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FORMULATION AND EVALUATION OF MOUTH DISSOLVING FILM OF CARIPRAZINE HYDROCHLORIDE

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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

Keywords: Mpouth dissolving, Cariprazine, Evaluation

Introduction

Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experienced difficulties in swallowing traditional oral solid-dosage forms. The novel technology of oral fast-dispersing dosage forms is also known as fast dissolve, rapid dissolve, rapid melt or quick disintegration. However, the function and concept of all these dosage forms are similar. By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing or fast-dissolving dosage form.[1-3]
Cariprazine is an atypical antipsychotic used in the treatment of schizophrenia and manic or mixed episodes of bipolar disorder. Cariprazine has been associated with a low rate of serum aminotransferase elevations during therapy, but it has not been linked to instances of clinically apparent acute liver injury.

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. Management of Psychosis differs from the treatment of other diseased conditions. Newer Anti-psychotic is an ideal drug candidate for an orally dissolving film formulation. The formulation of anti-psychotic as an orally dissolving strip, 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. Thus, the aim of this work was to design, develop and characterize mouth dissolving film of Anti-psychotic drugs i.e., Cariprazine

Material and Methods

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 point of of drugs will determined using digital melting point apparatus by capillary fusion method.

Determination of solubility

The dissolution and diffusion fluid for drug release and permeation studies respectively were selected based on

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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 coefficient of 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 for saturation 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 to obtain a stock solution 100 µg/ml. Then 1 ml of this stock solution was pipetted out in a 10 ml volumetric flask and volume was made upto the mark to obtained 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 obtained λ max was matched with the UV spectrum as reported in official monograph.

Formulation of mouth dissolving films

The mouth dissolving films of will be prepared by semi solid solvent casting technique. Different viscosity grades of polymers as film formers and plasticizers employed in the film.

Table 1: Formulation of mouth dissolving film of Cariprazine fumarate

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

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Evaluation of mouth dissolving films

The formulations were evaluated by the following tests.

hickness

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 m 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 from was studied by using dissolution test apparatus. Desired formulation 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

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.

Determination of Melting point

The melting point was determined of pure drug Cariprazine and was found to be 235-239^{0}C. The solubility was determined of pure drug Cariprazine in different solvent. The drug is soluble in Water.

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 is 4.32. The drug Cariprazine was scan to determine the λ max, the value obtained was compared with that of standard and is 218.

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 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.

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Table 2: 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

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 3

Table 3: Invitro drug release

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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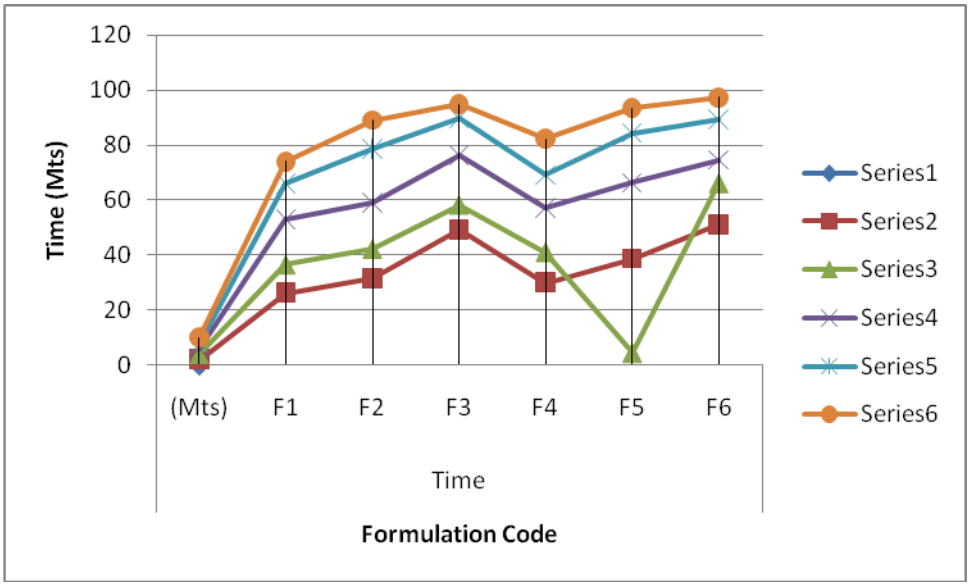

Fig. 1: Drug release of MDF of Cariprazine (F1 – F6)

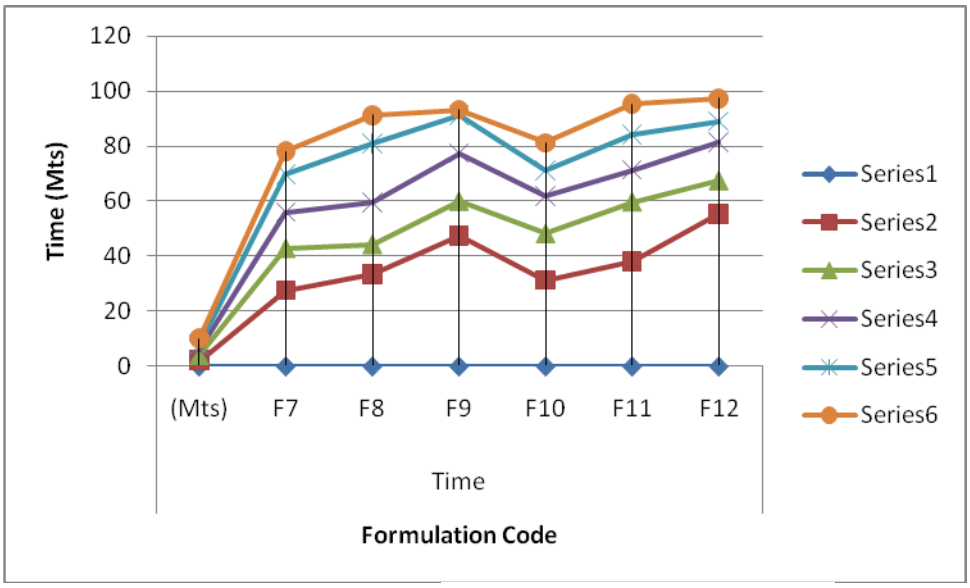

Fig. 6.2: Drug release of MDF of Cariprazine (F7 – F12)

Conclusion

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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