Development of Fast Dissolving Films of Sertraline Hydrochloride

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Abstract – Sertraline hydrochloride is widely used antidepressant drug but it is very bitter and poses challenge of being administered to depressed person. Generally, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. In order to assist these patients, fast dissolving films were developed. The films can be consumed without water, thus enabling administration easier in pediatric geriatric and dysphagic patient formulation. The dosage form allows discrete consumption of the dose, and smaller the size of the dosage form allows for shorter residence time within the oral cavity and potentially more effective avoidance of unpleasant taste. To avoid the bitter unpleasant taste sertraline hydrochloride –Beta cyclodextrin complex granules were utilized.

Index Terms – Schizophrenia, Sertraline, Fast dissolving/dispersible films.

1. INTRODUCTION

Sertraline hydrochloride is widely used antidepressant drug but it is very bitter and poses challenge of being administered to depressed person. Complex of Sertraline Hydrochloride-Beta Cyclodextrin (1:1 molar ratio) by solvent evaporation technique gives good taste masking efficiency when compared to drug alone. The primary aim of this works involves formulation of Fast dissolving films (FDF) using taste masked granules of Sertraline hydrochloride-Beta cylcodextrin.

2. EXPERIMENTAL METHODOLOGY

2.1. Formulation of Fast Dissolving Films

The taste masked granules of sertraline hydrochloride and Beta cyclodextrin were utilized to form fast dissolving films. The basic components of FDF are film forming agent, plasticizer, flavors and sweetener. Three film forming agents Xanthum gum, Carrageenan and Pullulan were evaluated. PEG-400 was used as plasticizer. Aspartame was used as sweetener. Citric acid, Menthol was used in adjuvant to flavor. Oral fast-dissolving film of sertraline cyclodextrin complex was prepared by the solvent-casting method. Aqueous solution I was prepared by dissolving the above optimized quantity of polymers and PEG-400 in specific proportion in distilled water and was allowed to stir for 3 hours and kept for 1 hour to remove all the entrapped air bubbles. Aqueous solution II was prepared by dissolving, aspartame, menthol, citric acid, tween-80, SSG, and flavor in specific proportion, followed by dissolving sertraline cyclodextrin complex in distilled water. Both aqueous solutions I and II were mixed and stirred for 1 hour. Then, the solution was casted onto a glass slide and it was dried in the oven at 350 C for 12 hour. The film was carefully removed from the glass slide, and cut according to the size required for testing (square film: 2.5 cm length X 2.5 cm width). The samples were stored in a glass container maintained at a temperature of 270 C and relative humidity 60±5%.

2.2. Evaluation of Fast Dissolving Films (FDFs)

Oral fast dissolving films of sertraline cyclodextrin complex were evaluated for their morphological study, weight of films, thickness of films, folding endurance and in vitro dissolution study of films. Weight of films was done using analytical single pan balance (Shimadzu AX 120). Film thickness was measured by using a micrometer screw gauge. Folding endurance of the films was measured manually by repeatedly folding the films till it breaks. Disintegration time was examined using the USP XXIV disintegration apparatus type II (900 ml phosphate buffer (pH 6.8) at 37±0.5 0 C, at 50 rpm).Content uniformity of the films were studied by UV-spectrophotometer. Morphology of the films was observed under scanning motic microscope at 100 X magnification. In-vitro dissolution study was conducted in 900 ml of SGF using U.S. Pharmacopoeia (USP) XXIV paddle apparatus II at 370±0.5°C and at 60 rpm. Taste of the films were evaluated by both Panel testing and spectrophotometric method. For spectrophotometric methods the Fast dissolving films containing the taste masked sertraline hydrochloride cyclodextrin complex was subjected to dissolution studies along with tablets of plain sertraline hydrochloride (control) in pH 6.8 (SSF) at 370 C for 10 min at 50 rpm .The initial time points of 1 minute and 5 minute were considered to be important to determine the efficiency of taste masking.

2.3. Evaluation of the FDFs in Juices

To study whether the patient is able to identify the presence of the medication in the juice a three way cross over study was planned using the following three juices

1) FDFs of plain drug were dispersed in 50 ml of water and added to fresh Orange juice of Tropicana.
2) FDFs of drug Beta Cyclodextrin complex were dispersed in 50 ml of water and added to fresh Orange juice of Tropicana.
3) FDFs without any drug (Placebo) were dispersed in 50 ml of water and added to fresh Orange juice of Tropicana.

2.4. Stability Assessment of FDFs

Selected film formulations were stored in aluminum foil pouches at 40^0C and 75 % relative humidity during a period of 6 months. Stability was assessed by comparing the results from in-vitro disintegration, dissolution studies, and residual moisture content analysis experiments at 0, 3, and 6 month storage. The results were checked for statistical significance using the one-way analysis of variance (ANOVA) F-test for testing the equality of several means. $p > 0.05$ was considered statistically insignificant.

3. RESULT AND DISCUSSION

3.1. Formulation of Fast Dissolving Films

Different formulation were manufactured with varying concentration of Xanthum gum, PEG-400, Aspartame & Menthol. Comparative composition of different formulation is summarized in Table 1. Out of all the formulation composition F2 formulation resulted in better fast dissolving film.

3.2. Evaluation of Fast Dissolving Films

Various physical parameters of F2 formulation is summarized in table 2.

Table 1: Comparative composition of various fast dissolving film formulations

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
	%							
Pullulan#	59.32	59.32	59.32	59.32	59.32	59.32	59.32	59.32
X.G	0.5	0.5	1	0.5	1	0.5	1	1
Carrageenan	1	1.5	1	1	1.5	1.5	1	1.5
Aspartame	6.6	6.6	6.6	5.9	6.6	5.9	5.9	5.9
PEG-400	14.3	14.3	14.3	12.8	14.17	12.7	12.7	12.7
Menthol	4.7	4.7	4.7	4.2	4.7	4.2	4.2	4.2
Citric acid	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Tween-80	1.8	1.8	1.8	1.6	1.7	1.6	1.6	1.6
Flavor	0.7	0.7	0.7	0.6	0.7	0.6	0.6	0.6
SSG	0.002	0.002	0.002	0.002	0.002	0.002	0.002	0.002
Sertraline Hydrochloride cyclodextrin complex	10.78	10.78	10.78	10.78	10.78	10.78	10.78	10.78

Table 2: Physical Parameters of Taste Masked Sertraline Hydrochloride Fast Dissolving Film

Parameters	**Observed values**
Morphology	Smooth texture, with no scratches and was free from bubbles
Weight (mg)	60 ±1.63 to 63 ±1.0 mg
Disintegration time	45 seconds

Thickness of film	9 ±0.53 to 12 ±1.51μm
Folding endurance	107±2.88 to191±5.33
Drug content	95.7±0.4 to 101.4±1.2
In-vitro release study (min) 900 ml SGF at 60 RPM	% Dissolution
1 min	1.55 %
5 min	91.11
6 min	99.33%
7 min	99.73%
10 min	100.54

Table 3: Evaluation of Taste of FDFs by Panel

Preparation	**No of volunteer rating the preparation as**					
	0	**1**	**2**	**3**	**4**	**5**
FDFs of plain drug						30
Unflavoured FDFs of Complex	1	27	2			
Flavoured FDFs of Complex	26	4				

0 =Good, 1 = Tasteless, 2 = slightly bitter, 3 = Bitter, 4 = very Bitter, 5 = Awful

3.3. Evaluation of the FDFs in Juices

The study to identify the presence of formulation in the juices indicated that the volunteers rated the Orange juice containing the FDFs of Sertraline hydrochloride Beta cyclodextrin complex almost in same lines as that of Orange juice with FDFs without any drug, while the juice containing the FDFs of plain Sertraline hydrochloride was poorly rated. The results are described in Table 4.

Table 4: Evaluation of taste of medicated juices by panel

Preparation	**No of volunteer rating the preparation as**					
	0	**1**	**2**	**3**	**4**	**5**
Juice containing FDFs of plain Sertraline hydrochlorid				21	5	4
Juice containing FDFs of Sertraline hydrochloride and Beta Cyclodextrin complex	24	6				
Juice containing FDFs without any drug	30					

0 =Good, 1 = Tasteless, 2 = slightly bitter, 3 = Bitter, 4 = very Bitter, 5 = Awful

3.4. Response surface and contour plot

The quadratic surface model obtained from the regresion analysis was used to build up 3-D surface and contour plots in which the responses were represented by curvature surface as a function of independent variables. The releationship between the response and independent variables can be directly visualized from the response surface plots.The response surface plots were generated using Design Expert 7.1.6 software and are presented in fig 1, 2 and 3.

These were used to observe the effects of independent variables on the studied responses such as % drug release. Graphical presentation of the data helped to show the relationship

between the response and the independent variables. The information given by graph was similar to that of mathematical equation obtained from statistical analyses.

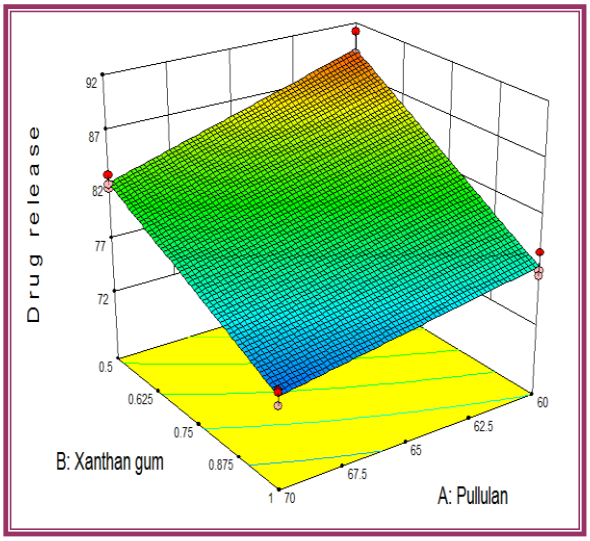

Fig 1: Response 3-D surface plot showing the influence of pullulan and xanthan gum on % drug release

Fig 1 showed the response surface plot showing the influence of pullulan and xanthan gum % drug release. From the plot it can be seen that as the concentration of xanthan gum and pullulan concentration were increased, concentration of drug release decreases. Fig 2 showed the contour plot having the relationship between various levels of two polymers.

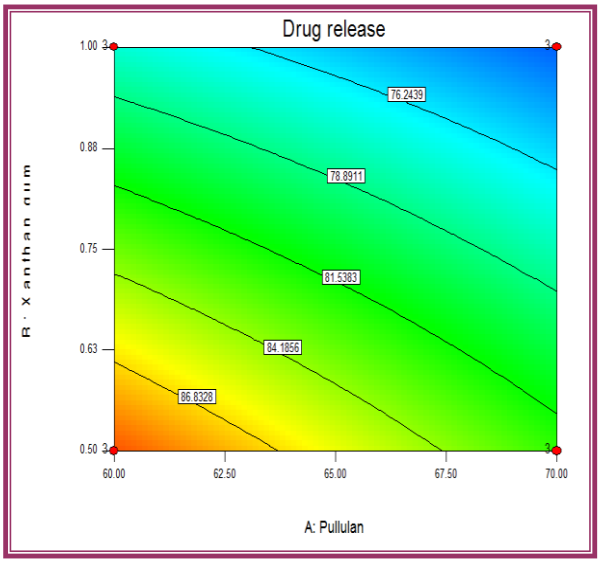

Fig 2: Contour plot showing the relationhip between various levels of two polymers on drug release

Fig 3 showed the response surface plot showing the influence of pullulan and carrageenan % drug release. From the plot it can be seen that as the concentration of carrageenan concentration is increased, percentage of drug release increased and when concentration of pullulan concentration is increased, percentage of drug release decreases. Fig 4 showed the contour plot having the relationship between various levels of two polymers.

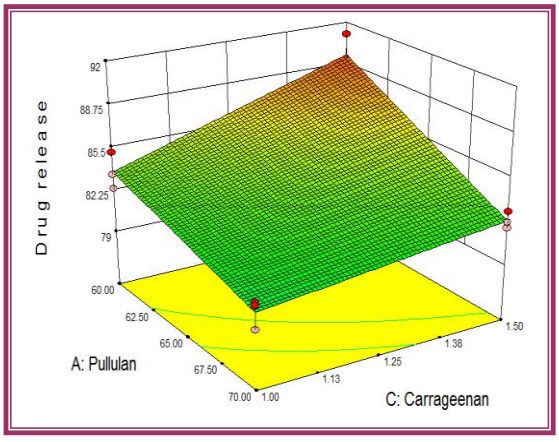

Fig 3: Response 3-D surface plot showing the influence of pullulan and carrageenan on % drug release

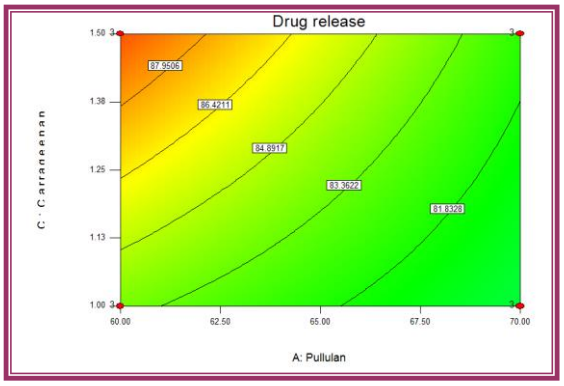

Fig 4: Contour plot showing the relationhip between various levels of two polymers on drug release

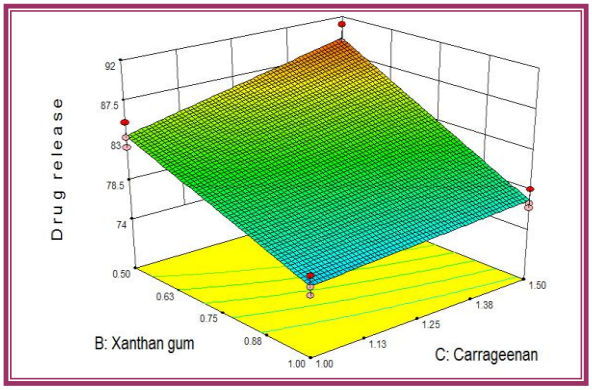

Fig 5: Response 3-D surface plot showing the influence of xanthan gum and carrageenan on % drug release

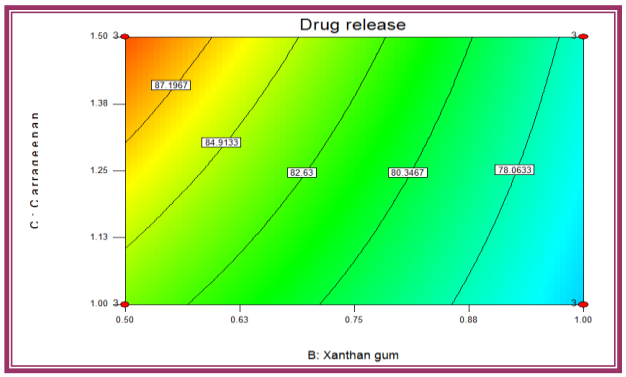

Fig 6 :Contour plot showing the relationhip between various levels of two polymers on drug release

Fig 5 revaled that response surface plot of the influence of xanthan gum and carrageenan on % drug release. From the plot it can be seen that as the concentration of carrageenan is increased, percentage drug release increased and when concentration of xanthan gum are increased, percentage of drug release decreased. Fig 6 showed the contour plot having the relationship between various levels of two polymers.

3.5. Stability Assessment of FDFs

Table 5 describes the various parameters evaluated for the FDFs for accelerated studies.

From table no 5 it is observed that there is no major change in any of the parameters analyzed. The assay also remains in limit throughout the conditions analyzed. Hence based on the accelerated data a shelf life of 2 years is predicted for the FDFs.

Table 5: Stability results of The FDFs at accelerated conditions

FDFs	**Initial**	**1M**	**3M**	**6M**
Colour	Off white	Off white	Off white	Off white
Disintegration time	45 sec	50 sec	55 sec	50 sec
Assay	100.3	99.7	99.7	99.6
Dissolution in SGF at 60 RPM				
5 min	87.1	88	79.8	84
6 min	97.13	100	98	99.3
7 min	98.43	101	99.5	100.5
10 min	99.71	101.2	100.4	101.8
Taste	O.K.	O.K.	O.K.	O.K.

4. CONCLUSION

The taste masked complex of Beta Cyclodextrin was used to prepare fast dissolving film. The slight bitter taste of the complex was further reduced by use of sweeteners and Flavourants. The solvent casting resulted in producing the desired film characteristics. Design Expert data showed with increase concentration of Xanthan & Pullulan, drug release was decreased, however with increase in concentration of Carragenan, drug release was increased.

Also from the studies on discreet administration in patients it was concluded that the fast dissolving film can be administered to the patients without their knowledge.

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