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Original Article

Formulation and Optimization of Fast Dissolving Thin Strips of Desvenlafaxine HCl by Using Quality by Design (QbD) Approach

Ganesh Kumar[1], Meenakshi Bhatt[2], Archana Dhyani[3,*]

[1]Department of Pharmaceutics, Himalayan School of Pharmaceutical Sciences, Swami Ram Himalayan University, Dehradun, Uttarakhand, INDIA.
[2]Food and Drug Administration, Price Monitoring Regulatory Unit, FDA, Dehradun, Uttarakhand, INDIA.
[3]Department of Pharmaceutics, School of Pharmacy, Graphic Era Hill University, Dehradun, Uttarakhand, INDIA.

ABSTRACT

Aim: The present work was aimed to formulate and optimize fast dissolving thin strips of Desvenlafaxine Hydrochloride using QbD. **Materials and Methods:** The solvent casting method was used to formulate fast dissolving thin strips. The drug (Desvenlafaxine HCl), polymer (pullulan), super disintegrant (Croscarmellose sodium), plasticizer (Poly Ethylene Glycol-(PEG-400), saliva stimulating agent (citric acid), sweetening agent (mannitol and aspartame) and water (solvent) were used in the preparation of the strips. The study involved a 3-level factorial design in which the effect of Pullulan Polymer (A), Croscarmellose Sodium (B) and Poly Ethylene Glycol (C) on 3 response variables disintegration Time (X), percent swelling index (Y) and percent Dissolution Efficiency ($DE\%_{15}$) were analyzed. Results: From the studies, it was found that F12 formulation (containing 30% pullulan, 5% CCS and 7.5% PEG) was the optimized formulation that showed improved important strip characteristics including disintegration time, swelling index and dissolution efficiency after 15 min.

Keywords: Crospovidone, Disintegration time, Dissolution efficiency, Dysphagia, Fast dissolving strips, Microcystalline Cellulose, Quality by Design.

Correspondence:
Dr. Archana Dhyani
Department of Pharmaceutics, School of Pharmacy, Graphic Era Hill University, Dehradun, Uttarakhand, INDIA.
Email: archana.dhyani@gmail.com

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INTRODUCTION

The oral route is the 1st choice for most patients for the administration of therapeutic agents.[1] In the market, approximately 60% of solid oral dosage forms are accessible in various forms such as tablets and capsules.[2] According to estimates, 30-40% of elderly individuals suffer from dysphasia.[3] Fast dissolving thin strips appear as an alternative technique to deliver the drug among pediatrics and geriatrics. The Fast-Dissolving Thin Strips (FDTS) are better than Fast Disintegrating Tablets (FDTs), which are connected with choking and friability issues. It can be easily used for dysphasic and schizophrenic patients and can be taken without water. For the formulation of FDTSs, many procedures are used; the most common are solvent casting and spraying methods. Hydrophilic polymers are commonly used in the preparation of FDTS, which allow strips to dissolve fast, releasing the Active Pharmaceutical Ingredient (API) within seconds.[4,5]

Desvenlafaxine HCl is selective serotonin and nor-epinephrine reuptake inhibitor and is used to treat depressive disorders in adults. As per Biopharmaceutical Drug Disposition Classification System (BDDCS) Desvenlafaxine is a class 3 drug (high solubility, poor metabolism, low permeability) while as per Biopharmaceutics Classification System (BCS), it is class 1 (high solubility, high permeability) compound which makes it a suitable candidate for FDTS. The current research aimed to develop and optimize fast dissolving thin strips of Desvenlafaxine HCl for ease of administration, patient compliance and can be easily given to pediatrics and geriatrics. It also offers the advantage of bypassing hepatic metabolism, resulting in increased bioavailability of drugs. The basic objective of the study was to formulate and evaluate fast dissolving thins strips of Desvenlafaxine HCl by Quality by Design. For the fabrication of strips, pullulan, cross carmellose, Polyethylene glycol was used. The strip was prepared by solvent casting method. Once the strips were prepared, it was evaluated for pH, folding endurance, moisture uptake, swelling index, disintegration time and dissolution efficiency. The effect of pullulan, croscarmellose sodium and PEG-400 on disintegration time, swelling index and dissolution efficiency was determined by contour plot and response surface plot.[6]

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MATERIALS AND METHODS

Desvenlafaxine was procured as a pure drug from Balaji Drugs in Mumbai, India. Central Drug House Ltd., New Delhi, supplied pullulan, croscarmellose sodium and polyethylene glycol. The excipients and reagents used in the study were of analytical quality. Quality Target Product Profile (QTPP) for Fast Dissolving Thin Strips (FDTSs) of Desvenlafaxine

QTPP as specified by the International Council for Harmonization (ICH) Q8 is an important component of a QbD strategy. The QTPP includes all product attributes essential to assure equal safety and efficacy of the product.[7]

Critical Quality Attributes (CQA)

CQA helps to obtain the desired product's physical, chemical, biological or microbiological properties within the specified limits. Excipients with the lowest disintegration time, highest swelling index and highest percent dissolution efficiency after 15 min were chosen as potential CQAs for the development of FDTS.[8,9]

Design of experiments (DoE)

Experimental Design is organized and orderly techniques for establishing a link between the parameters that factors affect process and the process's output. A 3-stage complete factorial design (3^3) was used for the creation and optimization of FDTSs. 3 variables were assessed at 3 levels in the design and experimental trials were carried out. In this study, a 3-level complete factorial design was utilized to optimize the 3 independent variables, Pullulan Polymer (A), Croscarmellose Sodium (B) and Poly Ethylene Glycol (C). The impact of these variables on disintegration Time (X), percent of the swelling index (Y) and percent Dissolution Efficiency were evaluated ($DE\%_{15}$). The experiments were designed using Stat-Ease Inc.'s Design Expert software version 13.0 (Minneapolis, MN, USA).[10,11] Table 1 represents the independent and dependent variables of factorial design.

Preparation of Oro-dispersible strips of Desvenlafaxine HCl

Each formulation's Plasticizer (PEG) and sweetener (mannitol) were measured out and put into a beaker with some distilled water. By adding more water, the necessary amount of polymer (pullulan) was added. One hour was given for the polymer to swell. Once the polymer was fully dissolved, the solution was agitated with a magnetic stirrer. Following that, the remaining distilled water was added together with the other excipients. The drug was introduced to the solution and vigorously stirred by means of magnetic stirrer. For each film 38 mg of the drug was used. The solution was poured in a Teflon-coated plate (area=2 cm^2). The films were carefully removed after being dried for 24 hr at 34°C in a universal oven. The film was kept in a desiccator at room temperature and wrapped in aluminum foil.[12,13] The composition of fast dissolving thin strip is mentioned in Table 2 which shows the different percentage of ingredients used in formulation.

Compatibility studies of drug and selected polymer by using FTIR

A Fourier transform infrared spectrophotometer (Perkin Elmer Spectrum Two TM) was used to determine the compatibility of Desvenlafaxine HCl with pullulan polymer, Croscarmellose sodium and other excipients. The drug sample was uniformly mixed with 100 mg of dry KBr powder. By exerting adequate high pressure with the device hydraulic press, the mixture is subsequently turned into a clear disc or pellets in a die. Dried potassium bromide was employed for the baseline correction. The spectrum was obtained by scanning a pellet made up of a combination of drug, polymer, excipients and potassium bromide between 400cm^{-1} and 4000 cm.[14]

Evaluation of DesvenlafaxineHCl Fast Dissolving Thin Strips (FDTS)

Thickness uniformity

The thickness of the formulated thin strip was determined using Vernier caliper.[15]

Table 1: Representation of independent variables and dependent variables of factorial design.

Independent Variables (Factors)	Low	middle	High
A: Pullulan (%).	30	40	50
B: Croscarmellose Sodium (%).	0	2.5	5
C: Poly Ethylene Glycol (PEG-400) (%).	5	7.5	10
Dependant Variable (Response).			
X: Disintegration Time (sec).			
Y: Swelling Index (%).			
Z: Dissolution efficiency at 15 min (%).			

Table 2: Composition of fast dissolving thin strip.

Formulation	Ingredients						
	Pullulan%	CCS%	PEG-400%	Citric Acid%	Mannitol (%)	Aspartame (%)	DesvenlafaxineHCl (mg)
F1	40	5	7.5	3.0	2.5	2.5	38
F2	30	0	10	3.0	2.5	2.5	38
F3	50	5	5	3.0	2.5	2.5	38
F4	30	2.5	5	3.0	2.5	2.5	38
F5	50	2.5	10	3.0	2.5	2.5	38
F6	30	2.5	7.5	3.0	2.5	2.5	38
F7	50	0	10	3.0	2.5	2.5	38
F8	30	5	10	3.0	2.5	2.5	38
F9	40	2.5	7.5	3.0	2.5	2.5	38
F10	40	00	10	3.0	2.5	2.5	38
F11	50	5	7.5	3.0	2.5	2.5	38
F12	30	5	7.5	3.0	2.5	2.5	38
F13	50	2.5	5	3.0	2.5	2.5	38
F14	50	00	5	3.0	2.5	2.5	38
F15	30	2.5	10	3.0	2.5	2.5	38
F16	40	2.5	5	3.0	2.5	2.5	38
F17	40	2.5	10	3.0	2.5	2.5	38
F18	50	5	10	3.0	2.5	2.5	38
F19	50	2.5	7.5	3.0	2.5	2.5	38
F20	50	0	7.5	3.0	2.5	2.5	38
F21	40	5	10	3.0	2.5	2.5	38
F22	30	0	7.5	3.0	2.5	2.5	38
F23	30	0	5	3.0	2.5	2.5	38
F24	40	0	5	3.0	2.5	2.5	38
F25	30	5	5	3.0	2.5	2.5	38
F26	40	5	5	3.0	2.5	2.5	38
F27	40	0	7.5	3.0	2.5	2.5	38

Folding endurance

The folding endurance of formulated strips was measured by folding the strips 1 cm^2 until the strips broke or cracked. The number of folds (the number of times the strips were folded at the same position without breaking) was recorded and the standard deviation was determined.[16]

Surface pH

A digital pH meter was used to determine the surface pH of the strips. 1 cm^2 strips were cut and dissolved in distilled water (5 mL). The pH of the strip was determined by allowing the electrode to equilibrate in contact with the solution for 1 min. The experiment was done 3 times with 3 strips from each formulation. The average result and standard deviation are computed and reported.[17]

Percent Moisture uptake

This test was performed to assess the physical stability of the strips under high humidity conditions. To calculate the percentage moisture uptake, 1 cm^2 strips were cut and weighed separately with a digital scale. The strip was then put in desiccators for 72 hr. After 72 hr, the strips were removed and reweighed after being subjected to a saturated solution of aluminum chloride. The average % moisture uptake of the strip was estimated using the following formula:[18]

$$\% \text{ Moisture uptake} = \frac{\text{Final weight} - \text{Initial Weight} \times 100}{Final\ Weight}$$

Drug content uniformity

A 1 cm^2 strip was dissolved in 25 mL of Phosphate Buffer Solution (PBS) pH 6.8. The solution was then solicited for 15 min with a

sonicator to completely dissolve the strip. The solution was then filtered using Whatman filter paper. Dilution was performed as needed and the solution was tested for absorbance using a UV-spectrophotometer (Elico SL-210) at 224 nm. The strips were acceptable when the drug content range was between 85 to 115%. This experiment was performed 3 times with 3 strips from each formulation and absorbance was recorded to produce an average value, which was then calculated to ascertain the percent drug content.[19]

Swelling index

The swelling index of the strip was studied in a 6.8 pH PBS. A strip was weighed and put in a stainless-steel wire sieve that had already been weighed. The strip-containing mesh was immersed in 15 mL of 6.8 pH buffer in a petri dish. At each interval (1 min), the rise in the strip weight was calculated until a steady weight was observed. In this test, 3 strips of each formula were used. The formula used to calculate the degree of swelling:[20]

$$SI = \frac{Wt - W\,o}{W\,o}:$$

Where, SI=Swelling index, W_t=Weight of the strip at time "t" and W_O=Weight of the strip at t=0.

Disintegration Test

2-3 mL of distilled water was poured into the petridish and a 1 cm^2 strip was placed on top of the petridish. The time at which the strip completely dissolves was recorded. 3 strips from each formulation were used. Following that, the average and standard deviation were computed.[21]

Dissolution Studies

Dissolution experiments were carried out utilizing a USP (Type II) dissolution apparatus. As a dissolution medium, 500 mL of PBS6.8 pH was employed, and the temperature was set at 37±0.5°C. 1 cm^2 strips were placed in the dissolution apparatus and the liquid medium was agitated at 50 rpm. Aliquots (5 mL) of samples were removed from the solution at 1 min intervals and the same volume was maintained by replacing it with a freshly prepared dissolution medium. The absorbance of the samples was measured at 224 nm using a UV-visible spectrophotometer against a suitable blank.[22,23]

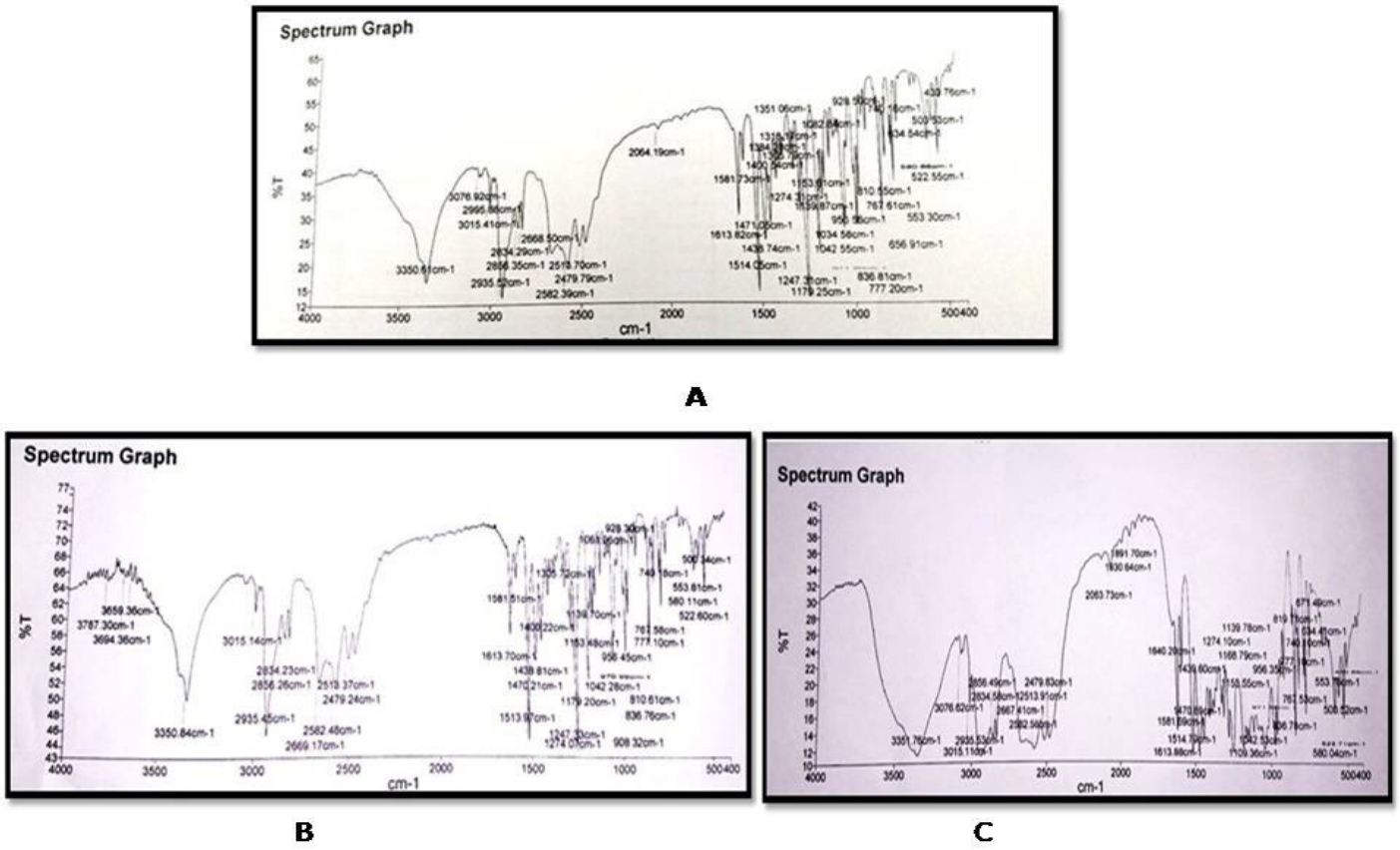

Figure 1: (A) FTIR spectra of Desvenlafaxine HCl, (B): FTIR spectra of Desvenlafaxine HCl+Pullulan Polymer, (C) FTIR spectra of Desvenlafaxine HCl+Cross Carmellose Sodium+PEG-400.

RESULTS

Compatibility studies of drug and selected polymer by using FTIR

The results of the FTIR of Desvenlafaxine HCl with the excipients show that there were no changes in characteristic peaks of FTIR of the drug. The results reveal that all the characteristics peak of Desvenlafaxine HCl which is C-H stretching (2850-2960), C=C bending (1500-1600), C-O stretching (1080-1300), C=O stretching (1690-1760), O-H stretching (3200-3600), C-N stretching (1180-1360) and C-H bending (675-870) were retained in FTIR spectra of drug and physical mixture. The results are represented in Figure 1(A), (B) and C).

Evaluation of Desvenlafaxine HCl Fast Dissolving Thin Strips (FDTS)

Thickness uniformity

The results of the thickness of the strips are shown in Table 3. The result varies from 0.17±0.90 to 0.26±0.44 mm, which indicates the strips are quite thin.

Folding endurance

The results of folding endurance range from 120±2.99 to 149±9.34, indicating that the strips can be easily broken after applying small mechanical strength. The results are represented in Table 3.

Surface pH

The pH for F1-F27 formulation varies between 3.1±0.04 to 4.56±0.46 (as shown in Table 3). The low pH value favors the easy disintegration of strips inside the oral cavity.

Percent Moisture uptake

The results of percentage moisture uptake (Table 3) vary from 0.86±0.53 to 4.89±0.33.

Drug content uniformity

The % drug content varies from 78.04%±0.66 to 96.06%±0.82, which is under the specified limit. The results of drug content are shown in Table 3.

Swelling index, Disintegration and dissolution efficiency

The effect of Pullulan, croscarmellose and PEG-400 on swelling index, disintegration time and % dissolution efficiency was determined by using ANOVA. The results were represented in Table 4.

DISCUSSION

The FDTS was formulated by solvent casting method. For the fabrication of FDTS pullulan, croscarmellose and PEG-400 were used. The formulated strips were then subjected to different evaluation parameters like thickness, pH, moisture uptake, swelling index, disintegration time and dissolution. The thickness of the strips varies from 0.18±0.83 to 0.22±0.8 mm for formulation F1 to F27.The results suggest that the strips were thin

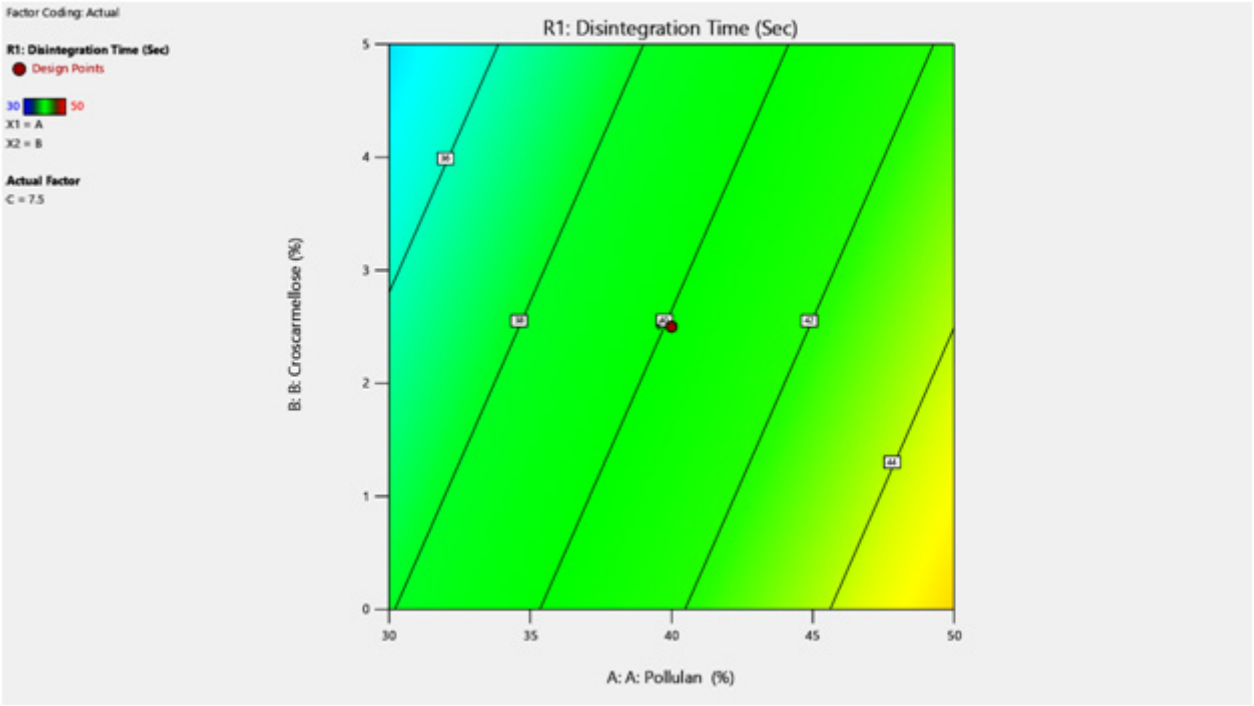

Figure 2: Contour plot for Disintegration Time.

Table 3: Evaluation parameters of Desvenlafaxine HCl fast dissolving oral strips.

Sl. No.	Formulation code	Thickness (mm) Mean±S.D. (*n*=3)	Folding endurance Mean±S.D. (*n*=3)	Surface pH Mean±S.D. (*n*=3)	Percent moisture uptake Mean±S.D. (*n*=3)	% Drug content Mean±S.D. (*n*=3)
1	F1	0.18±0.83	123±0.91	3.90±0.24	1.14 ±0.53	78.04%±0.66
2	F2	0.25±0.10	132±5.33	4.32±0.38	1.34 ±0.56	92.75%±0.39
3	F3	0.27±0.12	121± 6.23	3.52 ±0.75	3.46 ±0.67	96.21%±0.34
4	F4	0.19±0.80	123± 0.96	4.45±0.47	1.96 ±0.23	86.59%±0.22
5	F5	0.22±0.06	138±7.52	4.21±0.32	3.93 ±0.22	90.06%±0.89
6	F6	0.16±0.87	138±0.19	3.10± 0.04	1.92 ±0.94	79.30%±0.66
7	F7	0.17±0.90	145±8.04	4.08±0.76	3.86 ±0.53	89.59%±0.45
8	F8	0.21±0.47	149±9.34	4.18± 0.27	0.86 ±0.53	87.78%±0.88
9	F9	0.18±0.54	118±7.11	3.78±0.46	1.49 ±0.96	96.60%±0.38
10	F10	0.21±0.76	147± 3.11	4.78±0.23	3.67 ±0.07	88.59%±0.23
11	F11	0.19±0.82	132±1.56	4.37±0.33	3.89 ±0.44	92.53%±0.10
12	F12	0.23±0.42	139±5.94	3.45±0.97	1.69 ±0.56	96.08%±0.47
13	F13	0.27±0.06	121±2.30	4.03±0.12	4.89 ±0.47	97.96%±0.16
14	F14	0.21±0.51	124±0.32	3.79±0.65	3.18 ±0.26	89.04%±0.16
15	F15	0.19±0.17	143±1.86	4.08±0.29	2.04 ±0.77	88.64%±0.30
16	F16	0.23±0.90	120±2.99	4.25±0.37	4.89 ±0.33	89.47%±0.17
17	F17	0.17±0.13	139±0.94	3.70±0.70	0.98 ±0.56	95.55%±0.72
18	F18	0.18±0.45	142±0.04	4.19±0.93	3.76 ±0.45	97.65%±0.28
19	F19	0.23±0.72	140±9.01	4.56±0.46	3.69 ±0.57	93.32%±0.38
20	F20	0.26±0.44	132±7.04	4.24±0.58	4.22 ±0.69	96.14%±0.46
21	F21	0.20±0.80	143± 0.96	4.52±1.47	3.90 ±1.23	89.09%±0.22
22	F22	0.21±0.16	132±4.52	4.38±0.30	1.93 ±0.22	93.96%±0.81
23	F23	0.18±0.87	125±1.19	3.98±0.44	1.92 ±0.74	89.30%±0.61
24	F24	0.17±0.90	121±2.04	4.28±0.26	0.89 ±0.24	79.59%±0.65
25	F25	0.23±0.07	123±0.02	4.10±0.17	1.86 ±0.07	92.70%±0.08
26	F26	0.19±0.89	124± 0.06	4.20±0.47	4.34 ±0.53	86.52%±0.29
27	F27	0.22±0.86	129±5.52	3.96±1.22	2.93 ±0.22	96.06%±0.82

Mean±S.D. (*n*=3).

and thus can be easily dissolved.[24,25] The results were in co-relation with the research done by Chaudhary *et al.*, 2013. In their study, it was also found that the thickness of the film varies between 0.18 to 0.26 mm which helps it to easily dissolve and provides faster drug release.[26] Similarly, the surface pH for different formulations varies between 3.90±0.24 to 3.96±1.22 which indicates that it can be suitable for oral delivery. Similar results were obtained by Maher and his co-workers in which they found the pH of the formulations in the range of 3-4 which indicates that the formulations were suitable for oral delivery.[27] The folding endurance helps to determine the mechanical strength of the strip. It provides the information regarding the brittleness of the film. The results vary from 118±7.11 to 149±9.34 folds which show that the film was brittle. Similar types of results were obtained by Bala and her team. The value of folding endurance in their study was found to be between 94-110. The results suggested that all formulations were brittle and had good mechanical strength.[28] Results of moisture uptake vary from 0.86±0.53 to 4.89±0.4%. It was observed that on increasing pullulan and PEG concentrations moisture uptake increases. The results can be correlated with the earlier work done by Dinge *et al.*, 2008 where they found that on raising the concentration of pullulan, the moisture uptake was enhanced. Drug content (%) varies from 78.04%±0.66 to 96.06%±0.82 which is under the acceptable range. The results of drug content were in co-relation with the work done by Redai *et al.*, 2021.They obtained the drug content between 96-100%.[29,30]

The study also provides the effect of Pullulan, croscarmellose sodium and PEG-400 on disintegration time. Table 4 shows

Table 4: Analysis of variance for Desvenlafaxine HCl films.[29,30]

Source	Disintegration (Sec)		Swelling Index		% DE_{15}	
	Sum of Square	*p*-Value	Sum of Square	*p*-Value	Sum of Square	*p*-Value
A: Pullulan	207.10	<0.0001	30.50	<0.0001	1274.07	<0.0001
B: Croscarmellose Sod.	40.12	0.0170	5.99	0.0317	36.47	0.2736
C: PEG-400	18.11	0.0924	0.2071	0.6675	65.30	0.1501
AB			4.904	0.005	24.50	0.3659
AC					12.50	0.5151
BC					480.50	0.0011

Table 5: Summary of statistical parameters-Analysis of Variance test (ANOVA).

Response	SS	MS	DF	F-value	*p*-value	R^2	Adjusted R^2	Predicted R^2	Model Significance
Disintegration Time (X)	265.33	88.44	3	15.64	<0.0001	0.7457	0.7457	0.5566	significant
Swelling Index (Y)	36.70	12.23	3	11.31	0.0003	0.6796	0.6195	0.4488	significant
% Dissolution Efficiency after 15 Min (Z).	1893.34	315.56	6	11.31	0.0002	0.8392	0.7649	0.1510	significant

Table 6: Optimized formula composition of Desvenlafaxine HCl with predicted and observed responses.

Optimized Composition	Response	Predicted	Observed
Pullulan (A): 30% w/w+CCS (B): 5% w/w+PEG 400 (C): 7.5% w/w.	Disintegration Time (X)	24.06s	26.00±1.13
	Swelling Index (Y)	12.40	10.50± 0.67
	% Dissolution Efficiency after 15 Min (Z)	71.53%	64.73±0.05

the ANOVA for the disintegration time of desvenlafaxine HCl strips. Pullulan (A) had a significant (p<0.0001 and SS is 207.10) agonistic effect on strip disintegration time. As pullulan concentration increased, DT increased, indicating the direct relation between polymer concentration (pullulan) and DT. CCS (B), on the other hand, had an antagonistic (p=0.0170) effect on the DT. Furthermore, PEG (C) had a minor influence on the DT of the strips. It was found that on raising the PEG content, the disintegration time will decrease. This is evident in the contour plot and response surface plot (Figures 2 and 3). FDTS formulations F3, F5, F7, F11, F13, F14, F18, F19 and F20 (which include the maximum concentration of pullulan and variable concentrations of CCS and PEG) had extended disintegration time. This is due to high levels of pullulan which enhances the viscosity of the formulations. FDTS formulations F3, F11 and F18, which include maximum concentrations of pullulan, 5% CCS, showed moderate disintegration times, ranging between 26.00±1.13 and 48.00±0.61s (Figure 3). This is because CCS shows a stronger disintegrating effect at lower PEG concentrations. A similar type of study was conducted by Sahu *et al.*, 2019, in which the fast-dissolving films of Trazodone Hydrochloride (antidepressant drug) were formulated. The results of the study show that CCS acts as a strong disintegrant and helps in rapid disintegration.[19]

Figure 4 depicts the influence of several independent factors on the swelling index of desvenlafaxine HCl formulations. The ANOVA for the swelling index of desvenlafaxine HCl FDTSs is represented in Table 5. It was observed the interaction between pullulan and CCS was significant, followed by pullulan alone. The p value for swelling index was found to be 0.0003 and the SS value was 36.70, which indicates that the swelling index increases as CCS concentration increases. It was found that when the higher concentrations of polymer and super disintegrant concentrations are coupled, the swelling index decreases, with a p-value of 0.005 and a SS of 4.90497. Pullulan has a small but considerable influence on the swelling index. As pullulan concentration rises, the swelling index falls, with a p-value of 0.0001 and SS of 30.50. PEG (C) had little influence on the swelling index of the strips. The swelling index of the prepared FDTSs decreased as PEG concentration increased (p=0.6675 and SS=0.2071). The results are represented in Table 4.

FDTSs (Figure 5) demonstrated that at 5% PEG and an increase in pullulan concentration resulted in a lower swelling

index. Furthermore, researchers also found that using a high concentration of strip forming polymer (pullulan) enhanced the viscosity of the polymer solution which might help to prevent strip swelling. Furthermore, when the concentration of CCS rises, it favors the swelling index of the strip because of its water absorbing capacity. It was also found that as the concentration of super disintegrant rises the rate of drug dissolution from the formulation also rises. CCS has a better disintegration property when utilized at a concentration of 2-10% w/w. By wicking action, it can swell 7-12 folds in less than 30 seconds (porosity and capillary mechanism). Further, there is a connection between the swelling index and the DT. When the swelling index rises, the fast-dissolving strip may absorb more liquid and hence break more quickly, resulting in less disintegration time.

Figure 5 shows the result of independent variables on desvenlafaxine HCl formulations' $DE\%_{15}$. The effect of pullulan concentration, PEG and croscarmellose on $\%DE_{15}$ was studied. The results show that when the pullulan concentrations rise, $DE\%_{15}$ decreases with a p value of 0.0001 and a SS of 1274.07. The response surface 3D plot in Figure 6 shows that $DE\%_{15}$ falls dramatically when Pullulan (A) concentration rises (0.0001) while $DE\%_{15}$ decreases as CCS concentration was increases (p=0.2736). On the other hand, PEG (C) has a contradictory effect on $DE\%_{15}$. The $DE\%_{15}$ rose as the concentration of PEG increased up to 7.5%, after which the $DE\%_{15}$was declined. This might be explained by the fact that with increasing PEG levels, the strip's viscosity increases. The highest $DE\%_{15}$ values were observed in case of FDTSs formulations containing low pullulan concentrations; F2 (30% pullulan, 0% CCS and 10% PEG), F4 (30% pullulan, 2.5% CCS and 5% PEG), F6 (30% pullulan, 2.5% CCS and 7.5% PEG), F8 (30% pullulan, 5% CCS and 10% PEG), F12 (30% pullulan, 5% CCS and 7.5% PEG), F15 (30% pullulan, 2.5% CCS and 10% PEG), F22 (30% pullulan, 0% CCS and 7.5% PEG), F23 (30% pullulan, 0% CCS and 5% PEG) and F25 (30% pullulan, 5% CCS and 5% PEG). The $DE\%_{15}$ values for these formulations were 64.73±0.05, 62.05±1.36, 60.06±9.02,

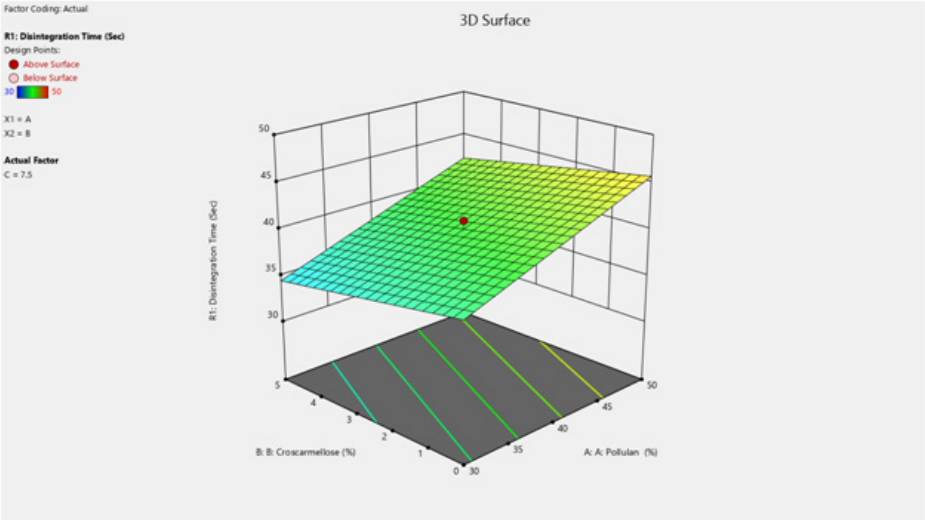

Figure 3: Response Surface Plot for Disintegration time.

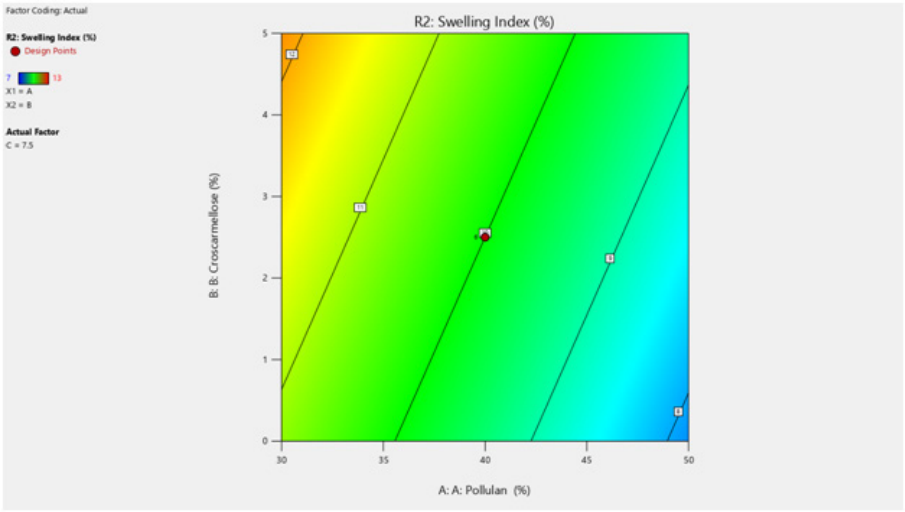

Figure 4: Contour plot for Swelling Index.

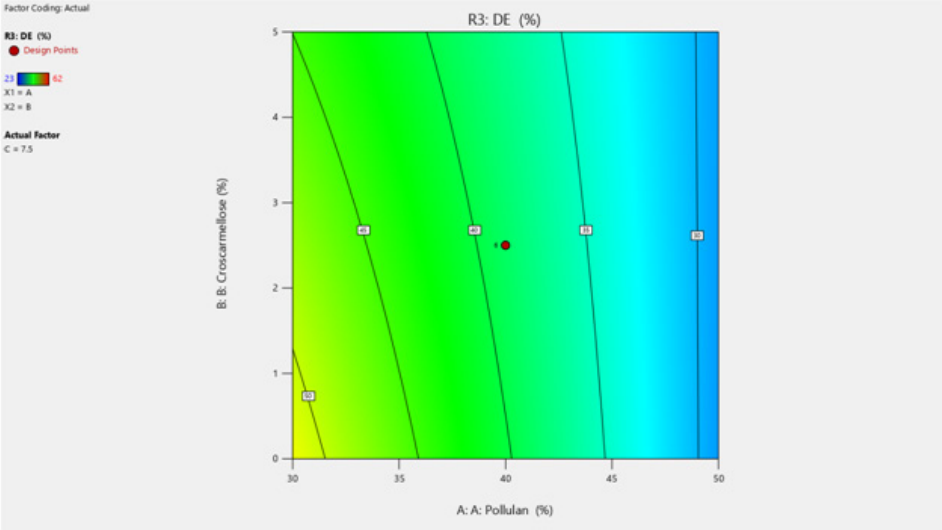

Figure 5: Contour plot for Dissolution Efficiency in 15 min.

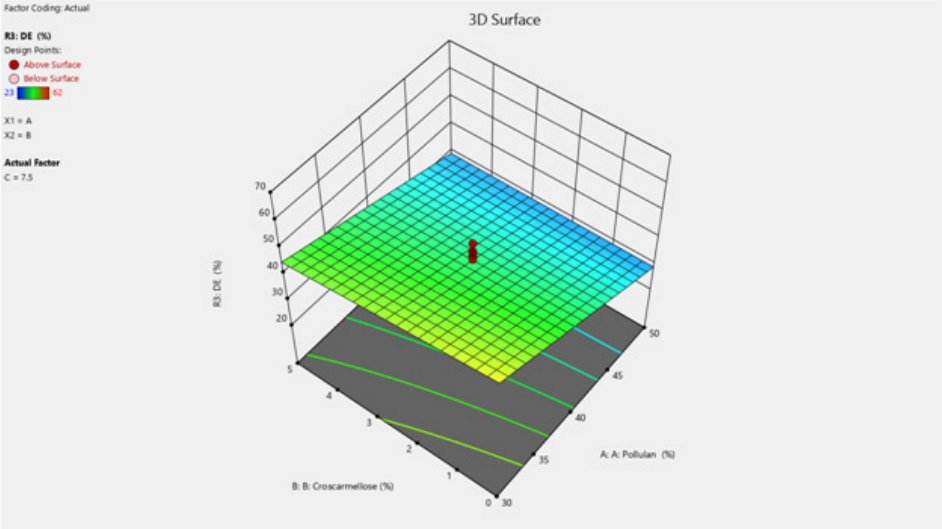

Figure 6: Response Surface Plot for Dissolution Efficiency in 15 min.

65.13±0.81, 58.08±3.19, 63.02±2.16, 60.09±0.21, 59.02±1.11 and 64.12±1.09 sec, respectively.

Lowest values for $DE\%_{15}$ were observed for F3 (50% pullulan, 5% CCS and 5% PEG), F5 (50% pullulan, 2.5% CCS and 10% PEG), F7 (50% pullulan, 0% CCS and 10% PEG), F11 (50% pullulan, 5% CCS and 7.5% PEG), F13 (50% pullulan, 2.5% CCS and 5% PEG), F14 (50% pullulan, 0% CCS and 5% PEG), F18 (50% pullulan, 5% CCS and 10% PEG), F19 (50% pullulan, 2.5% CCS and 7.5% PEG) and F20 (50% pullulan, 0% CCS and 7.5% PEG).The values for their respective $DE\%_{15}$were 36.50±2.13, 32.80±4.07, 30.54±0.15, 34.50±1.03, 40.09±0.43, 32.34±1.87, 39.15±0.56, 37.76±2.33 and 39.29±1.33 sec respectively (Figure 6). Further, it was found that the viscous nature of pullulan causes a thick matrix gel fluid when comes in contact with the media, delaying the drug release from the strips. Also, when the polymer concentration increases, the time required to wet and dissolve the drug molecules in the polymer matrix increases, resulting in a reduction in drug release.

The effect of CCS on $\%DE_{15}$ in the study was more important at higher concentration of PEG. CCS has an antagonistic effect on $\%DE_{15}$, as the concentration of CCS raises $\%DE_{15}$ decreases.

Variables on desvenlafaxine HCl

Optimized formula of desvenlafaxine hydrochloride FDTSs

Based on statistical program modeling and a desirability factor of 95%, the software recommended the following factors for the development of the best formulation: 30% pullulan, 5% CCS and 7.5% PEG as represented in Table 6.

CONCLUSION

All the findings show that the optimized formulation F12, which includes pullulan (30%) as a strip forming polymer and cross carmellose sodium (5%) as a super disintegrant, had a noticeable impact on Desvenlafaxine HCl FDTS characteristics such as disintegration time, swelling index and dissolution

efficiency after 15 min. It was able to meet the essential criterion of a fast-dissolving drug delivery system, namely, a quick onset of action in a short period, as well as solve the problems of dysphagia and low bioavailability. As a result, there was an increase in patient compliance, making fast-dissolving thin strips a better alternative than tablets and capsules.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

Qbd: Quality by design; **DT:** Disintegration time; **SI:** Swelling Index; **DE:** Dissolution Efficiency; **CCS:** Croscarmellose sodium; **FDTS:** Fast dissolving thin strips.

SUMMARY

The basic purpose of the study was formulation and optimization of fast dissolving thin strips of Desvenlafaxine Hydrochloride using QbD. The solvent casting method was utilized for fabrication of thin strips. The excipients used in the study were Croscarmellose sodium (super disintegrant), PEG-400 (plasticizer), citric acid (saliva stimulating agent), mannitol and aspartame (sweetening agents). The study was based on 3-level factorial design and Design Expert software version 13 was used. The results revealed that F12 (containing Pullulan 30%, CCS 5% and PEG -400 7.5% was the optimized formulation.

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