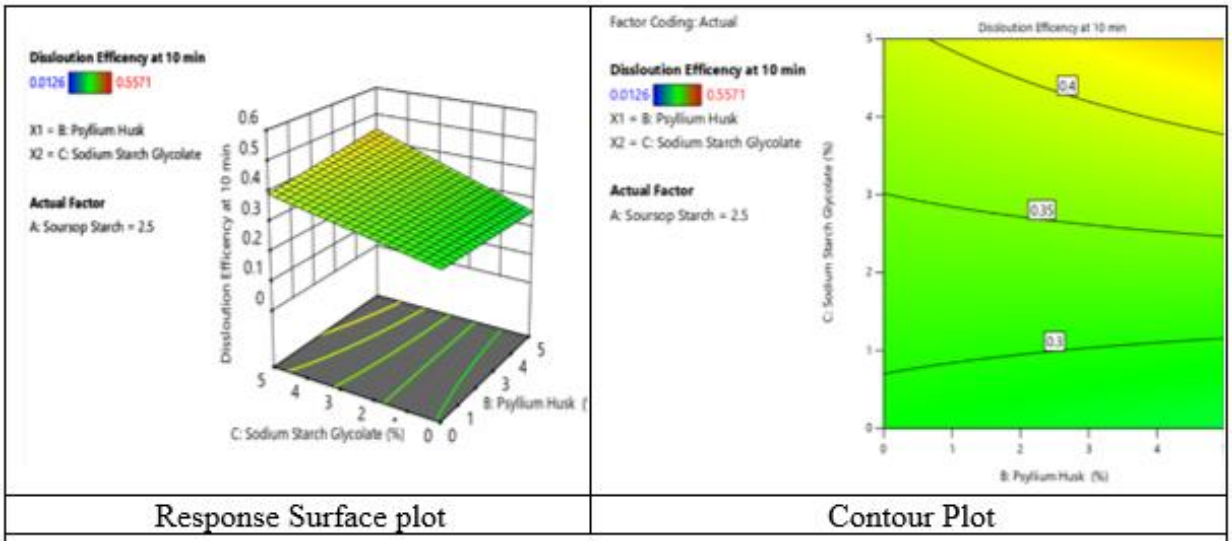

Fig. 18: Effect of B and C on dissolution efficiency

The factorial design reveals that the suggested range of superdisintegrant is from the 4-5 %. The isolated SSS alone (F2) at 5 % concentration is good enough for the desired DT, WT, maximal drug dissolution, and dissolution efficiency as other commercially available starches that are used in this study, i. e., Psyllium husk and SSG. Therefore, the F2 formula was regarded as an optimized formulation, indicating that SSS is a new natural superdisintegrant that can improve the dissolution of carvedilol.

Stability studies

The final formulation was exposed to accelerated stability conditions as per the International Conference on Harmonization (ICH) stability conditions 40 °C± 2 and 75 %±5 RH for 180 d, and the formulation was found to be stable. The stability data is provided below: There was No significant difference in any of the CQAs of the drug product till the 180 d study period.

Table 8: Accelerated stability studies of F2 formulation

Days	Weight variation (mg/tab)	Hardness (kg/cm²)	Drug content (%)	DT (Sec)	WT (Sec)	Dissolution (%)
Initial	100±1.49	4.30±0.79	98.59±0.48	22±1.38	24±0.58	99.05±0.21
30	101± 1.99	4.50±0.68	96.64±1.12	22±1.72	25±1.00	98.65±0.70
60	101± 2.17	4.10±0.91	96.80±1.05	22±2.07	23±2.00	98.55±0.61
90	102± 1.58	4.31±0.82	96.61±0.98	21±2.10	25±1.15	98.20±0.85
180	101± 2.39	4.50±0.99	97.28±0.84	21±1.05	23±1.73	97.50±1.28

All values are reported as mean±SD n=3.

CONCLUSION

In a nutshell, this research study is indicative that the isolated soursop starch is suitable to use as a natural biodegradable, biocompatible superdisintegrant at 4-5 % level in the formulation of BCS class-II antihypertensive drug carvedilol. The dissolution at 10 min for the prepared fast-dissolving tablets is promising that the amount of drugs released has significantly increased with the proposed superdisintegrant. The dissolution efficiency at 10 min is 44 times higher than that of no superdisintegrant formulation (F1). This may further amplify the bioavailability, dissolution, and solubility of the carvedilol by using this new natural superdisintegrant. In addition, the formulations have shown NO significant effect in any of the formulation characteristics like description, assay, and dissolution up to 180 d at 40 °C and 75 % RH. So, the formulation shelf life was extrapolated as per the ICH Q1 E, and it was found to be 24 mo.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Mr. Vasudeva Reddy is the research scholar who performed the research work and drafted the paper. Dr. R. Santosh Kumar is the research supervisor, designed the work, monitored the research outcomes and finalized the research paper for submission.

CONFLICT OF INTERESTS

The authors disclose no conflicts of interest.

REFERENCES

1. Anusha K, Rada SK. Oral disintegrating tablets: best approach for faster therapeutic action of poorly soluble drugs. Egypt Pharm J. 2021;20(2):105-14. doi: 10.4103/epj.epj_63_20.
2. Us department of health and human services food and drug administration center for drug evaluation and research (CDER). Guidance for industry: orally disintegrating tablets; 2008.
3. Chauhan K, Solanki R, Sharma S. A review on fast dissolving tablet. Int J App Pharm. 2018 Nov;10(6):1-7. doi: 10.22159/ijap.2018v10i6.28134.
4. Dash GS, Murthy PN, Chowdary KA. Selection and optimization of most efficient superdisintegrant for the formulation of dispersible tablets of tramadol hydrochloride. Int J Pharm Pharm Sci. 2022 Jul 1;14(7):21-6. doi: 10.22159/ijpps.2022v14i7.43638.
5. Kawale KA, Autade NB, Narhare HS, Mhetrea RL. A review on fast dissolving oral film. Asian J Pharm Clin Res. 2023 Oct;16(10):7-17. doi: 10.22159/ajpcr.2023.v16i10.48099.
6. Prabhu P, Dubey A, Kamath K. Formulation and evaluation of fast dissolving tablets of lisinopril. Egypt Pharm J. 2015;14(1):56-64. doi: 10.4103/1687-4315.154723.
7. Aboud HM, El Komy MH, Ali AA, El Menshawe SF, Abd Elbary A. Development optimization and evaluation of carvedilol loaded

solid lipid nanoparticles for intranasal drug delivery. AAPS Pharm Sci Tech. 2016;17(6):1353-65. doi: 10.1208/s12249-015-0440-8, PMID 26743643.

8. Drugs carvedilol dosage. Available from: https://www.com/dosage/carvedilol.html.
9. Masih A, Kumar A, Singh S, Tiwari AK. Fast dissolving tablets: a review. Int J Curr Pharm Sci. 2017;9(2):8-18. doi: 10.22159/ijcpr.2017v9i2.17382.
10. Santosh KR, Sahiti M. Formulation and evaluation of statistically designed ibuprofen fast dissolving tablets employing starch glutamate as a novel superdisintegrant. Asian J Pharm Clin Res. 2019 Sep;12(11):85-94. doi: 10.22159/ajpcr.2019.v12i11.35308.
11. DE Los Santos Santos MA, Balois Morales R, Bello Lara JE, Leon Fernandez AE, Jimenez Zurita JO, Bautista Rosales PU. Phytochemical compounds in soursop fruit starches (*Annona muricata* L.). Rev Bio Cienc. 2023;10.
12. Nwokocha LM, Williams PA. New starches: physicochemical properties of sweetsop (Annona squamosa) and soursop (Anonna muricata) starches. Carbohydr Polym. 2009;78(3):462-8. doi: 10.1016/j.carbpol.2009.05.003.
13. Lachman L, Libermann HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd ed; 1991. p. 233-5.
14. Malaquias LF, SA Barreto LC, Freire DO, Silva IC, Karan K, Durig T. Taste masking and rheology improvement of drug complexed with beta cyclodextrin and hydroxypropyl-β-cyclodextrin by hot melt extrusion. Carbohydr Polym. 2018 Apr 1;185:19-26. doi: 10.1016/j.carbpol.2018.01.011, PMID 29421056.
15. Kumar SR, Annu K. Design optimization and evaluation of acyclovir fast dissolving tablets employing starch phthalate a novel superdisintegrant. Asian J Pharm Chem Res. 2019;12(11):3547. doi: 10.22159/ajpcr.2019.v12i11.35474.
16. Preethi GB, Banerjee S, Shivakumar HN, Ravi Kumar M. Formulation of fast dissolving tablets of doxazosin mesylate drug by direct compression method. Int J App Pharm. 2017;9(5):22-8. doi: 10.22159/ijap.2017v9i5.18168.
17. Kumar RS, Yagnesh TN, Kumar VG. Optimization of ibuprofen fast dissolving tablets employing starch xanthate using 2^3factorial design. Int J App Pharm. 2017;9(5):51-9. doi: 10.22159/ijap.2017v9i5.19707.
18. Lubis MS. Evaluation of disintegration and dissolution test of metoclopramide orally disintegrating tablet using maltodextrins from banana starch (Musa paradisiaca L) as superdisintegrant. Asian J Pharm Clin Res. 2018 Apr;11(13) Suppl 1:210-3. doi: 10.22159/ajpcr.2018.v11s1.26609.
19. Kumar R, Patil S, Patil MB, Patil SR, Paschapur MS. Formulation evaluation of mouth dissolving tablets of fenofibrate using sublimation technique. Int J Chemtech Res Coden. 2022;24(1):412-6.
20. Mahajan N, Deshmukh S, Farooqui M. Degradation kinetics of carvedilol pharmaceutical dosage forms (tablets) through stress degradation study. Int J Curr Pharm Sci. 2022 Jan;14(1):54-9. doi: 10.22159/ijcpr.2022v14i1.44112.
21. Jire DS, Gosavi NS, Badhe RB, Jagdale DH. Mouth dissolving tablet: a novel drug delivery system. Asian J Pharm Res. 2021;11(3):180-6. doi: 10.52711/2231-5691.2021.00033.
22. Kusuma A, Santosh Kumar R. Optimization of fast dissolving tablets of carvedilol using 2^3 factorial design. Int J App Pharm. 2024 Jan;16(1):98-107. doi: 10.22159/ijap.2024v16i1.49535.
23. Panwar S, Nagori V, Chauhan J, Darwhekar GN, Jain DK. Formulation and evaluation of fast-dissolving tablet of piroxicam. Am J Pharm Tech Res. 2011;1(3):255-73.
24. Kusuma A, Santosh KR. Optimization of starch hyaluronate as a new superdisintegrant in the formulation of fast-dissolving tablets of nisoldipine. Eur Chem Bull. 2023;12(3):1606-32.
25. Madan J, Sharma AK, Singh R. Fast dissolving tablets of aloe vera gel. Trop J Pharm Res. 2009;8(1):63-70.
26. Gaur AK, Lalit K, Tyagi A, Kori ML, Sharma CS, Nema RK. Formulation and characterization of fast disintegrating tablet of aceclofenac by using sublimation method. Int J Pharm Sci Drug Res. 2011;3(1):19-22.
27. Parfati N, Rani KC, Charles N, Geovany V. Preparation and evaluation of atenolol-β-cyclodextrin orally disintegrating tablets using co-process crospovidone sodium starch glycolate. Int J App Pharm. 2018;10(5):190-4. doi: 10.22159/ijap.2018v10i5.27982.