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Formulation and Evaluation of Mouth Dissolving film using Semi Solid Casting Method

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Abstract

Mouth dissolving film is now a days preferred route of drug administration due to patient compliance. The developed film formulation is a patient-friendly formulation that would be useful for people who have difficulty of swallowing. The results have shown that the HPMC-K4M is good film former and shows bioadhesion property. In combination with PEG-400, it has shown promising fast drug release within 10 min. and good folding endurance. Hence a semi-synthetic cellulose derivative which is affordable and abundantly available can be used as a potential drug release modifier and also used to improve flexibility and processability in the mouth dissolving films. Successful formulation of Cariprazine mouth dissolving films may prevent first pass metabolism to a large possible extent. From the present study it can be concluded that HPMC-K4M based mouth dissolving films of Cariprazine can be successfully prepared with considerable good stability and improved bioavailability.

Key words: Mouth dissolving film, Formulation, Semi Casting Method

Introduction

Oral route is the preferred route for administration of therapeutic agents, providing a convenient method of effectively achieving both local and systemic effects. Routes of drug administration that can be utilized to achieve systemic delivery of a drug include parenteral, oral buccal, Transdermal, nasal and pulmonary. No single route matches all the physiological requirements of an "ideal" absorption site. But, considering surface area, low metabolic activity, contact time, blood supply, accessibility, lack of variability and permeability, relatively oral route is having more suitable characteristics for absorption of drugs. Among the pharmaceutical dosage forms, oral dosage forms are having maximum attribute of ideal dosage forms Patients are usually. [1-3] accustomed to orally delivered drugs and find the method non-invasive.

It is estimated that around 80% of all medications used utilize the oral route, in which tablets, capsules and granules continue to remain the dosage form of first choice. It is consequently important that oral drug delivery technology continues to proceed and improve the safety and efficacy of treatment. Oral dosage forms represent most of the drug delivery market because of the safety, efficacy, economic, and consumer compliance advantages they possess over alternative routes of delivery. [4-6]

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Hallucinations, dementia, and convulsions are all symptoms of psychosis. It must be treated early in order to limit the risk of long-term brain damage. Pharmacotherapy with antipsychotic medications is still the most prevalent treatment for psychosis. The treatment of psychosis differs from that of other illnesses. A newer antipsychotic in an orally dissolving film format is an appropriate pharmaceutical candidate. Antipsychotics designed as an orally dissolving strip that must be placed on the patient's tongue without being swallowed to deliver the dose would substantially simplify dose administration and improve patient compliance. The goal of this study was to design, develop, and characterise antipsychotic medication mouth dissolving films. Cariprazine Hydrochloride is a atypical antipsychotic drug that has demonstrated to be effective in the treatment of schizophrenia. Cariprazine hydrochloride is used to treat schizophrenia and mania. It is considered a BCS class II drug. It has a solubility problem. Cariprazine Hydrochloride is rapidly absorbed and extensively metabolised through demethylation. It binds to dopamine D_2 and D_3 receptors. [7-10]

The goal of this research is to develop an oral mouth dissolving film that will improve the medicine's solubility, Fast dissolving film provides several benefits, particularly for paediatric and geriatric patients who have difficulty swallowing regular pills and capsules, and it increases patient compliance.

Material and Methods [11-12]

Identification of Drug (Physical Appearance)

Through visual inspection, the physical appearance of pure drug will be carried out as per Indian Pharmacopoeia.

Determination of Melting Point

Melting range of substance is defined as those point of temperature within which or the point at which, the substance begins to coalesce and is completely melted. Melting point of Granisetron HCl is determined by capillary melt method using melting point apparatus. A small amount of drug sample was kept at open end of capillary tube and placed in melting point apparatus. The sample was observed continuously. The melting range was recorded from starting of first melt to completely melt of sample.

Determination of Solubility

The dissolution and diffusion fluid for drug release and permeation studies respectively were selected based on solubility data of Cariprazine in various fluids. The solubility of drug sample was determined by adding 100 mg of drug sample in successively increasing amount in various fluids. The volume of solvent required to dissolve the drug was recorded and solubility was determined.

Determination of Partition Coefficient

The partition coefficientof drug was determined in n-Octanol as a non-aqueous phase and phosphate buffer solution pH 7.4 (PBS pH 7.4) as an aqueous phase. These two phases were mixed in equal quantities and kept forsaturation with each other in separating funnel. After mixing the system remain undisturbed for 30 minutes. The partition coefficient was determined by taking 10 mg of drug in separating funnels containing 10 ml portion of each of n-Octanol and PBS pH 7.4. The separating funnels were shaken on mechanical shaker for 24 h. Two phases were separated and aqueous phase was filter through Whatman filter paper and the amount of the drug in aqueous phase was determined, after appropriate dilution by spectrophotometrically at λmax 318 and 248 nm by using phosphate buffer solution pH 7.4 as a blank.

Determination of UV Absorption Maxima

The accurately weighed quantity 100 mg of drug sample was dissolved in mixture of water and acetonitrile (1:1) (3 in 200,000) and volume make upto 100 ml using water and acetonitrile in 100 ml volumetric flask toobtain a stocksolution 100 µg/ml. Then 1 ml of this stocksolution was pipetted out in a 10 ml volumetric flask and volume was made upto the mark toobtained the concentration 10 µg/ml. The resulting solution was then scanned between 200-400 nm using UV-visible spectrophotometer(Model-1700, Shimadzu, Japan). The UV spectrum sample was recorded and obtainedλ max was matched with the UV spectrum as reported in officialmonograph. [44-]

Fourier Transform Infrared (FT-IR) Spectroscopy

The infrared spectroscopyof the pure drug sample was carried outto identity the drug. A pellet of drug was prepared by compressingof the drug with IR grade potassiumbromide by applying of 5.5 metric tonofpressure in KBr press. The pellet

was mounted in IR compartment and scanned between wave number 4000-450 cm-1 using FTIR spectrophotometer (Model-8400 S, Shimadzu, Japan).

Calibration Curve

Preparation of standard stock solution (100 µg/ml) in 0.1N HCL

Accurately weighed 100 mg of drug in 10ml volumetric flask. The volume was then made upto 100 ml by using 0.1N HCL solution to obtain the solution of 100µg/ml. From the stock solution (100 µg/ml) 1ml was pippeted and diluted to 10 ml by using 0.1N HCL solution into different volumetric flask and made up to 10 ml with 0.1N HCL solution so as to get concentration of 1.0 to 5.0 µg/ml

Preparation of standard working solution

From the stock solution (100 µg/ml) 1ml was pippeted and diluted to 10ml by using 0.1N HCL solution. From the solution appropriate aliquuots was taken into different volumetric flask and made up to 10ml with 0.1N HCL solution so as to get concentration of 1.0 to 5.0 µg/ml

The calibration curve of drug in 0.1 N HCl was prepared with dissolving accurately weighed 100 mg of drug in 100 ml volumetric flask. The volume was then made upto 100ml by using 0.1N HCL solution to obtain the solution of 100µg/ml and was scanned in UV spectrophotometer and the sample obeys the beer-lamberts law.[46-47]

Formulation of Mouth Dissolving Films

The mouth dissolving films of Cariprazine was prepared by semi solid casting method. Different viscosity grades of polymers as film formers and plasticizers employed in the film.

Preliminary Screening of Polymers and Batch Preparation with Preliminary Evaluation

The drugs Cariprazine along with various ingredients like polymer, plasticizer, solvent, sweetening agents, flavoring agents and preservatives were used in different proportion as mentioned below to form the moth dissolving films and after the successful optimization the final formula was made.

Tabel No. 1: List of ingredients

Abbr./Ingredients	Name
D	Drug (Cariprazine)
P1	HPMC E5 (hydroxypropyl methylcellulose)
P2	HPMC K4M (hydroxypropyl methylcellulose)
P3	PVA (polyvinyl alcohol)
P4	PVP (polyvinylpyrrolidone)
P5	Acacia
P6	Tragacanth
P7	Gelatin
P8	Xanthum gum
PL1	PEG 200 (polyethylene glycol)
PL2	PEG 400 (polyethylene glycol)
PL3	PEG 800 (polyethylene glycol)
PL4	Crospovidone
PL5	Kyron T-314
PL6	Banana powder
Sweetening agents	Aspartame Mannitol
Flavoring agents	Orange flavour
Preservatives	Citric acid Methyl paraben Propyl paraben
Solvent	Distilled water

Table 1: Preliminary trial batch for selection of polymer P1 & P2

Ingredients	PT1	PT2	PT3	PT4	PT5	PT6
Drug	100	100	100	100	100	100
P1	0.25	0.50	0.75	1.0	1.25	1.50
P2	1.50	1.25	1.0	0.75	0.50	0.25
PEG 200	0.2	0.2	0.2	0.2	0.2	0.2
DW	Qs	Qs	Qs	Qs	Qs	qs

Table 2: Preliminary trial batch for selection of polymer P3 & P4

Ingredients	PT7	PT8	PT9	PT10	PT11	PT12
Drug	100	100	100	100	100	100
P3	0.25	0.50	0.75	1.0	1.25	1.50
P4	1.50	1.25	1.0	0.75	0.50	0.25
PEG 200	0.2	0.2	0.2	0.2	0.2	0.2
DW	Qs	Qs	Qs	qs	Qs	qs

Table 3: Preliminary trial batch for selection of polymer P5 & P6

Ingredients	PT13	PT14	PT15	PT16	PT17	PT18
Drug	100	100	100	100	100	100
P5	0.25	0.50	0.75	1.0	1.25	1.50
P6	1.50	1.25	1.0	0.75	0.50	0.25
PEG 200	0.2	0.2	0.2	0.2	0.2	0.2
DW	Qs	Qs	Qs	qs	Qs	qs

Table 4: Preliminary trial batch for selection of polymer P7 & P8

Ingredients	PT19	PT20	PT21	PT22	PT23	PT24
Drug	100	100	100	100	100	100
P7	0.25	0.50	0.75	1.0	1.25	1.50
P8	1.50	1.25	1.0	0.75	0.50	0.25
PEG 200	0.2	0.2	0.2	0.2	0.2	0.2
DW	Qs	qs	Qs	qs	Qs	qs

Table 5: Preliminary trial batch for selection of plasticizer PL1 & PL2

Ingredients	PT25	PT26	PT27	PT28	PT29	PT30
Drug	100	100	100	100	100	100
PL1	0.25	0.50	0.75	1.0	1.25	1.50
PL2	1.50	1.25	1.0	0.75	0.50	0.25
P1	0.5	0.75	1	-	-	-
P2	-	-	-	0.5	0.75	1
DW	Qs	Qs	Qs	qs	qs	qs

Table 6: Preliminary trial batch for selection of plasticizer PL3 & PL4

Ingredients	PT31	PT32	PT33	PT34	PT35	PT36
Drug	100	100	100	100	100	100
PL3	0.25	0.50	0.75	1.0	1.25	1.50
PL4	1.50	1.25	1.0	0.75	0.50	0.25
P1	0.5	0.75	1	-	-	-
P2	-	-	-	0.5	0.75	1
DW	Qs	Qs	Qs	qs	qs	qs

Table 7: Preliminary trial batch for selection of plasticizer PL5 & PL6

Ingredients	PT37	PT38	PT39	PT40	PT41	PT42
Drug	100	100	100	100	100	100
PL5	0.25	0.50	0.75	1.0	1.25	1.50
PL6	1.50	1.25	1.0	0.75	0.50	0.25
P1	0.5	0.75	1	-	-	-
P2	-	-	-	0.5	0.75	1
DW	Qs	Qs	Qs	qs	Qs	qs

Table 8: Formulation of mouth dissolving film of Cariprazine Hydrochloride

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug (mg)	100	100	100	100	100	100	100	100	100	100	100	100
HPMC E5 (gm)	0.5	0.75	1	-	-	-	1	0.5	0.75	-	-	-
HPMC K4M (gm)	-	-	-	0.5	0.75	1	-	-	-	1	0.5	0.75
PEG 400 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Citric acid (mg)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Aspartame (mg)	10	20	30	10	20	30	10	20	30	10	20	30
Mannitol (mg)	100	75	50	100	75	50	100	75	50	100	75	50
Orange Flavor (ml)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Methyl Paraben (mg)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Propyl Paraben (mg)	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
DW (ml)	qs	qs	Qs	Qs	qs	Qs	qs	qs	qs	qs	qs	Qs

Evaluation of Mouth Dissolving Films

The formulations were evaluated by the following tests. [13-15]

Thickness

Randomly 10 films were selected and thickness was measured using a digital screw gauge, (Digimatic outside micrometer, Mitutoyo, Japan). The individual film was placed between two anvils of the screw gauge and sliding knob was rotated until the film was fitted. The digital reading displayed was noted.

Weight variation

20 films were randomly selected from each formulation and the average weight variations were determined.

Drug Content

Each Film was taken in 100 ml volumetric flask containing phosphate buffer pH 6.8 and sonicated for 20 minutes and the volume was made up to 100 ml. An aliquot of solution was filtered through 0.22 µ filter and the UV absorbance was measured and the drug concentration was determined, using standard graph obtained between concentrations (1 to 8 µg/ml).

Measurement of mechanical properties

Microprocessor based advanced force gauge tensiometer (DS 2 series) equipped with a 50 kg load cell was used to determine the mechanical properties of OFDFs. Film of 60x10 mm2 was fixed between two clamps separated by a distance of 3 cm. The lower clamp was held stationary and the strips were pulled apart by the upper clamp moving at a rate of 2 mm/sec until the strip broke. The force and elongation of the film at the point when the strip broke was recorded. The tensile strength and percent elongation values were calculated using the following formula.

Tensile strength = load at breakage/film thickness × film width

% Elongation = increase in length ×100/original length

Folding endurance

Folding endurance was determined by folding of the strip repeatedly at the same place till the strip breaks. Number of times the film is folded without breaking is computed as the folding endurance value.

Physical appearance and texture analysis of the films

These parameters were checked simply with visual infection of films and by feel or touch.

***In vitro* disintegration test**

The film of (4.15cm2) size (unit dose) was placed on a petridish containing 10 ml of distilled water. The time required for the film to break was noted as cursive *in vitro* disintegration time.

***In vitro* dissolution studies**

Drug release of film was studied by using dissolution test apparatus. Desired formulation (film) were placed in the vessels of dissolution apparatus. Samples were collected at time intervals of 2, 5,10,15,20,25,30,40 and 60 m, replenished with equal volume of the blank solution. The samples were filtered immediately and analyzed for the drug concentration and calculated the percentage (%) of drug dissolved or released. The release studies were performed on 3 films and mean values were taken.

Results and Discussion

Fast dissolving films for oral administration was a novel approach,for the patients who experience difficulties in swallowing tablets or capsules. Geriatric, pediatric and dysphasic patients associated with many medical conditions face a problem of difficulty in swallowing the solid dosage forms. Psychosis is a condition characterized by the hallucination, dementia etc. seizures. It requires quick management of in order to avoid the risk of permanent brain damage. Pharmacotherapy with anti-psychotic drugs remains the major treatment modality for psychosis. The formulation of anti-psychotic as a mouth dissolving film is the need required to be placed on the patient's tongue without swallowing for dose administration, would significantly facilitate dose administration, with subsequent improvement in patient compliance. The present work carries the result aim of this work was to design, develop and characterize mouth dissolving film of the drug Cariprazine for the treatment of psychosis.

Physical Appearance

Through visual inspection, the physical appearance of pure drug was carried out as per Indian Pharmacopoeia. In this study color odor and taste was evaluated by our sense i.e., eye, tounge and nose. It was revealed that the drug is white in color having characteristics odor and bitter taste. Results were presented in table 6.1.

Determination of Melting point

The melting point was determined of pure drug Cariprazine and was found to be 235-239^{0}C. A comparison with standard has been mentioned in table 6.2.

Table 5.1: Preliminary screening of drug

S/No.	Parameters	Cariprazine
1.	Color	White
2.	Odor	Characteristics
3.	Taste	Bitter

Table 5.2: Determination of melting point of drug

S/No.	Sample	Melting Point	
		Observed value	Standard value
1.	Cariprazine	235-239^{0}C	235-239^{0}C

Determination of solubility

The solubility was determined of pure drug Cariprazine in different solvents as mentioned in table 6.3 the drug is soluble in Water.

Determination of partition coefficient

The partition coefficient was determined of pure drug Cariprazine in n-Octanol as a non-aqueous phase and phosphate buffer solution pH 7.4 (PBS pH 7.4) as an aqueous phase. The results obtained were mentioned in table 6.4.

Determination of UV absorption maxima

The drug Cariprazine was scan to determine the λ max, the value obtained was compared with that of standard.

Table 5.3: Determination of Solubility of Cariprazine

S/No.	Solvent	Inference
1.	HCl	Soluble
2.	Ethanol	Freely Soluble
3.	Methanol	Freely Soluble
4.	Water	Sparingly Soluble
5.	DMSO	Soluble

Table 5.4: Determination of Partition Coefficient of selected Drug

S/No.	Sample	Partition Coefficient
1.	Cariprazine	4.32

Table 5.5: Wavelength maximum (λ max) of Cariprazine

Drug	λ max	
	Actual λ max	Observed λ max
Cariprazine	**218**	**220**

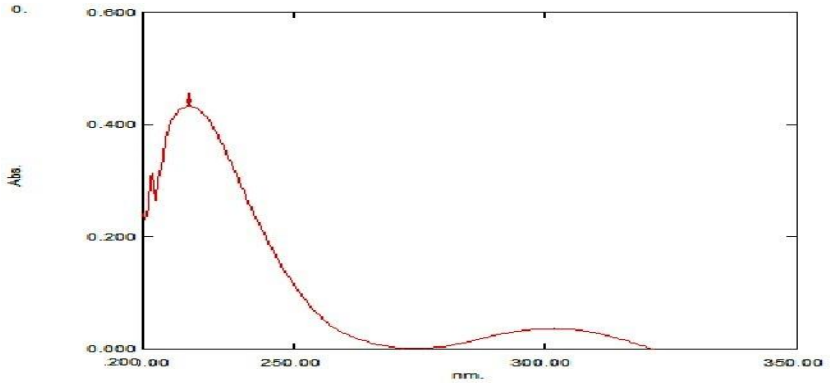
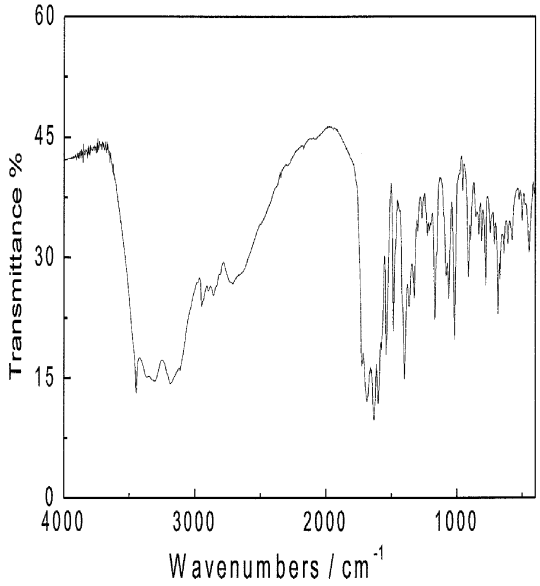


Fig. 5.1: UV Spectrum of Cariprazine

Fourier Transform infrared (FT-IR) Spectroscopy



Calibration curve

The calibration curve of drug Cariprazine in 0.1 N HCl was prepared with dissolving accurately weighed 100 mg of drug in 100 ml volumetric flask. The volume was then made upto 100ml by using 0.1N HCL solution to obtain the solution of 100µg/ml and was scanned in UV spectrophotometer and the sample obeys the beer-lamberts law.

Table 5.7: Calibration Curve of Cariprazine in 0.1 N HCl (pH 1.2)

Conc. (µg/ml)	Absorbance (nm) Mean ±SD; n=3
1	0.144±0.882
2	0.192±0.003
3	0.318±0.193
4	0.439±0.176
5	0.556±0.851
6	0.591±0.004
7	0.714±0.410
8	0.779±0.028
9	0.931±0.190
10	0.978±0.002

The pure drug was scan for FTIR in order to characterize the drug. The detail scan image and data are presented in figure 6.2 and table 6.6

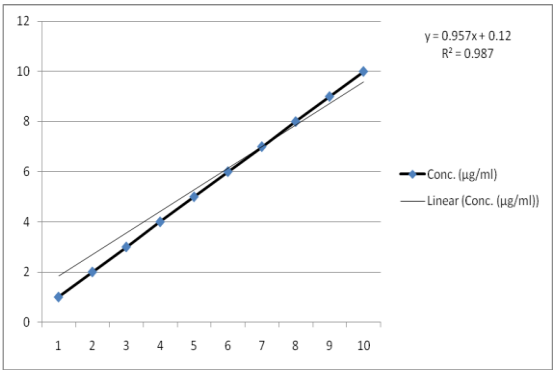


Fig. 5.3: Standard curve of Cariprazinein 0.1 N HCl (pH 1.2) at 248 nm

Selection of polymers and batch preparation

The drugs Cariprazine along with various ingredients like polymer, plasticizer, solvent, sweetening agents, flavoring agents and preservatives were used in different proportion as mentioned below to form the moth dissolving films and after the successful optimization the final formula was made. The results for various preliminary batches were given in table 6.6 and 6.7. From the results obtained in preliminary trial batches for selection of polymer P1 to P8 it was observed that the best results were obtained in polymer **P1** and **P2** in the concentration range of **0.5, 0.75** & **1.0**, therefore these two polymers were selected for the formulation of final MDFs. From the results obtained in preliminary trial batches for selection of plasticizer PL1 to PL6 it was observed that the best results were obtained in **PL2** in the concentration range of **0.5**, therefore it was selected for the formulation of final MDFs.

Table 5.8: Results for physicochemical properties of trial batches of mouth dissolving film of Cariprazine

Batch	Physical appearance	Surface Texture	Weight uniformity (mg) (Mean±SEM)	Surface pH (Mean±SEM)	Thickness (mm) (Mean±SEM)
PT1	Transparent	Smooth	98±0.48	6.9±0.21	0.15±0.006
PT2	Transparent	Smooth	100±0.03	6.9±0.12	0.16±0.007
PT3	Transparent & non-sticky	Smooth	98±0.36	6.4±0.19	0.17±0.009
PT4	Transparent & non-sticky	Smooth	101±0.28	6.8±0.01	0.17±0.004
PT5	Transparent & non-sticky	Smooth	100±0.68	6.7±0.02	0.16±0.008
PT6	Transparent & non-sticky	Smooth	99.97±0.34	6.4±0.0.10	0.16±0.002
PT7	Transparent & non-sticky	Smooth	98±0.01	7.0±0.29	0.12±0.003
PT8	Transparent	Smooth	110±0.03	7.1±0.39	0.11±0.004
PT9	Transparent& non-sticky	Smooth	104±0.18	6.2±0.39	0.11±0.002
PT10	Transparent	Smooth	99±0.19	7.2±0.22	0.12±0.04
PT11	Transparent	Smooth	101±0.27	6.7±0.39	0.18±0.003
PT12	Transparent	Smooth	110±0.11	7.1±0.42	0.17±0.001
PT13	Sticky & Transparent	Flexible	110±0.53	7.0±0.87	0.16±0.003
PT14	Sticky	Flexible	99±0.22	7.2±0.22	0.22±0.010
PT15	Sticky	Flexible	99.08±0.34	7.2±0.12	0.29±0.003
PT16	Sticky	Flexible	100±0.34	7.1±0.43	0.22±0.002
PT17	Sticky	Flexible	101±0.27	7.3±0.71	0.29±0.002
PT18	Sticky Transparent	Flexible	110±0.11	7.3±0.39	0.32±0.221
PT19	Sticky	Smooth	101±0.34	7.1±0.82	0.33±0.002
PT20	Sticky Transparent	Smooth	108±0.11	6.9±0.33	0.30±0.009
PT21	Sticky Transparent	Smooth	109±0.22	6.3±0.18	0.22±0.110
PT22	Sticky	Smooth	99±0.19	6.4±0.49	0.32±0.221
PT23	Sticky	Smooth	98±0.08	6.9±0.51	0.31±0.010
PT24	Sticky	Smooth	101±0.02	6.8±0.44	0.28±0.009
PT25	Breakable	Flexible	103±0.91	7.0±0.29	0.19±0.011
PT26	Breakable	Flexible	110±0.24	7.1±0.28	0.18±0.018
PT27	Breakable & Sticky	Flexible	103±0.24	6.7±0.02	0.19±0.019
PT28	Breakable & Sticky	Flexible	102±0.03	6.8±0.11	0.11±0.003
PT29	Transparent & non-sticky	Smooth	100±0.14	6.4±0.27	0.15±0.006
PT30	Breakable	Smooth	98±0.88	6.5±0.27	0.13±0.002
PT31	Breakable	Flexible	98±0.36	6.7±0.12	0.14±0.002
PT32	Breakable	Flexible	101±0.28	7.0±0.28	0.19±0.01
PT33	Breakable & non-Sticky	Flexible	99±0.29	7.3±0.29	0.11±0.003
PT34	Breakable & Sticky	Flexible	105±0.09	7.2±0.33	0.33±0.101
PT35	Breakable and sticky	Flexible	107±0.27	7.9±0.82	0.30±0.001
PT36	Breakable	Flexible	101±0.27	6.7±0.43	0.22±0.002

PT37	Breakable & Sticky	Flexible	110±0.11	7.1±0.77	0.22±0.210
PT38	Breakable & Sticky	Flexible	110±0.53	7.0±0.39	0.29±0.001
PT39	Breakable & Sticky	Flexible	104±0.29	6.3±0.18	0.31±0.010
PT40	Breakable & Sticky	Flexible	110±0.28	6.4±0.49	0.28±0.009
PT41	Breakable & Sticky	Flexible	104±0.18	6.9±0.51	0.19±0.011
PT42	Breakable & Sticky	Flexible	107±0.26	6.8±0.44	0.18±0.018

Note: *values expressed as mean ± S.D. (n=3)

Formulation of Mouth Dissolving Film

From the results obtained in above mentioned preliminary trial batches for polymer and other excipients it was observed that the best results were obtained in polymer P1 and P2 along with PEG 400 in both the drugs therefore these combinations were used for furthest investigations.

Evaluation of Mouth Dissolving Film

The formulated mouth dissolving film of Cariprazine was evaluated. The results of evaluation parameters were presented in table 6.7. the results obtained indicates that as the concentration of the polymer increases the drug content also increases. As shown in table 6.7 the maximum drug content is 99.18±0.28 of F6 having 1 gm of HPMC K 4M followed by 98.34±0.19 of F12 in which also the 1 gm of HPMC K 4M is used.

Table 5.9: Evaluation parameters of MDF of Cariprazine

Formulation Code	Thickness (mm)	Weight variations (mg)	Drug content (%)	Tensile strength (N/mm^2)	Folding endurance	Surface texture	Surface pH	DT (Sec.)
F1	0.15±0.01	30.7±0.39	95.20±0.78	8.75±0.01	181±1.72	Smooth	7.0±0.29	12±0.91
F2	0.16±0.04	31.8±0.29	94.38±0.59	8.50±0.01	183±1.92	Smooth	7.1±0.39	18±0.93
F3	0.18±0.20	37.2±0.17	96.38±0.29	9.10±0.02	179±1.01	Smooth	6.2±0.39	19±1.02
F4	0.17±0.22	41.8±0.38	97.62±0.89	9.11±0.003	183±1.1.82	Smooth	7.2±0.22	17±1.28
F5	0.16±0.10	52.3±0.48	95.16±0.20	9.15±0.03	193±1.02	Smooth	6.7±0.39	14±0.89
*F6	0.19±0.03	53.6±0.29	99.18±0.28	9.21±0.01	220±1.78	Smooth	7.0±0.29	10±0.92
F7	0.18±0.19	31.2±0.18	97.29±0.l1	8.96±0.03	197±1.20	Smooth	6.3±0.18	16±1.10
F8	0.17±0.18	33.8±0.11	98.33±0.19	8.98±0.82	201±1.83	Smooth	6.4±0.49	18±1.29
F9	0.18±0.01	39.5±0.67	96.10±0.39	9.10±0.04	199±1.20	Smooth	6.9±0.51	16±1.29
F10	0.15±0.05	40.8±0.89	94.38±0.29	9.11±0.81	185±1.38	Smooth	6.3±0.18	18±1.11
F11	0.16±0.06	50.1±0.29	96.29±0.11	9.13±0.99	205±1.02	Smooth	6.4±0.49	17±0.96
F12	0.15±0.11	52.9±0.26	98.34±0.19	9.16±0.91	219±1.74	Smooth	6.9±0.51	14±0.98

Note: All values are Mean ±SEM, n=3

Dissolution test (*In Vitro* drug release studies):

In-vitro drug release study showed that as the concentration of polymer increases, drug release from mouth dissolving films increases. An immediate drug release was successfully observed for all HPMC films. The results were mentioned in the table 6.10

Table 5.10: *In Vitro* drug release studies of MDF of Cariprazine

Time (Mts)	F1	F2	F3	F4	F5	*F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
2	26.35	31.67	49.37	30.10	38.74	51.29	27.54	33.43	47.34	31.30	38.04	55.45
4	36.52	42.18	58.30	41.09	4.407	66.10	42.85	44.29	59.89	48.20	59.67	67.39
6	52.89	58.93	76.28	57.03	66.29	74.49	55.92	59.54	77.20	61.84	71.19	81.29
8	66.01	78.49	89.84	69.19	84.39	89.20	69.94	81.10	91.38	71.26	84.25	89.14
10	74.13	89.10	94.89	82.29	93.49	97.44	78.10	91.20	93.20	81.20	95.30	97.29

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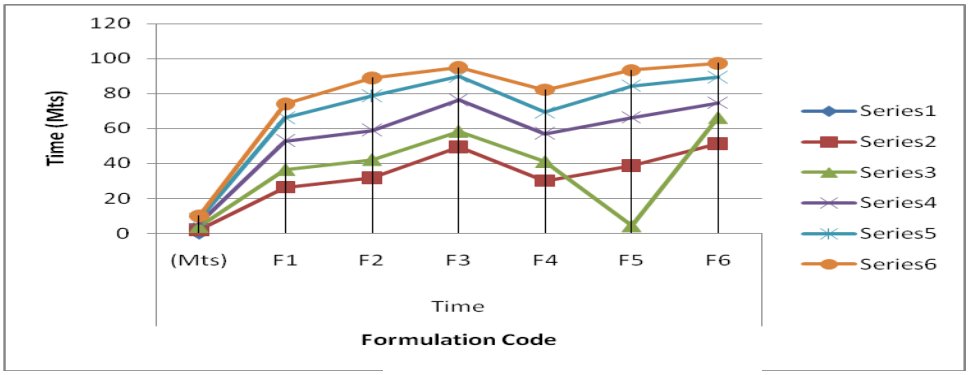

Fig. 5.11: Drug release of MDF of Cariprazine (F1 – F6)

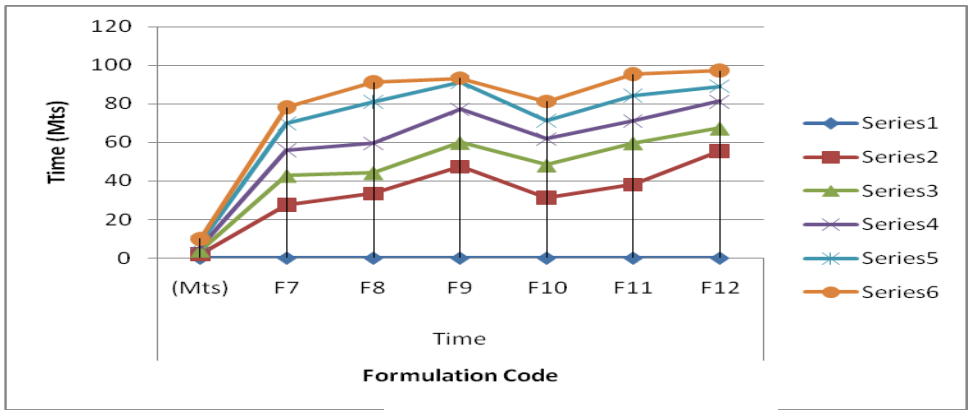

Fig. 5.12: Drug release of MDF of Cariprazine (F7 – F12)

Conclusion

The fundamentals of a successful pharmaceutical formulation depend on the delivery of the medicament to the target site at therapeutically relevant level, with negligible or minimum discomfort and side effects to the patient. In this respect, the route of drug administration has major influence. Among all the routes of drug administration, the oral route is the most common form of delivery of drugs because it has advantage of easy administration. But also has potential drawbacks like poor bioavailability due to first pass effect and tendency to produce rapid high and low plasma concentrationof drug, due to this, the patient compliance occurs. To overcome the drawbacks of oral route, the continuous intravenous infusion has been recognized to maintain a constant and sustained concentration of drug within therapeutic range for prolonged period of time. But this mode of drug administration also have certain drawbacks like needle pain and accidental needle sticks, therefore necessitates of regular hospitalization during treatment and requires under medical supervision.

Mouth dissolving film is now a days preferred route of drug administration due to patient compliance. The developed film formulation is a patient-friendly formulation that would be useful for people who have difficulty of swallowing. The results have shown that the HPMC-K4M is good film former and shows bioadhesion property. In combination with PEG-400, it has shown promising fast drug release within 10 min. and good folding endurance. Hence a semi-synthetic cellulose derivative which is affordable and abundantly available can be used as a potential drug release modifier and also used to improve flexibility and processability in the mouth dissolving films. Successful formulation of Cariprazine mouth dissolving films may prevent first pass metabolism to a large possible extent. From the present study it can be concluded that HPMC-K4M based mouth dissolving films of Cariprazine can be successfully prepared with considerable good stability and improved bioavailability.

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