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Research Article

FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILM OF CLOZAPINE

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A R T I C L E I N F O

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A B S T R A C T

Objective: The aim of the present study was to develop the mouth dissolving film of Clozapine to treat the symptoms of schizophrenia. Solubility of drug was enhanced by cyclodextrin inclusion complexes, β-CD and HP β-CD, from which HP β-CD shows high solubility.Clozapine is a tricyclic dibenzodiazepine, classified as an atypical antipsychotic agent. Schizophrenia is a mental disorder characterized by a breakdown of thought processes and by a deficit of typical emotional responses. Schizophrenia is a challenging disorder that makes it difficult to distinguish between what is real and unreal, think clearly, manages emotions, and functions normally. So, dosage form which gives quick onset of action is needed. MDF was suitable dosage form. The objective was to formulate MDF having least disintegration time with a better mechanical strength which ultimately gives faster onset of action. **Experimental work:** The films were formulated by various film forming polymers (PVA, HPMC E15, PVP K30, Guar Gum and Xanthan Gum), Plasticizers (PEG 400, PG, and Glycerin), saliva stimulating agent (citric acid), sweetening agent (mannitol) and surfactant (tween 80), solubility enhancer (Hydroxyl propyl β-cyclodextrine). MDF were prepared by solvent casting technique. Trial batches were formulated to optimize plasticizer, polymer and polymer combination. The optimized plasticizer and polymer combination was selected, 3^2 factorial designs was applied and from factorial batches the batch with least DT and good mechanical properties was optimized and kept for stability study for 1 month.

Result: Trail batches, PG was optimized as plasticizer. While single polymer was not able to produce the film with desired quality, polymer combination was used. The polymer combination of HPMC E15 and PVA was optimized. Solubility of clozapine has been enhanced by Hydroxyl propyl β-cyclodextrin inclusion complex. Further factorial design was applied, the batch with 1000mg of HPMC E15 and 200mg of PVA was optimized and found stable after 1 month.The optimized batch of clozapine film having desired DT and mechanical propertiesthat is potentially usefulfor the treatment of depression were fast onset of action is required.

INTRODUCTION

The oral route is the most suitable and preferred route among all the other delivery for the administration of drug because of its ease administration, cost effective, no pain, easily acceptable, convenient and patient compliance. In recent times, fast dissolving dosage forms have been started gaining more recognition and acceptance. Oral dissolving films are helpful to the patient having difficulty in swallowing, pediatric and geriatric patients who have fear of choking traditional oral solid dosage form and as an alternate to tablet, capsules. The films are like similar to postage stamp in their size, shape and thickness. This type of dosage forms is mostly suitable for pain, CNS disorder, cough, nausea, allergic conditions etc.[6,7,8]

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Films, when placed on tongue, immediately hydrates by soaking saliva following disintegration and/ or dissolution releasing active pharmaceutical ingredient from the dosage form. This type of system consists of solid dosage forms that dissolve and/ or disintegrate rapidly in the oral cavity without the administration of water. The film is an ideal intra oral fast dissolving dosage form, which is easy to handle and administer, maintains a simple and convenient packaging, improve unpleasant taste. The film is placed on the top or the floor of the tongue, which holds on to the site of application and quickly releases the active agent for local and/or systemic absorption.[9,10]

Clozapine(6-chloro-10-(4-methylpiperazin-1-yl)-2,9-diazatricyclo[9.4.0.0^{3,8}]pentadeca-1(15),3,5,7,9,11,13-heptaene) is a tricyclic dibenzodiazepine, classified as an atypical antipsychotic agent. It binds several types of central nervous system receptors, and displays a unique pharmacological profile. Clozapine is a serotonin antagonist,

with strong binding to 5-HT 2A/2C receptor subtype. It also displays strong affinity to several dopaminergic receptors, but shows only weak antagonism at the dopamine D2 receptor, a receptor commonly thought to modulate neuroleptic activity. It is a Class II drug (High Permeability, low solubility).Main positive symptoms associated with this disease are hallucinations, delusions, disorganized thoughts, restlessness, insomnia, anxiety, fighting, aggression. Other negative symptoms are social withdrawal, poverty of speech, affective flattening.So, the above all mentioned symptoms require fast relief so for this MDF is most suitable which give fast action and it fits in the parameters for ideal characteristics for drug for MDF. (1) Low dose 12.5mg. (2) Low molecular weight 326.83 gm/mol.[11,12,13]

Mouth dissolving film**:** Ease of administration and may enhanced patient compliance especially in case of pediatric, geriatric. Convenient for dysphasic patient having difficulty in swallowing tablets and capsules. Convenient to administer during travelling without need of water. Fast disintegration, rapid release, fast absorption, quick onset of action. Large surface area available for dissolution of MDF than ODT. May enhanced oral bioavailability of molecule. Avoid first pass metabolism and smaller dose.Dosage form can be consumed at any place and any time as per convenience of the individual.[14,15]

MATERIAL AND METHOD

Material

Clozapine (Drug) powder was obtained from Swiss Pharma. And other Excipients like HPMC, PVP K30, PVA, Xanthan gum, Guargum, PG, Glycerin, PEG 400, Mannitol, Citric acid andTween 80were obtained from ACS chemicals.

Preparation of mouth dissolving film by Solvent casting technique

- Mouth dissolving films were prepared by using solvent casting technique. The required amount of film forming polymer was allowed to hydrate in a minimum amount of distilled water for10-12hours.Then it uniformly dispersed to get clear viscous solution of film forming polymer. Then after plasticizer was added to polymer solution. Then add other ingredients.
- Add HP β-CD inclusion complex to above solution with constant stirring to form clear viscous aqueous solution containing homogeneously dispersed drug. The above produced solution was set aside in uninterrupted condition until entrapped air bubbles were removed. The aqueous solution was casted in petridish made up of glass (62.17cm^2).

Dose calculation of Clozapine[17,18]

Oral dose of Clozapine is 12.5mg
Each film contains 12.5 mg of Clozapine
Area of each film = 2*2 =4 cm^2
Area of petridish =πr^2 (where r = Radius of petridish)
=3.14*(4.45)^2
=62.17cm^2
4 cm^2 area of film contains 12.5mg Clozapine
62.17cm^{2}area of film contains =62.17*25/4=194.28 mg of clozapine

To prepare clozapine-HP β- CD complexation, amount of clozapine and HP β-CD were taken according to 1:1 molar ratio.
Molecular weight of Clozapine= 326.83 gm/mol
Molecular weight of Hydroxyl propyl β cyclodextrin= 1375.371

SO, total amount of complex= 1375.371+ 326.823= 1702.194 mg of complex

Now, 326.823 mg of clozapine in 1702.194 mg of complex
12.5 mg of clozapine in 65.1038 mg of complex
So, for assay 65.1038 mg drug hydroxyl propyl β cyclodextrin was taken
Assay = 90%

So, according to assay
11.25 mg of clozapine in 65.1038 mg complex
12.5 mg of clozapine in 72.337 mg complex
So, according to area of petridish drug complex=

$\frac{62.17*72.337}{4}$= 1124.297 mg of complex was taken

RESULT AND DISCUSSION

Identification of drug

(1) By melting point: The melting point of drug was found out by capillary method and measured value was compared with the literature survey. 182ºC Reported (STD 180-184ºC)
(2) By λmax: Solution of Clozapine (5-40µg/ml) was prepared in the stimulated saliva (pH 6.8) and the solution was scanned for absorbance at 290 nm using UV spectrophotometer.

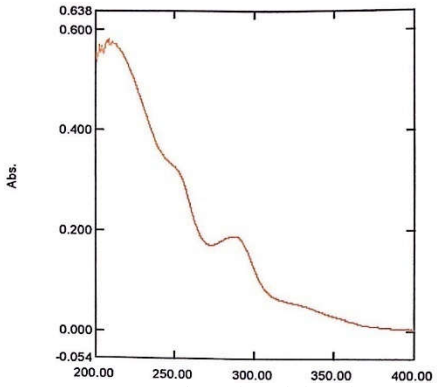

Figure 1 U.V absorption ofClozapine

By FTIR:The IR studies were carried out by Fourier Transform Infrared (FTIR) instrument.

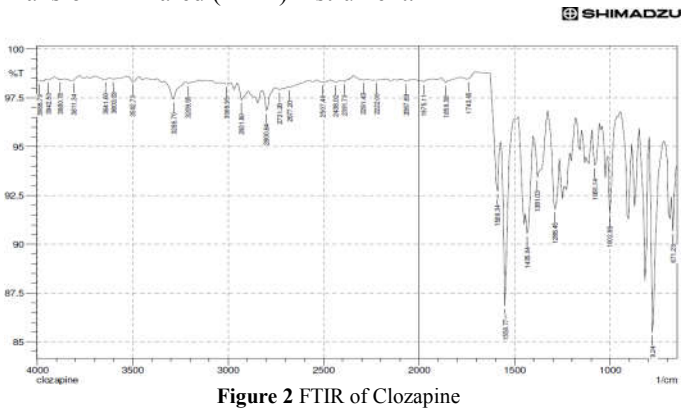

Figure 2 FTIR of Clozapine

Drug polymer interaction study by FTIR

Clozapine was mixed with combination of polymers in ratio of 1:1 and kept in FT-IR (Shimadzu Miracle 10)

Clozapine along with other excipients.

Table 1 Interpretation data of FTIR of drug and polymers

Functional group	Observed peaks
N=C	1690-1640 cm^{-1}
C-Cl	850-550 cm^{-1}
C=C	1600-1475 cm^{-1}
C-N-C	3300-3228 cm^{-1}

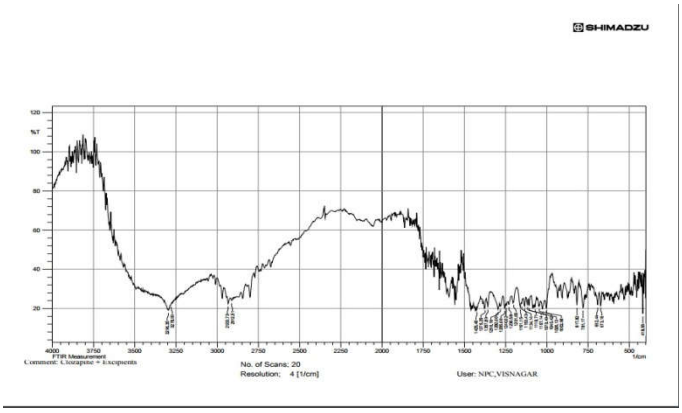

Figure 3 FTIR of Drugand Excipients

Observation from FTIR[20]

The interaction of clozapine with polymers like β-CD and HP β-CD was stuided using FT-IR spectroscopy method and it was found that clozapine had no interaction with polymers as revealed from figures and tables. So, clozapine is compatible with all the polymers.

Calibration curve in 6.8 phosphate buffer

Table 2 U.V. Spectrophotometer readings of Clozapine at 290 nm.[21]

calibration curve of clozapine in simulatory salivary fluid at λ max = 290 nm				
Concentration	Absorbance			Average
(µg/mL)	1	2	3	Absorbance ± SD
0	0	0	0	0
5	0.103	0.117	0.111	0.110 ± 0.007
10	0.172	0.179	0.175	0.175 ± 0.004
15	0.260	0.267	0.258	0.262 ± 0.005
20	0.320	0.332	0.336	0.329 ± 0.008
25	0.420	0.425	0.437	0.427 ± 0.009
30	0.507	0.519	0.518	0.515 ± 0.007
35	0.624	0.631	0.636	0.630 ± 0.006
40	0.695	0.702	0.704	0.700 ± 0.005
Absorbance = 0.0174x + 0.0028				
Correlation Coefficient = 0.997				

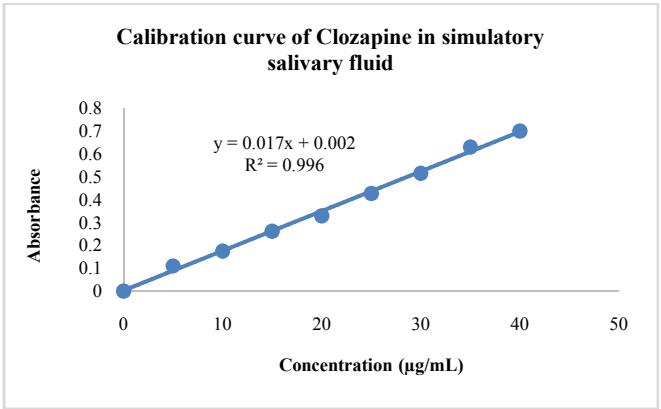

Figure 4 Calibration curve of Clozapine

Optimization of Plasticizer

Table 3 Formulations for optimization of plasticizer B1 to B5.

INGREDIENTS(mg)	B1	B2	B3	B4	B5
HPMC E15	1000	1000	1000	1000	1000
PolyvinylAlcohol (PVA)	200	200	200	200	200
Glycerin	2	-	-	-	-
PolyethyleneGlycol (PEG400)	-	2	-	-	-
Propylene glycol(PG)	-	-	0.7	1	1.5
Mannitol	80	80	80	80	80
Citric acid	60	60	60	60	60
Tween 80	q.s.	q.s.	q.s.	q.s	q.s
Distilled water	q.s	q.s	q.s.	q.s.	q.s

Above table include the material weighed for whole petridish area.

Table 4 Evaluation parameter for B1 toB5 batches.

Evaluationparameter	P1	P2	P3	P4	P5
1.Appearance	Moderate	Poor	Good	Good	Good
2.Mechanical Properties:					
Folding endurance	151	48	209	174	164
Tensile strength(gm/cm^2)	12	5	17	14	15
% Elongation	9.1	6.25	11.5	10.2	8.4
3. Thickness(mm)	0.08	0.1	0.11	0.11	0.11
4. Surface pH	6.57	6.59	6.56	6.55	6.57
5. Disintegration time (sec)	30	45	18	16	17

DISCUSSION

B1 batch contains glycerin as plasticizer. Films prepared thus having good appearance somewhat hard and films formed were transparent. It was having moderate plasticity. B2 batch contains PEG 400as plasticizer. Films thus prepared were found to be sticky and white spots were appearing in the film formed and showed less folding endurance. B3 batch contains PG as plasticizer, it has elegant transparent appearance as well as it can being easily separable from Petridish. Films were having good folding endurance as well as desired plasticity. Also film shows non sticky nature. According to above results, batch B3 produced the films of desired quality thus PG is optimized Plasticizer. Then from batch B3, B4, B5 it can be concluded that B3 20% W/W of polymer weight was given maximum folding endurance amongst all three batches. And elasticity was found to be good. And were transparent.[23,24]

Phase solubility study

Solubility measurement was performed by a reported method of Higuchi and Connors.

- The excess amount of pure drug is placed into a 10 ml vial containing different concentration of carriers in 10 ml of simulatory salivary fluid.
- The samples were placed on ultra sonicator and agitated for 24hrs.
- After attainment of the equilibrium, the content of each flask was then centrifuged.
- The supernant layer was diluted and assayed spectrophotometrically for clozapine content at 290nm.

Phase Solubility Study

- The solubility of Clozapine in simulatory salivary fluid was found to be 0.159 mg/ml.

- The influence of the inclusion complex upon the solubility of clozapine is presented figures.
- The influence of the inclusion complex upon the solubility of clozapine is presented in figures.
- The increase in the solubility was linear ($R^2 \approx 0.990$) with respect to the mole fraction of the inclusion complex.
- The increase in the solubility with increase in inclusion complex concentration indicates the solvent properties of carriers for thedrug.
- Indeed, carriers causes a decrease of the interfacial tension between the drug and the dissolutionmedium.

Preparation of inclusion complex[25]

Various ratios of inclusion complexes were prepared using β– Cyclodextrine and hydroxyl propyl β– Cyclodextrine by using solvent evaporation method and kneading method.

- Batches of inclusion complexes wereprepared
- β- CD:- 1:1, 1:2,1:3, 1:4 and1:5
- Hydroxyl propyl β- CD:- 1:1, 1:2,1:3, 1:4 and 1:5

Evaluation of inclusion complex of drug: HP β-CD

Table 5 Increase in solubility for β- CD inclusion complex by solvent evaporation method

Batch no.	Ratio of Clozapine: β- CD	Fold increase in solubility
Drug	Drug	0.159
PB1	1:1	3.51
PB2	1:2	3.55
PB3	1:3	3.07
PB4	1:4	2.55
PB5	1:5	2.10

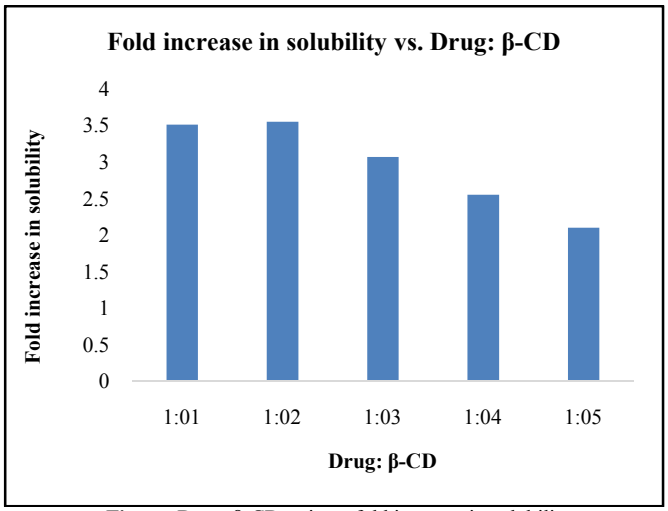

Figure Drug: β-CD ratio vs fold increase in solubility

Table 6 Increase in solubility of HP β- CD inclusion complex by solvent evaporation method

Batch no.	Ratio of Clozapine: HP β-CD	Fold increase in solubility
Drug	Drug	0.159
PH1	1:1	4.75
PH2	1:2	3.47
PH3	1:3	3.80
PH4	1:4	3.90
PH5	1:5	3.15

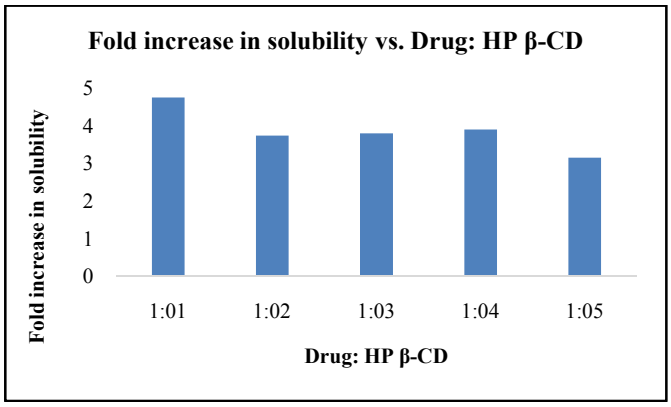

Figure Drug: HP β-CD ratio vs fold increase in solubility
Optimization of polymer

- From above evaluation parameters, it was found that the inclusion complex of HP β-CD shows better result as compared to β - CD.
- From above evaluation parameters, it was found that the inclusion complex with ratio 1:1 by solvent evaporation method gives most favorable result as compared to otherratios.
- This optimized polymer for inclusion complex was then utilized to find applicability in the development of dosageform.

Characterization of inclusion complexes Differential scanning calorimetry (DSC) study

Differential scanning calorimetry measurements were carried out with a differential scanning calorimeter (DSC 60) under nitrogen flow. Samples each of 2 mg were accurately weighed using a Sartorius electronic microbalance and sealed in aluminum DSC pans and placed in the DSC cell. The DSC was calibrated for temperature and enthalpy measurements in the standard way, using the melting of pure indium metal, as reference material. DSC runs were conducted over a temperature range from 50.00°C to 300°C at 10.00°C/min under nitrogen flow rate of 40 mL/min. An empty aluminum pan was used asreference. [26,27]

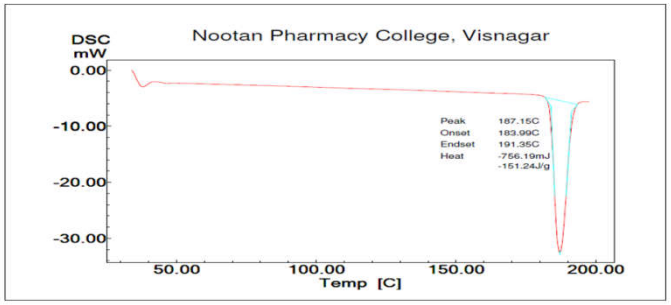

Figure 7 DSC peak of Clozapine

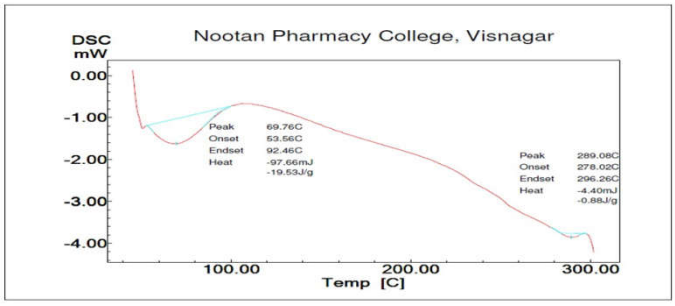

Figure 8 DSC peak of HP β- CD

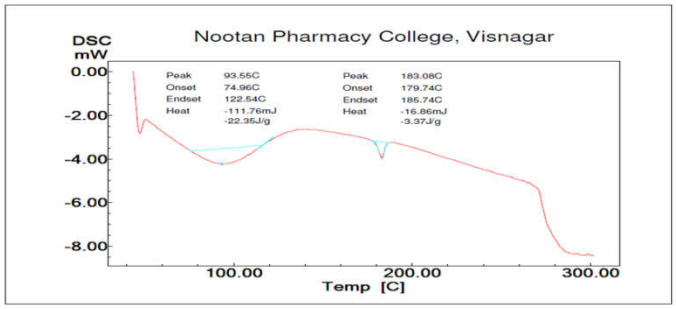

Figure 9 DSC peak of Clozapine: HP β- CD inclusion complex

The DSC curve of Clozapine showed a sharp endothermic peak (Peak =187.15 °C) corresponding to its melting point, indicating its crystalline nature. The thermal behavior of the HP β- CD is that expected for amorphous substances, with a large endothermic effect in the 183.08 °C range due to polymer dehydration. Thermal behavior of Clozapine and corresponding drug carrier system are depicted in Figure.

Optimization of Polymer[28]

Table 5 Formulations for optimization of polymer B6 to B10.

INGREDIENTS(mg)	B6	B7	B8	B9	B10
Clozapine+ HP β- CD complex	1124.297	1124.297	1124.297	1124.297	1124.297
Polyvinyl pyrrolidone K30 (PVP K30)	200	-	-	-	-
Polyvinyl Alcohol (PVA)	-	200	-	-	-
HPMC E15	-	-	1000	-	-
Xanthan gum	-	-	-	200	-
Guar gum	-	-	-	-	200
Propylene glycol (PG)	0.7	0.7	0.7	0.7	0.7
Mannitol	80	80	80	80	80
Citric acid	60	60	60	60	60
Tween 80	q.s.	q.s.	q.s.	q.s.	q.s.
Distilled water	q.s	q.s.	q.s.	q.s.	q.s.

Above table include the material weighed for whole petridish area.

Table 6 Evaluation parameter for B6 toB10 batches.

Evaluationparameter	P6	P7	P8	P9	P10
1.Appearance	Sticky	Good	Good	Sticky	Moderate
2.Mechanical Properties:					
Folding endurance	-	298	280	240	240
Tensile strength(gm/cm^2)	-	30.25	18.21	0.09	2
% Elongation	-	18.75	13.68	4.67	3.98
3. Thickness(mm)	-	0.13	0.1	0.09	0.1
4. Surface pH	-	7.43	6.57	6.43	6.47
5.Assay	-	79.42	80.2	72.8	67.74
5. Disintegration time (sec)	-	24	10	32	39

Table 7 In vitro drug release for B7 to B10.

TIME(min)	% CDR				
	B6	B7	B8	B9	B10
0	-	0	0	0	0
1	-	36.26	42.72	16.2	35.67
2	-	51.10	52.5	36.45	89.29
3	-	63.5	69.37	49.14	95.53
4	-	73.35	77.29	59.28	98.12
5	-	82.2	85.16	73.41	98.56

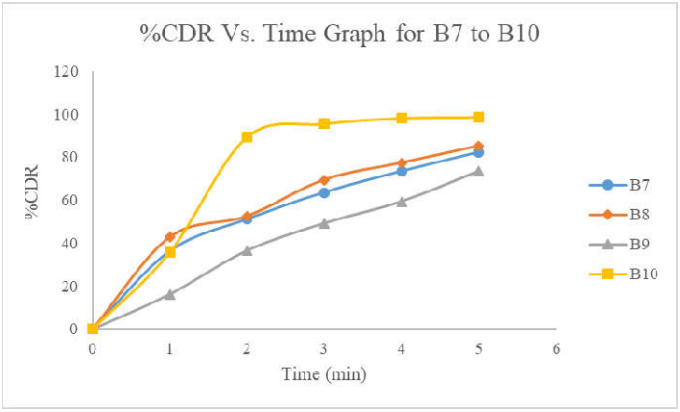

Figure 6 % CDR for batches B7 to B10.

DISCUSSION

B6 batch contains PVPK30 which is a highly hygroscopic and sticky material films produced by using PVPK30 showed poor separability from petridish and so, peeling of film was not possible and it had an unacceptable physical characteristic. B7 batch contains PVA, that produced soft film and drug release from this was found to be good. Also it had good folding endurance value and % Elongation is high. B8 batch contains HPMC that produced thin and plastic like film. It showed very fast disintegration i.e. less disintegration time and gives good drug release profile. B9 batch contains Xanthan Gum it is dispersed uniformly in a petridish and produces the film and somewhat sticky nature. On contact with dissolution medium it swells and forms viscous solution which doesn't allow desirable drug release. B10 batch contains Guar gum that wasn't dispersed uniformly in the solvent and the solution became hazy and films produced were not transparent. Here uniform drug release didn't obtain due to ununiform film layer. According to above results obtained of these batches, we can say that no individual polymer was able to produce film of desired property and quality, to overcome this problem the combination of polymers were taken for further batches. Combination of HPMC E15 with other polymers was chosen because HPMC E15 has low viscosity and it helps in faster disintegration of film.[29]

Optimization of Polymer combination[30,31]

For the consistency of each batch, two formulations were formulated for each batch and evaluation was done for that.

Table 8 Formulations for optimization of polymer combination B11 to B14.

INGREDIENTS(mg)	B11	B12	B13	B14
Clozapine+ HP β- CD complex	1124.297	1124.297	1124.297	1124.297
HPMC E15	1000	1000	1000	1000
PVA	200	-	-	-
PVPK30	-	200	-	-
Xanthan Gum	-	-	200	-
Guar Gum	-	-	-	200
Proplene glycol(PG)	0.7	0.7	0.7	0.7
Mannitol	80	80	80	80
Citric acid	60	60	60	60
Tween 80	q.s.	q.s.	q.s.	q.s.
Distilled water	q.s.	q.s.	q.s.	q.s.

Table 9 Evaluation parameter for B11 toB14 batches.

Evaluation Parameter	P11	P12	P13	P14
1.Appearance	Good	moderate	poor	Moderate
2.Mechanical Properties				
Folding endurance	298	59	55	78
Tensile strength(gm/cm^2)	23	2.45	3.84	1.72
% Elongation	11.45	2.36	6.75	6.52
3. Thickness(mm)	0.1	0.1	0.11	0.11
4. Surface pH	6.56	6.48	6.31	6.31
5. Assay(%)	86.45	73.45	75.62	78.62
6. Disintegration time(sec)	21	46	36	49

Table10 In vitro drug release for B11 to B14.

TIME(min)	% CDR			
	B11	B12	B13	B14
0	0	0	0	0
1	62.49	30.23	26.42	39.53
2	70.55	34.49	32.19	47.28
3	84.32	70.98	50.09	51.49
4	86.82	71.12	74.15	89.52
5	87.09	74.95	78.61	

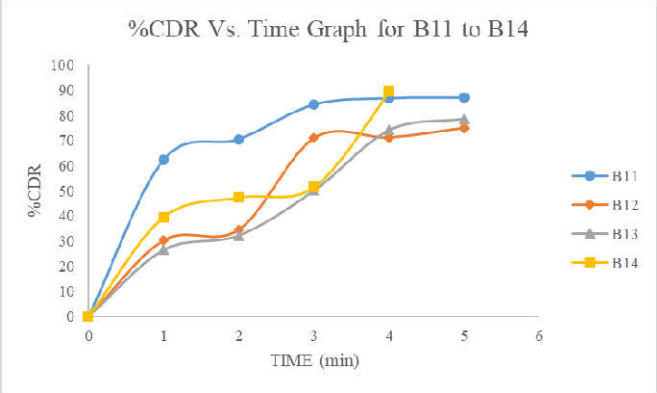

Figure7 %CDR for Batches B11 to B14

DISCUSSION

B11 batch contains combination of HPMC E15 and PVA, films formed were smooth and soft tensile strength value was found to be moderate and % elongation value was found to be high (good).The good drug release profile was also good. B12 batch contains combination of HPMCE15 and PVP K30, films formed were found to be smooth and hard. Drug release was less as compare to individual polymer.B13 batch contains combination of HPMC E15 and Xanthan gum, films produced were transparent but white spot were observed on surface of film after a time interval. Drug release was found to be slower than desired. B14 batch contains combination of HPMCE15 and Guar gum. Films produced were soft but white spots are seen within film and tensile strength was poor. Uneven drug release was found. From above results it can be concluded that films prepared by B11 batch acquires desired characteristics. And hence the polymer combination of HPMCE15 and PVA was the optimized one.[32]

3^2 factorial design was applied to optimized batch

Table11 Formulation of factorial batches F1 to F9.

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clozapine+HP β Cyclodextrine	1124.297	1124.297	1124.297	1124.297	1124.297	1124.297	1124.297	1124.297	1124.297
HPMC E15	500	1000	1500	500	1000	1500	500	1000	1500
PVA	200	200	200	300	300	300	400	400	400
Propylene glycol	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Mannitol	80	80	80	80	80	80	80	80	80
Citric acid	60	60	60	60	60	60	60	60	60
Tween 80	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table12 Evaluation Parameters for F1 to F5:

Evaluation Parameters	Factorial Batch				
	F1	F2	F3	F4	F5
Appearance	Good	Moderate	Good	Moderate	Good
Separability	++	+	++	+	++
Folding Endurance	>150	>200	>200	>275	>275
Mechanical Properties					
• Tensile Strength (gm/cm^2)	22.20±0.45	25.48±0.64	29.25±0.54	56.12±0.54	43.72±0.21
• % Elongation	9.45	11.48	10.19	24.34	27.55
Thickness (mm)	0.09±0.013	0.10±0.011	0.10±0.012	0.10±0.01	0.10±0.008
Surface pH	6.52	6.23	5.92	5.77	6.48
Disintegration Time (sec)	14	20	32	23	14
Assay (%)	93.32	85.89	98.35	93.84	93.83
Bitter Index	2	2	1	1	1

Table13 In Vitro drug release for F1 to F5

Time (min)	%CDR				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	41.32±0.64	39.23±0.89	47.26±0.61	47.09±0.51	51.36±0.43
2	49.08±0.64	47.17±0.75	53.28±0.62	63.75±0.47	69.16±0.69
3	56.92±0.42	61.28±0.67	74.8±0.65	69.95±0.68	79.04±0.58
4	69.2±0.68	67.09±0.25	80.18±0.31	76.57±0.57	85.01±0.84
5	86.63±0.39	83.95±0.54	87.4±0.44	83.21±0.74	92.75±0.56

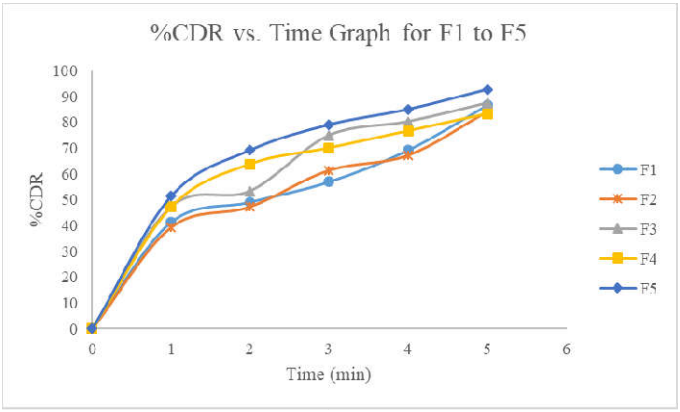

Figure 8 % CDR for batches F1 to F5

Table14 Evaluation Parameters for F6 to F9

Evaluation Parameters	Factorial Batch			
	F6	F7	F8	F9
Appearance	Moderate	Good	Good	Good
Separability	++	+	++	++
Folding Endurance	>300	>300	>250	>250
Mechanical Properties				
• Tensile Strength	60.86±0.25	51.36±0.28	66.44±0.64	77.08±0.17

(gm/cm^2)				
• % Elongation	21.29	25.33	32.57	27..48
Thickness (mm)	0.1±0.04	0.09±0.02	0.11±0.013	0.12±0.008
Surface pH	6.78	6.73	5.98	6.25
Disintegration Time (sec)	35	18	27	40
Assay (%)	98.68	87.79	79.14	90.82
Bitter Index	1	1	2	1

Table15 In Vitro drug release for F6 to F9

Time	%CDR			
(min)	F6	F7	F8	F9
0	0	0	0	0
1	45.39±0.03	43.79±0.46	56.28±0.36	55.82±0.60
2	68.37±0.17	65.09±0.70	65.28±0.83	72.09±0.53
3	76.43±0.73	75.39±0.29	72.67±0.47	78.68±0.45
4	82.3±0.67	83.68±0.58	81.39±0.39	82.07±0.50
5	87.16±0.71	88.16±0.41	82.17±0.74	87.43±0.57

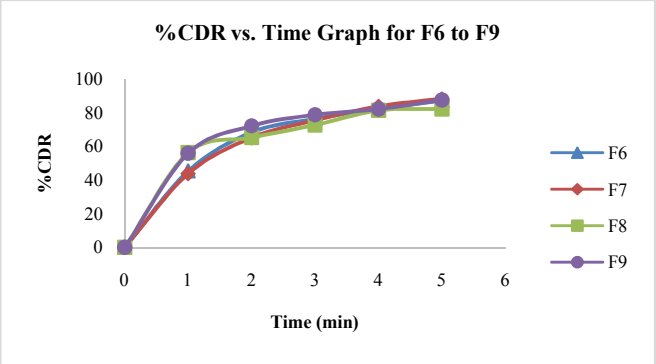

Figure 9 % CDR for batches F6 to F9

DISCUSSION

Factorial batch F1 produced films having good appearance and were having good separability but tensile strength value was less as compared to other and drug release profile was not desirable. F2 batch produced film with moderate appearance. Factorial batch F3 produced film having good appearance, but here disintegration time measured was also somewhat high. Factorial batches F4, F6, F7 produced films having somewhat higher disintegration time as compared to F4 batch. F6 curled on edges. And F4, F6, F7 they have good tensile strength. Factorial Batch F9 produced films having very high tensile strength which was not desirable and F8 produce film with moderate tensile strength but disintegration time was somewhat higher as compared to F5. Batch F9 was gave desirable drug release profile due to higher PVA content, but it having higher disintegration time as compared to all other batches because of higher polymer content. Factorial batch F5 has given less disintegration time. Also it having desirable mechanical properties that are comparatively moderate tensile strength and having desirable % elongation that means soft and tough film formulated. Thus, F5 considered as an optimized batch. Also it releases the drug in a desirable manner.[33,34]

Stability Study

Stability studies were done according to ICH guidelines. The stability studies were carried out on the optimized satisfactory formulations as per ICH guidelines. The optimized formulation after factorial design batch F4 was sealed in aluminum foil packaging and kept in humidity chamber at fixed temperature and humidity. Here stability study was carried out in accelerated conditions at 40 ± 2° C and 75 ± 5 % RH for 1 month.

Table 16 Evaluation after one month.

Evaluation parameters	Batch F5	
	Initial Data	After 1 month
Appearance	Good	Moderate
Separability	++	-
Folding Endurance	>300	>250
Mechanical Properties		
• Tensile Strength (gm/cm^2)	43.12	38.10
• % Elongation	27.58	26.42
Thickness (mm)	0.10	0.10
Surface pH	6.45	6.32
Disintegration Time (sec)	15	14
Assay (%)	96.12	93.91
Bitter Index	1	1

Table 17 In vitro drug release before and after.

Time (min)	%CDR (F5 Batch)	
	Initial Data	After 1 month
0	0	0
1	51.36	53.52
2	69.16	67.63
3	79.04	75.93
4	85.01	81.69
5	92.75	89.98

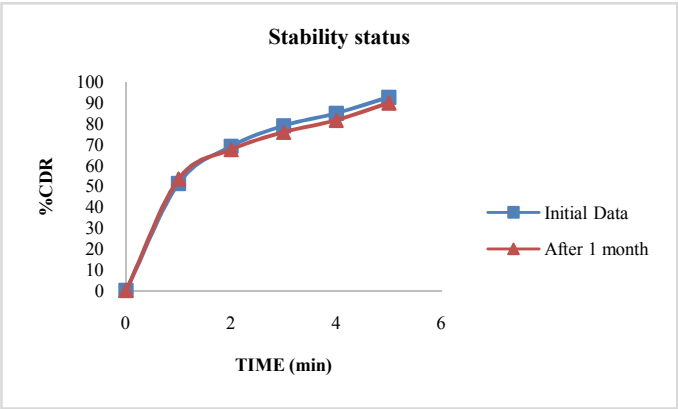

Figure10 %CDR vs. Time Graph for Batch of stability study.

From the above stability data at 40°C/75% RH, shows that there was no significant difference in %CDR of the formulation F4 before and after a month results. This concluded that the optimized formulation has sufficient stability at 40 °C and 75 % RH and extrapolated that formulation was stable at room temperature. . So, the formulation after one month was found to be stable.[36,37]

CONCLUSION

According to various batches formulated, it was concluded that amongst Preliminary batches B1 to B5 (plasticizer and its concentration) batch B4 containing PG was optimized as plasticizer as it produced clear and smooth film with good elasticity and folding endurance. From B6 to B10 (single polymer batches) no one was able to produce film with desired properties. So, Batches B11 to B14 were formulated that had combination of Polymer. From that B11 batch was optimized one which contained combination of polymer HPMC E15 and PVA.Then 3^2 factorial designs were applied and all the F1 to F9 batches were evaluated. Factorial batch F5 was concluded as optimized batch by taken in consideration of different

evaluation parameters which have desired properties. Factorial batch F5 had contained HPMC E15 and PVA in 1000mg and 300mg quantity respectively in a combination. Optimized batch F5 was kept for stability study for a month and readings were taken after one month.

The optimized batch produced the film containing drug Clozapine was having desired disintegration time and mechanical properties that is potentially useful for the treatment of depression where faster onset of action is required.

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