wjpmr, 2019,5(8), 166-177

SJIF Impact Factor: 4.639

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

FORMULATION AND EVALUATION OF CEVIMELINE HYDROCHLORIDE ORALLY DISSOLVING FILM FOR SJOGRENS SYNDROME BY OPTIMAL DESIGN

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Article Received on 11/06/2019 **Article Revised on 01/07/2019** **Article Accepted on 22/07/2019**

ABSTRACT

The aim of present study includes formulation and optimization of oral film loaded with cevimeline HCL by two factors and their three levels as optimal (custom) designs. The two viz. factor A (HPMC E15) and factor B (PEG 400) was selected on the basis of preliminary feasibility study. The percent drug dissolution in 10 minutes (R1), Disintegration time in sec (R2) and folding endurance (R3) were selected as dependent variables. Cevimeline hydrochloride is Para-sympathomimetic agent which stimulates muscarinic receptor (M_3). It can significantly help to improve symptoms of dry mouth as well as increases salivary output in sjogrens syndrome. Orally dissolving film which produces local action in dry mouth condition, prevents first pass metabolism, and ultimately increase in systemic bioavailability. The oral film is formulated by solvent casting method using HPMC E15 as film forming agent, PEG 400 as plasticizer, tween 80 as surfactant, citric acid as saliva stimulating agent, sodium saccharin as sweetener and orange flavour etc. These films were evaluated for parameter like their appearance, weight variation, thickness, surface pH, folding endurance, percent elongation, percent moisture loss, drug content, *In-vitro* disintegration time and *In-vitro* dissolution study. The formulation F5 has more promising responses as per D-optimal design are % drug dissolution in 10 min about 99.90 %, average disintegration time about 23.66 second and folding endurance is 127. The formulation F5 was selected as optimised formulation.

KEYWORDS: orally dissolving film, sjogrens syndrome, cevimeline HCL, HPMC E15, solvent casting method, Optimal (custom) designs etc.

INTRODUCTION

In 1970s, fast dissolving drug delivery system was developed with the aim as an alternative to solid dosage form to overcome difficulties of swallowing in paediatrics and geriatrics. According to one study about 26 % of 1576 patients faced difficulties in swallowing tablet. Many pharmaceutical company and research scientists are involved in developing orally dissolving dosage form. Orally dissolving film having certain advantages over tablet, capsule and syrup viz. avoid first pass metabolism, higher in bioavailability, immediate action and patient acceptance.[1] Cevimeline Hydrochloride is cholinergic agent with stronger affinity for M3 muscarinic receptors and stimulates secretion of exocrine glands such as salivary and sweats glands. It is used to treat symptoms of dry mouth in Sjogrens syndrome.[2] Cevimeline Hydrochloride is orally administered as 30 mg capsule thrice daily. After single dose administration it can rapidly absorbed with a mean time to peak concentration of 1.5 to 2 hours. There is no accumulation of active drug or its metabolites after multiple dose administration.[3] Present experimental design generates runs and ultimately minimises cost of investigation. D- Optimal design is model dependent approach in which optimization is based upon model that will best fits in selected constraints. [4] The outcomes from independent variables were studied on 9 different runs generated from D- optimal experimental design.

MATERIALS AND METHODS

Materials

Cevimeline Hydrochloride (Gift sample from Aurobindo Pharmaceuticals Pvt. Ltd. Hyderabad), Hydroxy Propyl Methyl Cellulose E3, E5, E15 (DOW chemicals), Polyethylene Glycol 400 and Tween 80 LR (SDFCL Mumbai), citric acid (Merck Chemicals Ltd., Mumbai), Sodium Saccharin, orange flavour (Burgoyne Burbidges & Co, Mumbai, India). All other reagents of analytical grade were used.

Preliminary feasibility study for selection of polymer and plasticizer

Initial formulation carried out using HPMC E5, E15, Polyvinyl alcohol and sodium alginate etc. as film former with 2 % w/v, 3 % w/v, 4 % w/v and 5 % w/v etc. From that sodium alginate film was easily breaks. Polyvinyl

alcohol film was not easy to peel off as well as unsatisfied disintegration time. HPMC E5 forms very thin film with low folding endurance. HPMC E15 has good film forming property, satisfied disintegration time and good folding endurance, but above 4 % w/v it shows sticky nature and forms more thick film. Hence for further optimization was carried out using HPMC E15 in the range 2 – 3 % w/v. In preliminary trail less than 0.4 % w/v of PEG 400 shows low flexibility, whereas above 0.8 % w/v shows sticky appearance. So that further optimization was carried out between 0.4 % w/v to 0.8 % w/v of PEG 400.

Formulation of drug loaded oral film

Films were prepared as per formula given in Table 1. Solvent casting method was used for preparation of films using polymers HPMC E15. Initially the polymer was weighed accurately and dissolved in 5 ml of water on magnetic stirrer. In above polymeric solution PEG 400 was added. Sodium saccharine, citric acid and orange flavour were both dissolved in 3 ml of water in the watch glass. This solution was added to the polymeric solution and stirred well using a magnetic stirrer to obtain a homogenous solution. In separate beaker accurately weighed drug was dissolved in 2 ml of water and added in above polymeric solution slowly. This solution was allowed to stand for 30 min for de-aeration of the solution. Solution was then casted in to petri dish and kept in hot air oven for 8-10 h at 50ºC. After drying, films were removed. Thus the obtained large film was cut into 2 × 2 cm^2. Film was stored in a butter paper covered with aluminium foil and stored in a desiccator.

Formulation of HPMC based oral film of Cevimeline HCL using optimal design with design expert® 11

In order to optimise the formulation variable, two factor viz. concentration of HPMC E15 and concentration of PEG 400 were selected for further study. These variables were taken at three different level i.e. lower, medium and higher level. Those variables were stipulated on the basis of preliminary feasibility study earlier to design of experiment. The dependent variables or response evaluated were % dissolution in 10 min, disintegration time in second and folding endurance etc. The total 9 run were generated by *Design-Expert® 11 software*, the experimental data were analyzed using analysis of variance (ANOVA) by fitting responses in respective run.

Table 1: Composition of films (F1-F9) prepared by solvent casting method.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Cevimeline HCL	30	30	30	30	30	30	30	30	30
HPMC E5	400	400	400	300	300	300	200	200	200
PEG 400	80	60	40	60	80	40	60	80	40
Tween 80 (ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sod. Saccharin	40	40	40	40	40	40	40	40	40
Citric acid	40	40	40	40	40	40	40	40	40
Orange flavour	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Water (ml)	10	10	10	10	10	10	10	10	10

Calculation of amount of drug per batch

Dose of drug per film =30 mg

Area of one film = 4 cm^2

Area of petri plate = 68.39 cm2

Drug to be added per batch = (Dose of drug per film × Area of petri plate)/Area of one film

= (30 × 68.39) / 4 = 512.92 mg.

Total number of film forms = (area of petri plate/ area of one film)

(68.39 / 4) = 17.09 films.

Standard calibration curve of cevimeline HCL

100 mg of Cevimeline HCL was dissolved in 10 ml of 6.8 pH phosphate buffer and volume was made up to 100 ml with the 6.8 pH phosphate buffer (1000 µg/ml). 10 ml of the above solution was diluted up to 100 ml with 6.8 pH phosphate buffer (100 µg/ml). Then by serial dilution solutions with concentrations 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml, 50µg/ml and 60µg/ml were prepared. Absorbance was measured on a Shimadzu 1800 Double Beam Spectrophotometer in the range of 200 to 400 nm. Finally a spectrum and wavelength of maximum absorption was recorded.

Evaluation of cevimeline HCL loaded oral dissolving film

Drug excipients compatibility studies

Fourier transforms infrared spectroscopy (FTIR)

The FTIR absorption spectra of the pure drug, Polymer and their mixture were recorded in the range of 4000-400cm^{-1} by KBr disc method using FTIR spectrophotometer (Jasco FT/IR- 4100).[5]

Differential scanning Calorimetry (DSC)

Thermal analysis studies were performed for assessment of possible incompatibility between API and polymer. The DSC thermograms of pure API cevimeline HCl and optimized film formulations of cevimeline HCl were recorded using DSC (Mettler DSC star system, Mettler-Toledo, Switzerland). The samples were sealed in aluminium pan and heated at 10ºC /min rate from 40–300ºC with empty aluminium pan kept as reference sample.[6]

Appearance

All formulated films were evaluated for their appearances either they are transparent or opaque by

visual inspection or surface texture was evaluated by touch or feel of the film. [7]

Weight variation
The individual weight each of 10 films of 2×2 cm^2 for each formulation on electronic balance. The average weight was calculated.[8]

Thickness
The thickness of the oral film was determined by using digital Vernier Calliper (Digimatic, Mitutoyo, Japan) with a least count of 0.01 mm. The thickness was measured at five different places of the film and average was taken and standard deviation was calculated.[9]

Surface pH
The pH value was determined by dissolving one oral film in 10 ml distilled water and measuring the pH of the obtained solution. All determinations were performed in triplicate. It is necessary that strip should have nearly uniform pH value.[10]

Folding endurance
It was determined by repeatedly folding the film of uniform cross sectional area and thickness until it breaks. The number of times film was folded without breaking computed as the folding endurance value. This test ensures the tensile strength of the film. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.[11]

Percent Elongation
When stress is applied to the film sample stretches and is referred to as strain. Strain is basically the deformation of the film divided by the original dimension of the film. Generally elongation of the film increases as the plasticizer concentration increases. Percentage elongation was calculated by measuring the increase in length of the film after tensile strength measurement by using the following formula.[12]

Percentage Elongation = [L-L0] X 100 / L0
Where, L = Final length, L0 = initial length

Percentage moisture loss
The percent moisture loss was estimated by placing prepared film in desiccators containing anhydrous calcium chloride. After three days, the film was taken and reweighed. The percent moisture loss was calculated using following formula. [13]

$$\% \text{ Moisture loss} = \frac{\text{Initial weight}}{\text{Initial weight} - \text{Final weight}} \text{ X } 100$$

Uniformity of drug content
A film of size 2 × 2 cm^2 is cut and put in 100 ml of volumetric flask containing 6.8 pH phosphate buffer. This solution was sonicated for 10 minute to get a homogeneous solution and filtered. The drug content is determined spectroscopically after appropriate dilution. Cevimeline HCL concentrations were assayed spectrophotometrically at 206.5 nm.

***In-vitro* Dissolution study**
The dissolution test was performed according to USP type I Basket apparatus (Electrolab Dissolution tester, EDT-08Lx). The dissolution medium was 900 ml of 6.8 pH phosphate buffer, maintained at 37 ± 10^0C and stirred at 50 rpm. Each square cut film sample (2 cm x 2 cm) was placed into the dissolution media and appropriate aliquots were withdrawn at 2, 4, 6, 8 and 10 minute time intervals and again replaced with same volume of dissolution media. The sample were filtered through Whatman filter paper for all the batches and analyzed spectrophotometrically at 206.5 nm (Model UV-1800 UV Visible spectrophotometer, Shimadzu, Japan). Sink conditions were maintained throughout the experiment. The dissolution test was performed in triplicate for each batch.[14]

***In vitro* Disintegration study**
The film size to be required for delivering active pharmaceutical ingredient (4 cm^2) was placed on a glass Petri dish containing 10 ml of 6.8 pH phosphate buffer. The time required for the film to break was noted as *in vitro* disintegration time.

Data analysis: Kinetic Data / Model fitting
Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a dosage forms. The dissolution data obtained from various batches is fitted to mathematical models and the best fit is obtained to describe the release mechanism of the drug. A number of mathematical models have been developed to describe the drug dissolution kinetics from drug delivery system e.g., Higuchi (cumulative % drug release versus square root of time); First order (log cumulative % drug remaining versus time), Zero order (cumulative % drug release versus time) and Peppas and Korsenmeyer model (log cumulative % drug release versus log time).[15]

Stability study
The stability study of the optimised formulation was carried out storage conditions as per ICH guidelines. The individual film wrapped in butter paper followed by packing in aluminium foil and subjected to accelerated stability testing at 40 ± 2 °C and 75 ± 5% RH for the period of 3 months. Samples were taken at regular interval and analyzed for folding endurance, drug content and in-vitro drug release. [16]

RESULTS AND DISCUSSION

Optimization of independent variable
Initially placebo oral films were prepared with different polymers like HPMC (E5, E15), PVA and sodium alginate. Finally, from these trials made and results obtained, HPMC E15 and PEG 400 were selected with

different level for further development. The polymer HPMC E15 and plasticizer PEG 400 were taken at three different level i.e. lower, medium and higher level. Thus total 9 run were generated by *Design-Expert® 11 software* and the dependent variables or response evaluated were % dissolution in 10 min, disintegration time in second and folding endurance are shown in Table 2.

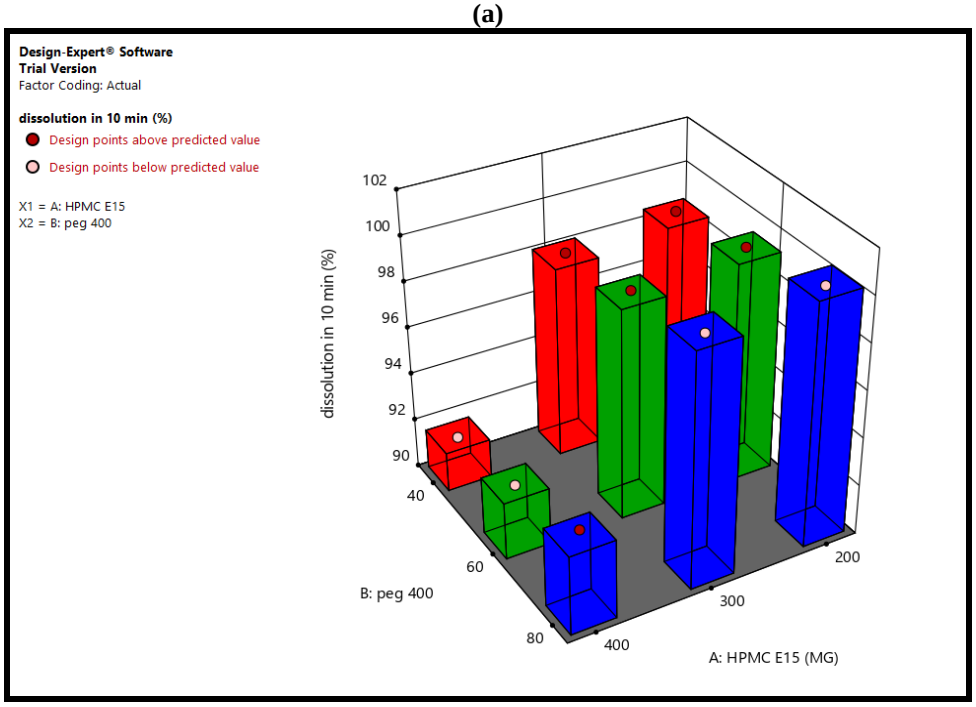
Table 2: Optimization parameters of cevimeline HCL loaded oral films.

Run	Independent variables		Dependent variables		
	Factor 1 HPMC E15 (mg)	Factor 2 PEG (mg)	Drug Release (%)	DT (Sec)	Folding Endurance
F1	400	80	93.59	31.66	149
F2	400	60	92.40	33	142
F3	400	40	91.61	36	134
F4	300	60	99.11	26.33	114
F5	300	80	99.90	23.66	127
F6	300	40	98.32	29.66	105
F7	200	60	99.51	17.33	98
F8	200	80	100.30	13.66	86
F9	200	40	98.80	20.33	75

Table 3: ANOVA for cevimeline HCl orally dissolving film from D-optimal design.

Source	*d.f*	Sum square	Mean square	*F value*	*P value*
Dissolution in 10 min (Response 1)					
A-HPMC E15	2	92.48	46.24	2281.61	< 0.0001
B-peg 400	2	4.28	2.14	105.59	0.0003
Model	4	96.76	24.19	1193.60	< 0.0001
Disintegration time (Response 2)					
A-HPMC E15	2	455.27	203.47	430.30	< 0.0001
B-peg 400	2	406.95	24.16	51.09	0.0014
Model	4	48.32	113.82	240.70	< 0.0001
Folding endurance (Response 3)					
A-HPMC E15	2	4596.22	2298.11	50.76	0.0014
B-peg 400	2	440.89	220.44	4.87	0.0848
Model	4	5037.11	1259.28	27.81	0.0035

(a)



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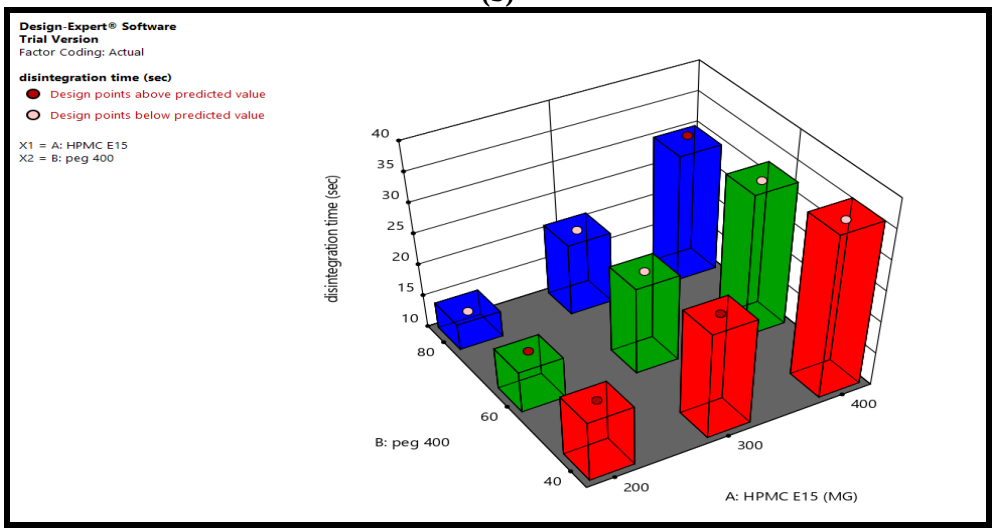

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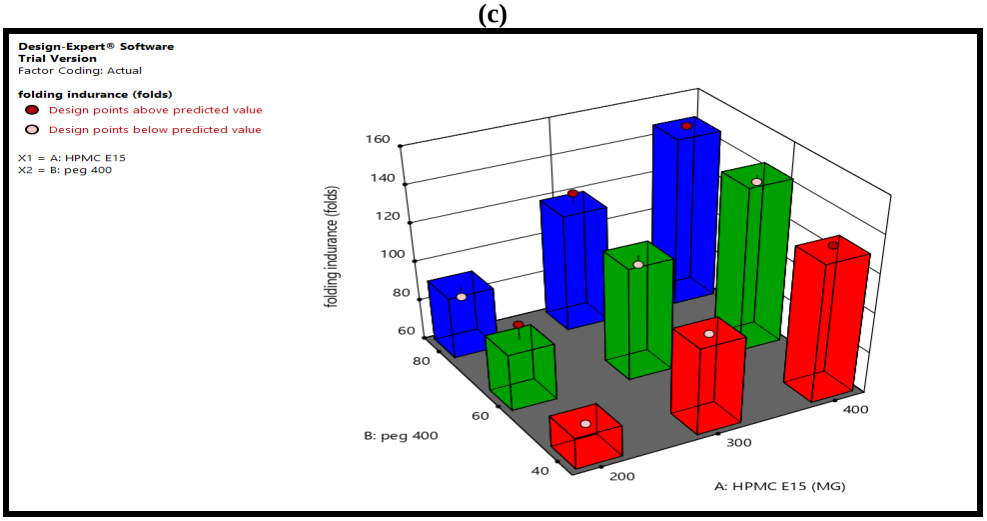

Figure 1: Images of 3-dimensional surface response plots (a-c) showing the effect of independent variable on dependent variable on in vitro disintegration time (Y1), drug release (Y2) and folding endurance (Y3).

Numerical Optimization

Table 4: Constraints for independent variables.

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A: HPMC E15	is in range	200	400	1	1	3
B: PEG 400	is in range	40	80	1	1	3
Dissolution in 10 Min	is target = 100	91.61	100.3	1	1	3
Disintegration Time (Sec)	Minimize	13.66	36	1	1	4
Folding Endurance (Folds)	Maximize	75	149	1	1	5

Table 5: various solutions for 9 combinations.

Number	HPMC E15	PEG 400	Dissolution in 10 min	Disintegration Time	Folding Endurance	Desirability	
1	**300**	**80**	**99.980**	**21.812**	**121.556**	**0.708**	**selected**
2	300	60	99.057	24.369	118.889	0.628	
3	200	60	99.483	16.922	89.889	0.479	
4	300	40	98.293	27.479	105.556	0.474	
5	400	80	93.403	30.812	147.889	0.415	
6	400	60	92.480	33.369	145.222	0.272	
7	200	40	98.720	20.032	76.556	0.172	

Table 6: Summary of regression analysis of responses Y1, Y2 and Y3.

Factorial Model	R^2	Adjusted R^2	Predicted R^2	SD	% CV
Y1 dissolution in 10 min	0.9992	0.9983	0.9958	0.1424	0.1467
Y2 Disintegration time (sec)	0.9959	0.9917	0.9791	0.6876	2.74
Y3 folding endurance (folds)	0.9653	0.9306	0.8243	6.73	5.88

Determination of λ max

Concentration of 60 µg/ml was prepared from standard cevimeline HCL solution and scanned by UV visible spectrophotometer in range of 200-400 nm using 6.8 pH phosphate buffer as blank then the maximum wavelength (λ-max) was determined (Fig.2).

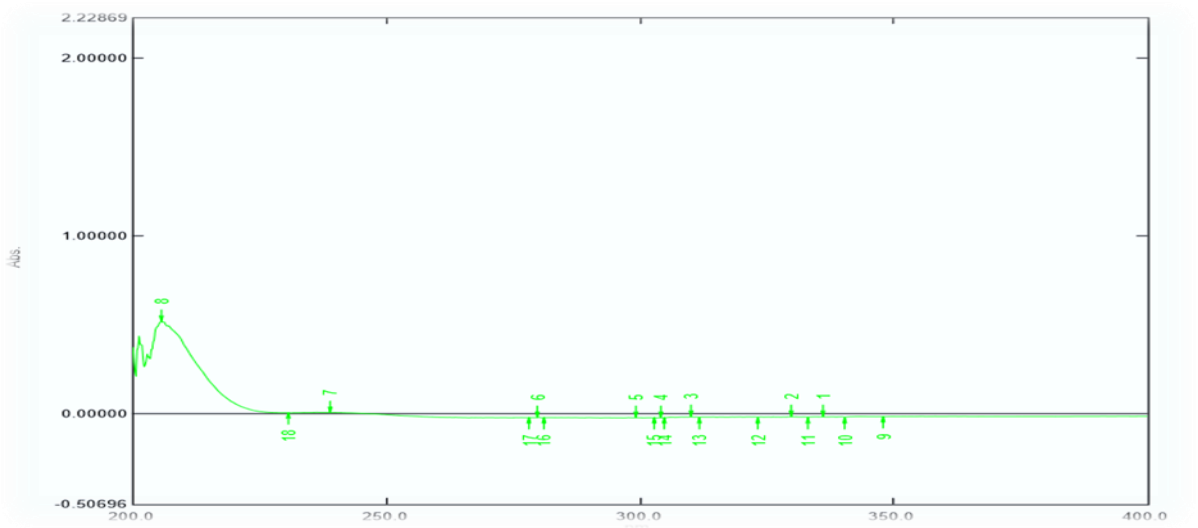

Figure 2: UV spectrum of cevimeline HCl.

Standard calibration curve of Cevimeline HCL in 6.8 pH phosphate buffer: cevimeline HCl showed maximum absorption at wavelength 206.5 nm in 6.8 pH phosphate buffer. Standard curve was plotted by taking absorption of diluted stock solutions (10, 20, 30, 40, 50 and 60 µg/ml) at wavelength 206.5 nm.

Table 7: Standard calibration curve of Cevimeline HCL in 6.8 pH phosphate buffer.

Sr. No	Concentration (µg/ml)	Absorbance at 206.5 nm
1	10	0.153
2	20	0.215
3	30	0.295
4	40	0.375
5	50	0.463
6	60	0.517

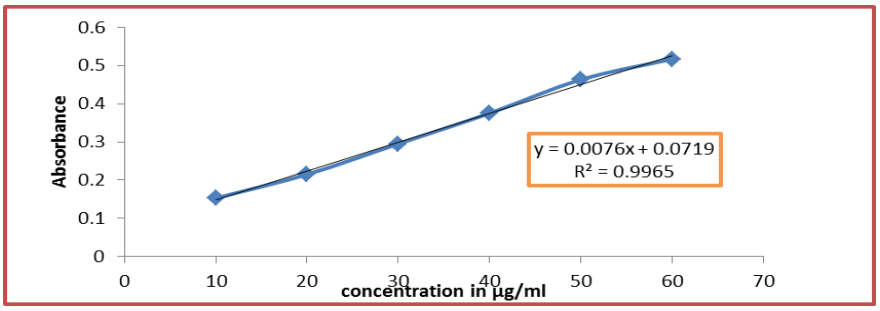

Figure 3: Calibration curve of Cevimeline HCL in 6.8 pH phosphate buffer.

Preparation and physical characterization of Cevimeline HCL orally dissolving film

Initially placebo oral films were prepared with different polymers like HPMC (E5, E15), PVA and sodium alginate. Finally, from these trials made and results obtained, HPMC E15 and PEG 400 were selected with different level for further development.

Drug Excipients Compatibility study

Fourier transforms infrared spectroscopy (FTIR)

IR spectrum of Cevimeline HCL and physical mixture with polymer HPMC E15 was recorded and it was found in accordance with the reported peaks. It is shown in below figure (Fig 4 and 5). The IR spectra of Cevimeline HCL comply with its chemical structure and show peaks for principal group's .The structural assignments for the characteristics absorption bands are listed in following table no.8**.**

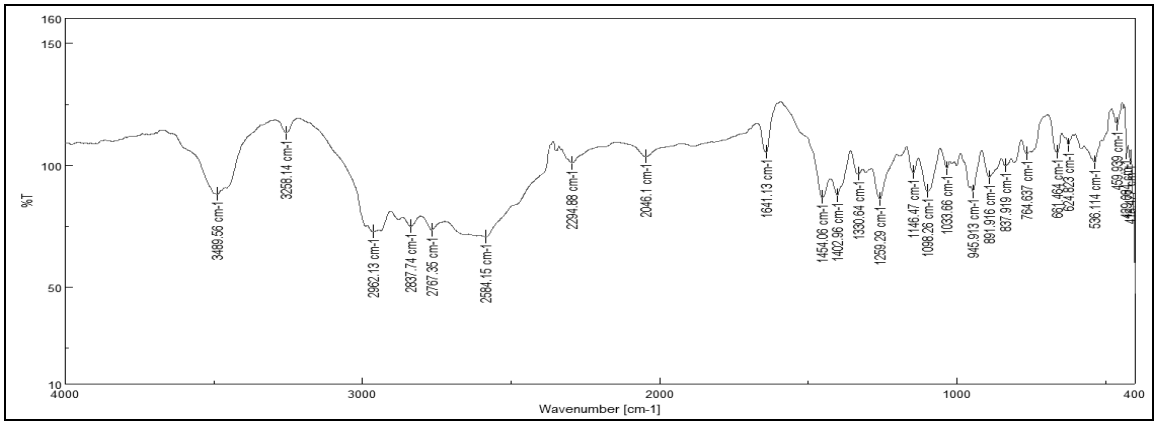

Figure 4: IR Spectrum of cevimeline HCL.

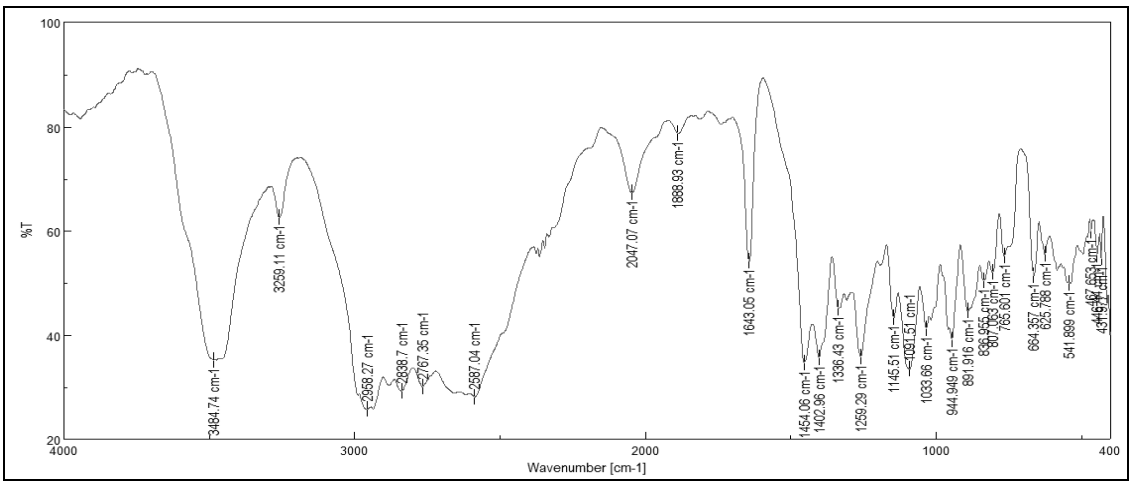

Figure 5: IR Spectrum of cevimeline HCL and HPMC E15.

Table 8: Infrared Spectral assignment for Cevimeline HCl.

Type	Pure Drug	Drug, HPMC E15
N-H Stretching	3489.56	3484.74
C-H Stretching	2962.13	2958.27
S-H stretching	2584.15	2587.04
C-H Bending	1330.64	1333.66
C-N stretching	1259.29	1259.29
C-O stretching	1146.47	1145.51
N-H Bending	837.919	836.955

In physical mixtures of cevimeline HCL and HPMC E15, there was neither masking of single characteristic peak nor existence of additional peak in drug spectra. So it was concluded that cevimeline HCL and HPMC E15 were compatible with each other.

Differential scanning Calorimetry (DSC)

Differential Scanning Calorimeter (DSC) thermogram of cevimeline HCL exhibited endothermic peak at 208.14°C (Fig.6). while physical mixture (1:1) of cevimeline HCL and HPMC E15 exhibited an endothermic peak at 204.95 °C and 96.52°C respectively (Fig.7). The peak of cevimeline HCL was slightly shifted by 4°C in physical mixture with HPMC E15. There were no significant change in position of peaks observed after carrying physical mixture (1:1) drug and polymer. Hence, indicated no chemical reaction between drug and polymer.

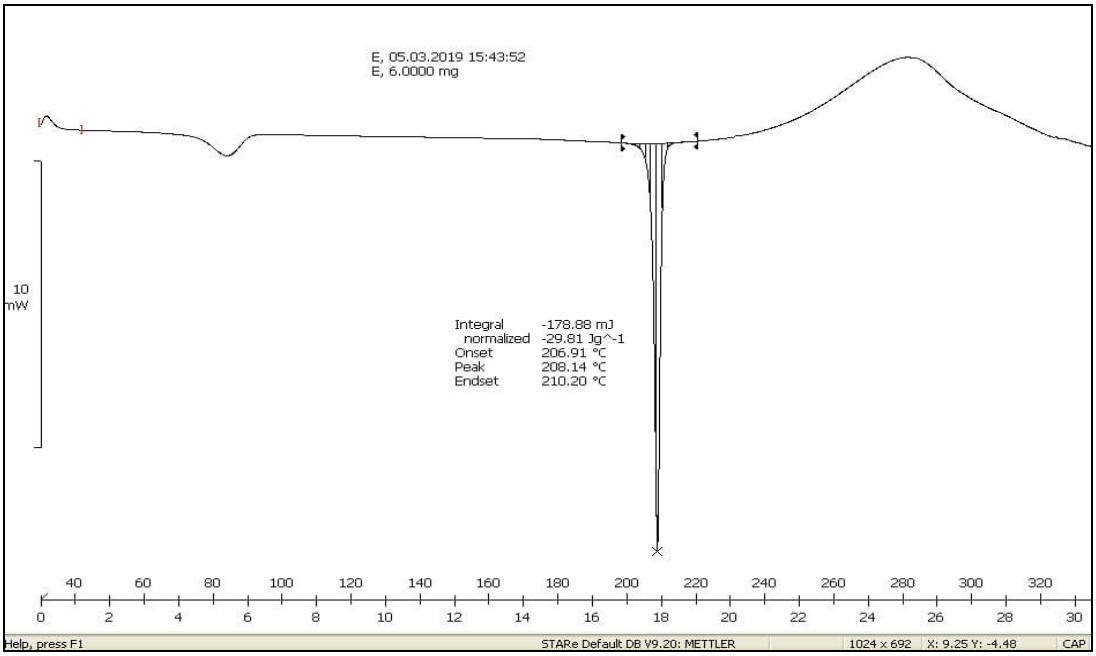

Figure 6: DSC thermogram of cevimeline HCL.

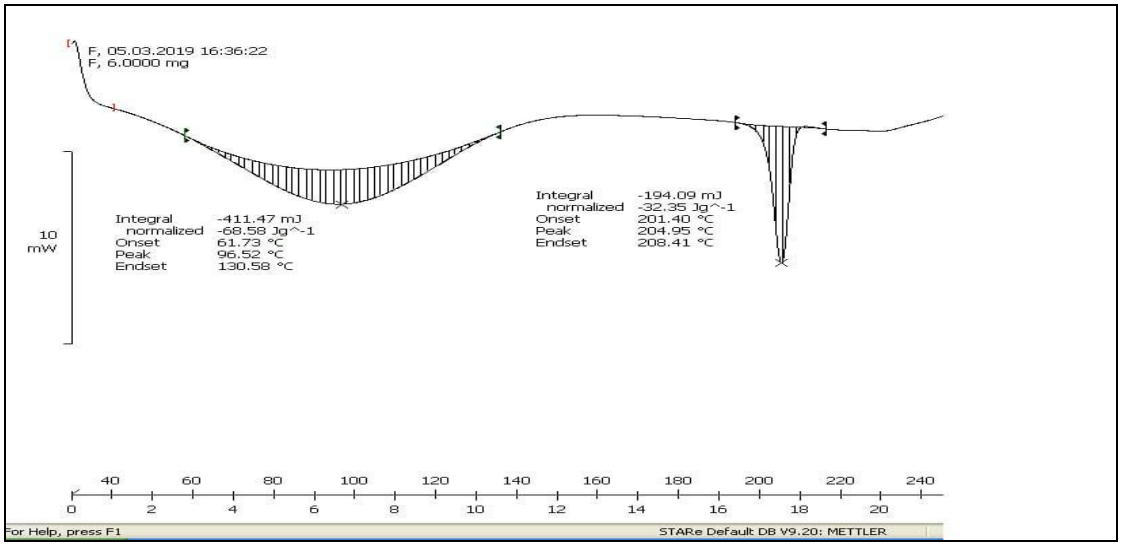

Figure 7: DSC thermogram of cevimeline HCL and HPMC E15.

Evaluation of films

Appearance

Oral films were visually evaluated for homogeneity, transparency, color and smoothness and the results were given in Table 9. All the formulations showed no change in the properties at the end of 3 month time period and especially no crystallization of the drugs was observed.

Table 9: Physical appearance of oral film.

Run	Appearance
F1	Easy to peel off, Homogenous, Transparent, smooth, thick film
F2	Easy to peel off, Homogenous, Transparent, smooth, thick film
F3	Easy to peel off, Homogenous, Transparent, smooth, thick film
F4	Easier to peel off, Homogenous, Transparent, Smooth, thin film
F5	Easier to peel off, Homogenous, Transparent, Smooth, thin film
F6	Easier to peel off, Homogenous, Transparent, Smooth, thin film
F7	Little difficulty to peel off, Homogenous, Transparent, smooth, thin film
F8	Little difficulty to peel off, Homogenous, Transparent, smooth, thin film
F9	Little difficulty to peel off, Homogenous, Transparent, smooth, thin film

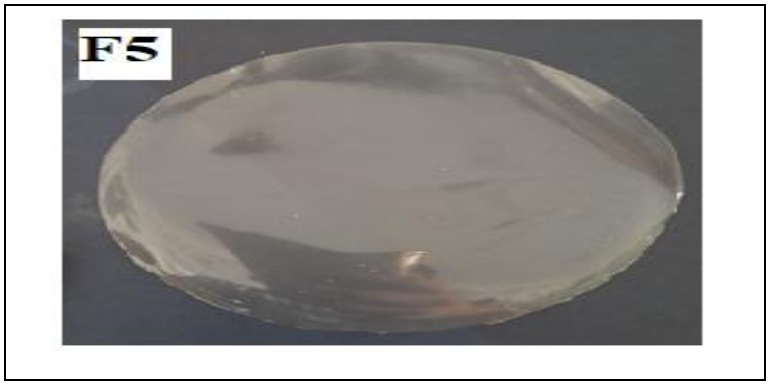

Figure 8: Image of optimised formulation (F5) of orally dissolving film.

Wt. variation
The weight of orally dissolving film was determined using digital weighing balance and the average weight of all Fast dissolving film was found to be in the range of 50-62 mg. (As shown in table 10)

Thickness
The thickness of the orally dissolving films was measured using digital Vernier calliper and the average thickness of all Fast dissolving film was found in between 0.080 – 0.445 mm (n=3). (As shown in table 10)

Surface pH
The surface pH was noted by pH meter near the surface of fast dissolving film and allowing equilibrating for 1 min and the surface pH of all fast dissolving film was found to in between 6.63-6.89 pH (n=3). (As shown in table 10).

Folding endurance
The average folding endurance of all Fast dissolving film was ranges from 75-149. (As shown in table 2).

% Elongation
The average % elongation for formulation F1 to F9 were found in the range of 9.49 ± 0.31 % to 15.34 ± 0.89 %. (As shown in table 10).

Percentage moisture loss
The % moisture loss of formulations F1 to F9 was estimated. The average % moisture loss found in range of 1.477 ± 0.009 % to 2.143 ± 0.002 %. These films shows significantly low percent moisture loss may be a direct result of high water permeability of HPMC polymer. (As shown in table 10).

Uniformity of drug content
The percentage drug content for all run F1 to F9 was found in range of 98.89 ± 0.96 % to 99.92 ± 0.15 %. This estimate reflects excellent uniformity of drug content in orally dissolving film of cevimeline HCl. (As shown in table 10).

In-vitro Dissolution study
In-vitro dissolution investigation of cevimeline HCL fast dissolving film was carried out in pH 6.8 phosphate buffer solution (shown in fig. 9). Drug release from F1 to F9 was more than 90 % within 10 min. (As shown in table 11).

In-vitro Disintegration study
Film of dimension 2 x 2 cm^2 size taken and disintegration time observed visually. Average disintegration times of three fast dissolving films were calculated and the results were shown in table no 5. Disintegration time ranges from 13-36 seconds, which indicates disintegration time of film obtained within a minute. (As shown in table 2).

Table 10: Formulation development result.

Run	Weight (mg)	Thickness (mm)	Surface pH	% Elongation	% Moisture loss	Drug content (%)
F1	62 ± 0.43	0.445 ± 0.015	6.64 ± 0.13	10.14 ± 0.74	1.798 ± 0.003	99.84 ± 0.33
F2	62 ± 0.89	0.437 ± 0.017	6.65 ± 0.27	9.84 ± 0.89	1.477 ± 0.009	98.89 ± 0.96
F3	60 ± 0.71	0.429 ± 0.029	6.81 ± 0.19	9.49 ± 0.31	2.143 ± 0.002	99.30 ± 0.45
F4	55 ± 0.39	0.205 ± 0.015	6.79 ± 0.17	13.08 ± 0.74	1.537 ± 0.004	99.48 ± 0.37
F5	56 ± 0.57	0.2025 ± 0.025	6.84 ± 0.31	13.27 ± 0.89	1.778 ± 0.004	99.92 ± 0.15
F6	56 ± 0.11	0.192 ± 0.002	6.63 ± 0.11	12.68 ± 0.39	1.981 ± 0.001	99.59 ± 0.21
F7	50 ± 0.91	0.080 ± 0.01	6.69 ± 0.18	15.11 ± 0.44	1.663 ± 0.002	98.97 ± 0.18
F8	51 ± 0.28	0.100 ±0.019	6.89 ± 0.09	15.34 ± 0.89	1.793 ± 0.006	99.81 ± 0.10
F9	50 ± 0. 41	0.090 ± 0.012	6.66 ± 0.13	14.5 ± 0.81	1.486 ± 0.003	99.31 ± 0.37

Table 11: In-vitro Dissolution (% release) Profile of fast dissolving films.

Batches	% cumulative Drug Release					
	2 min	4 min	6 min	8 min	10 min	12 min
F1	23.32	46.22	63.98	87.27	93.59	99.51
F2	20.96	44.25	61.61	85.3	92.4	97.93
F3	17.4	42.27	59.25	83.32	91.61	96.75
F4	27.27	57.67	70.3	86.48	99.11	-
F5	32.4	59.64	72.67	89.25	99.9	-
F6	25.3	55.69	67.93	83.72	98.32	-
F7	45.03	63.19	76.22	95.17	99.51	-
F8	46.61	65.17	78.98	96.75	100.3	-
F9	39.9	61.61	74.64	93.98	98.8	-

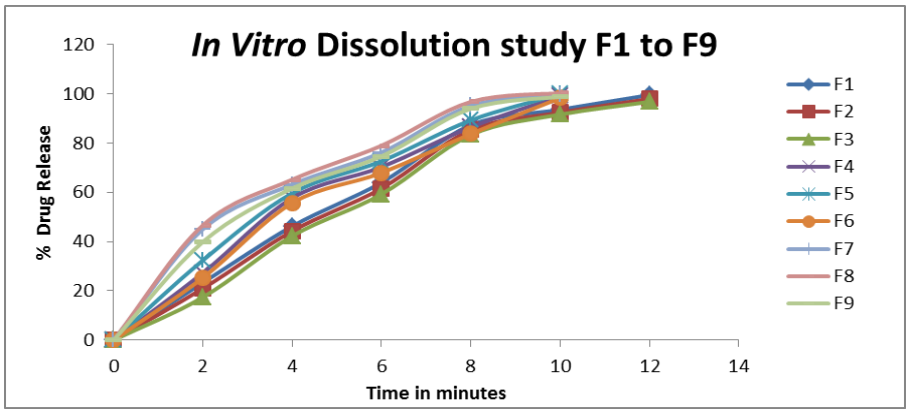

Figure 9: Comparative study of *In-vitro* dissolution profile between F1 to F9.

Data analysis: Kinetic Data / Model fitting

The obtained In-vitro dissolution data was fitted into different equations and kinetic models to explain permeation profiles. Model fitting data was represented in. The coefficient of correlation of each of the kinetics was calculated and compared. From that drug release was best fitted into Higuchi square root model with r^2 = 0.984 (Figure 13) which reflect drug release from oral film (F5) is square root of time dependent process and diffusion controlled.

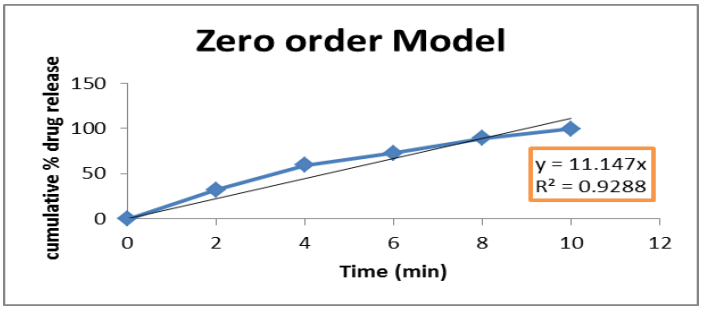

Figure 10: Zero order kinetic release for optimised formulation F5.

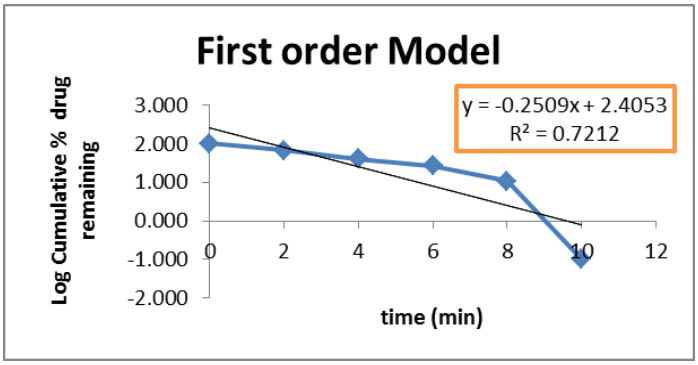

Figure 11: First order kinetic release for optimised formulation F5.

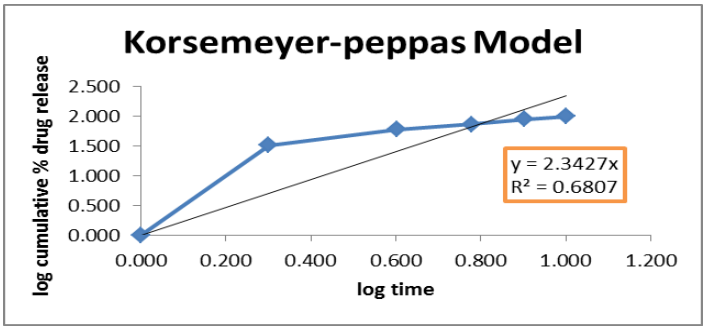

Figure 12: Korsemeyer-peppas kinetic release for optimised formulation F5.

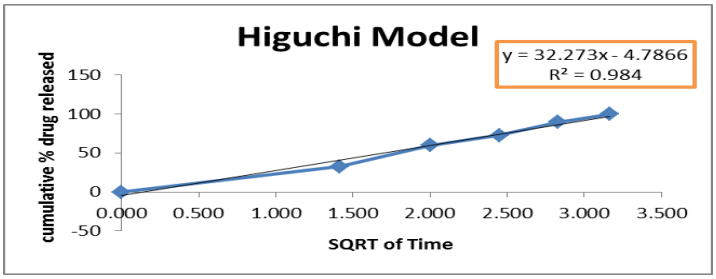

Figure 13: Higuchi model kinetic release for optimised formulation F5.

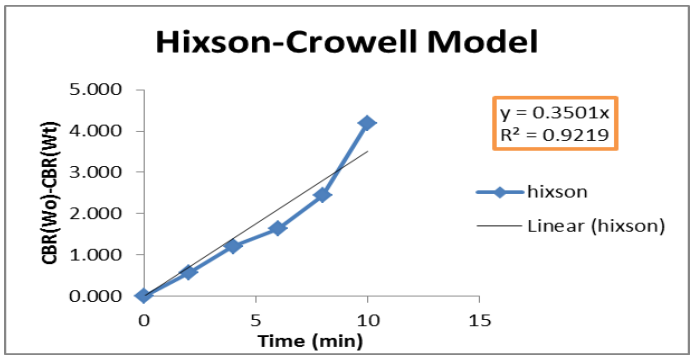

Figure 14: Hixson-Crowell model kinetic release for optimised formulation F5.

Stability study

Optimized formulation (F5) shows no major change in appearance, folding endurance, Drug content and In Vitro Drug Release after placing in the Accelerated Stability Studies. (As shown in table 12). Hence the formulation (F5) was found to be stable.

Table 12: Parameters after Accelerated Stability Study of optimised Formulation F5.

Parameter for study	Maintained Temperature at 40 ± 2°C and Relative Humidity (RH) at 75% 5%RH			
	Initial	After1 month	After 2 month	After 3 month
Folding Endurance	127	124	122	125
Drug Content (%)	99.31 ± 0.37	99.56 ± 0.22	99.19 ± 0.39	99.27 ± 0.15
In Vitro Drug Release in 10 min (%)	99.9	99.87	99.80	99.75

CONCLUSION

Orally dissolving films of cevimeline HCL were formulated with HPMC E15 and PEG 400 by using solvent casting technique. All formulation shows good drug release profile, drug content, folding endurance, disintegration time, pH and % elongation etc. Among that formulation F5 shows highest drug release, disintegration time, folding endurance and found to be stable at accelerated stability condition. Thus F5 batch considered as optimised formulation. Hence orally dissolving film of cevimeline HCL was found to be suitable for treatment of sjogrens disease.

ACKNOWLEDGEMENTS

The authors thank Aurobindo pharma ltd. Research centre II Hyderabad for providing cevimeline HCl drug as gift samples for this work. They also thank for providing required facilities to carry out this research work at School of Pharmacy SRTM University Nanded, Maharashtra, India.

CONFLICT OF INTEREST

None.

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