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Formulation and evaluation of mouth dissolving film of antipsychotic drug aripiprazole

Mona Nagar*[1], Mayank Nagar[2] and Vikram Chopra[2]

[1] Acropolis Institute of Pharmaceutical Education & Research (AIPER), Indore Bypass Road, Manglia Square, 453771, Madhya Pradesh, India.
[2]Ranbaxy Laboratories Limited, Industrial Area-3, Dewas, M.P 455001

ABSTRACT

The oral route is the most preferred route, though preoral administration of drug has disadvantage like hepatic first pass metabolism and enzymatic degradation within the GI tract however trans mucosal routes of drug delivery (i.e. Mucosal lining of nasal, rectal, vaginal, ocular, & oral cavities) offer distinct advantage over preoral administration because mucosa are permeable and well supplied with vascular and lymphatic drainage. Their other advantages include bypass of first pass effects and avoidance of pre-systematic elimination within GI tract. The present investigation highlights the formulation and evaluation of matrix type mouth dissolving films of Aripiprazole, prepared by solvent evaporation technique using Hydroxy propyl Methyl Cellulose (HPMC) - 3 cps. The formulated films were evaluated for their physiochemical parameters like mouth dissolving time, surface pH, thickness & weight of the films, PMA, PML, folding endurance, taste, drug content, stability and in vitro bioequivalence. In vitro release studies were also performed in solutions of different pH. The mouth dissolving film was found to be bioequivalent to the conventional solid dosage form of Aripiprazole.

Keywords: Matrix Mouth Dissolving films, Solvent evaporation technique, HPMC, Aripiprazole.

INTRODUCTION

Mouth dissolving films offers an attractive route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well supplied vascular and lymphatic drainage Also large surface area of absorption, easy ingestion & swallowing, pain avoidance make the oral mucosa a very attractive and feasible site for systemic drug delivery (1-2).

The delivery system consist of a very thin oral strip, which is simply based on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto site of application. It then disintegrates and dissolves to release the medication

Schizophrenia is a severe brain disorder that results in disturbances in thinking, perception, and behavior and is common form of mental illness. Antipsychotic drugs given in form of mouth dissolving matrix films are advantageous for patients suffering from these types of syndromes as they provide better patient compliance. Idio-synchronies in behavior of patients is also well managed, since the drug can be disguised with aesthetic appearance, sweet taste and likely flavors which resembles more with a mouth freshener than a medicine. Aripiprazole is one of the most useful drugs for psychotic disorders. It is chemically a quinolinone derivative (Fig. 1.), (7-[4-[4-(2, 3-dichlorophenyl) piperazin-1-yl] butoxy] - 3, 4-dihydro- 1H-quinolin- 2-one). Aripiprazole shows partial agonist activity at dopamine D-2 receptors & serotonin 5-HT1A receptors and antagonist activity at serotonin 5-HT2A receptors. It is insoluble in water and has a partition co-efficient of 4.537. It is well absorbed, with peak plasma

concentrations occurring within 3-5 hr with 87 % oral availability and mean elimination half lives of approximately 75 & 94 hr for drug and its active metabolite, dehydroaripiprazole. (3-7).

The present investigation highlights the formulation and evaluation of matrix type mouth dissolving films of Aripiprazole. The films were prepared by solvent evaporation technique using polymers of hydroxy propyl methyl cellulose (HPMC) -3 cps.

Objective: The objective of present study is to develop mouth dissolving films of Aripiprazole for better patient compliance and to provide effective mode of treatment to the impaired and non-cooperative patients suffering from Schizophrenia.

MATERIALS AND METHODS

1.1. Materials

Aripiprazole (Dr. Reddys Lab. Hyderabad, India), Hydroxy Propyl Methyl Cellulose-3 cps (FMC, Germany). Maltodextrin, Rice Starch, PEG 1000, Sodium Chloride, Potassium Sorbate, Sucralose, Thymol, Flavor and Cremophore EL were received as generous gift from Ranbaxy Labs Ltd. (Dewas, India). All other reagents and chemicals were of analytical grade.

1.2. Method of Preparation

2.2.1. Preparation of the Matrix Films

Matrix films of Aripiprazole were prepared by solvent evaporation technique. A calculated quantity of HPMC - 3 cps (16 mg) was dissolved in a mixture of 20 ml of ethanol and 5 ml of water (A). Accurately weighed 10 mg Aripiprazole was incorporated in this solution. Maltodextrin (6 mg) and rice starch (7 mg) were dissolved in 10 ml of water and 10 ml of ethanol respectively and was incorporated in the polymeric solution (A) with stirring. PEG 1000 (3 mg), Sodium Chloride (0.100 mg), Potassium Sorbate (2 mg) and Sucralose (0.600 mg) and Color (0.05 mg) were added to 20 ml of ethanol and mixed with solution (A). Thymol (0.400 mg) and flavor (12 mg) were dissolved in Cremophore EL (2 mg) and the solution was added in (A) with stirring. The liquid suspension was rolled into films using the appropriate machine and film was then allowed to dry at 42^{O}C for 1 hr. Aluminum foil was used as backing film. The patches were cut in a size of 3.05 x 2.05 cm and used for evaluation.

1.3. Evaluation Parameters and Method

The film was evaluated for mouth dissolving time, taste, surface pH, uniformity of thickness, weight, folding endurance, drug content uniformity, *in vitro* release, percent moisture loss (PML), percent moisture absorption (PMA), swelling percentage, stability and bioequivalence (8- 13)

1.3.1. Surface pH of films

Film was left to swell for 2 hrs on the surface of an agar plate. Agar plate was prepared by dissolving 2 % (w/v) agar in warm isotonic phosphate buffer (pH 6.8) with stirring and then pouring the solution into a petridish and allowing it to gel at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen film.

1.3.2. Film weight and thickness

For evaluation of film weight and thickness films were taken and weighed individually on a digital balance. The film thickness was measured using Digital Vernier caliper (Miyutoyo) at six different places and the average value was calculated.

1.3.3. Folding endurance

Folding endurance of the film was determined by repeatedly folding one film at the same place till it broke. Number of times the film could be folded at the same place without breaking gave the value of the folding endurance. This evaluation was done for three films.

1.3.4. Percentage moisture absorption (PMA)

The PMA test was carried out to check the physical stability of the mouth dissolving film at high humid conditions. Three films were taken, weighed accurately and placed in a desiccator containing saturated solution of aluminum chloride, keeping the humidity inside the desiccators at 79.5 %. After 72 hours the films were removed, weighed and percentage moisture absorption was calculated by using the following formulae (Equation – 1).

$$PMA = \frac{(\text{Final weight} - \text{Initial weight}) \times 100}{\text{Initial weight}} \quad \text{(Equation – 1)}$$

1.3.5. Percentage moisture loss (PML)

Percentage moisture loss was calculated to check the integrity of films at dry condition. Three 1cm square films was cut out and weighed accurately and kept in desiccators containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. The percentage moisture loss was calculated by using (Equation – 2)

$$PML = \frac{(\text{Initial weight} - \text{Final weight}) \times 100}{\text{Initial weight}} \quad \text{(Equation – 2)}$$

1.3.6. Swelling Percentage (% S)

A drug loaded film was placed in a beaker and 50 ml of phosphate buffer (pH 6.8) was poured into the beaker (Fig 3). An increase in the weight of the film was noted after every 15 minutes for 60 minutes. The swelling percentage was calculated by using the following formula (Equation – 3).

$$\% S = \frac{(X_t - X_0) \times 100}{X_0} \quad \text{(Equation – 3)}$$

Where, % S - swelling percentage, Xt - the weight of swollen film after time t, X_0 - weight of film at zero time.

1.3.7. Mouth dissolution time of the film and Taste

Mouth dissolving time of the film was determined by calculating the time required for the film to completely dissolve in the mouth. Taste acceptability was measured by a taste panel with 10 mg drug and subsequently 10-mg film sample held in the mouth for 5–10 s, then spat out, and the taste was recorded (6, 14). Volunteers were asked to gargle with distilled water between the drug and sample administration. The following scale was used:

- + = good
- ++ = very good
- +++ = excellent

1.3.8. Drug content uniformity

Three films were taken in separate flasks. 100 ml of 0.01 N HCl (pH 2.0) was added and continuously stirred for 2 hrs. The solutions were filtered, suitably diluted and analyzed at 217 nm by HPLC (Waters LC Modular 717 auto sampler, USA).

1.3.9. In vitro drug release study

The drug release studies were performed using USP dissolution test apparatus type II (Paddle type) using solutions of different pH. The USP dissolution apparatus was set at the temperature of 37 ± 1^0C and stirring speed of 60 rpm. Each film was fixed on a glass slide with the help of adhesive so that the drug could be release only from upper face. Then the slide has immersed in the vessels containing 900 ml of phosphate buffer solution (pH 6.8), 0.01 N HCl (pH 2.0), 0.1 N HCl (pH 1.2) and acetate buffer (pH 4.5) respectively. The aliquots of 1 ml were withdrawn at the definite time intervals and replaced with equal volume of the respective dissolution medium. Sink conditions were maintained throughout the study. Cumulative drug release was calculated at various time intervals.

The drug release study analysis was performed in triplicate by HPLC (Waters LC Modular 717 auto sampler, USA). The mobile phase consisted of a mixture of triethylamine and acetonitrile [(triethylamine: water, adjusted to pH 3.0 with orthophosphoric acid): acetonitrile (30:70 v/v)] isocratically eluted at a flow rate of 1.0 ml/min. and monitored at 217 nm. The reverse phase column was, Kromasil C8 (15 cm X 4.6 mm, 5 µm). The sample taken for analysis was mixed with the diluents, prepared by taking 5 ml of triethylamine in 1000 ml of water. 600 ml of this solution was taken and the volume was made up to 1000 ml with acetonitrile. pH of the diluent was adjusted to 2.5 with orthophosphoric acid. The column temperature was maintained at 30 °C. 10 µl sample solution was injected. The runtime for the assay was 30 min. Serum Aripiprazole was analyzed by a validated HPLC method.

1.3.10. Stability Studies

Stability studies were conducted on matrix films to assess their stability with respect to their physical appearance, drug content and drug release characteristics after storing them at 40° C/75 % RH for 6 months. Samples were withdrawn at 0, 30, 90 and 180 days.

1.3.11. *Bioequivalence Studies*

The bioequivalence studies were performed by USP dissolution test apparatus type II (Paddle type) using 0.01 N HCl between conventional tablet and mouth dissolving film of Aripiprazole.

RESULTS AND DISCUSSION

Matrix films of Aripiprazole were prepared by the method of solvent evaporation technique. Ethanol is used as the solvent. PEG 1000 was used as the plasticizer as well as wetting agent. The prepared Aripiprazole mouth dissolving films were evaluated or characterized based upon their physico-chemical characteristics like mouth dissolving time, surface pH, swelling percentage, PMA, PML, thickness, weight, folding endurance and drug content uniformity. These results are shown in Table.1. The ingredients added in the formulation had specific uses like, Maltodextrin (viscosity enhancer), Sucralose (sweetener), potassium Sorbate and Thymol (preservative), Cremophore EL (emulsifying and wetting agent), and rice starch (diluents and binder). Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the rate of hydration of the polymers, the surface pH of the films were determined by using suitable means. The prepared formulation of Aripiprazole mouth dissolving films was within the range of salivary pH i.e. 6.6 to 6.8 (Table - 1). The physical stability of the film was evaluated at high humid conditions and at dry conditions. The observed results of PMA and PML are shown in Table - 1 and it was well within the proposed specifications. The swelling percentage of the formulated film was observed in phosphate buffer, pH 6.8 (Table - 1). The film thicknesses were observed using digital vernier calipers and found to be in the range of 0.193 to 0.205. The weight of the film was found in the range of 58.8 mg to 59.2 mg (Table - 1). The folding endurance was measured by folding the film repeatedly at a point till it broke. The result is shown in Table - 1. The data indicates that the drug product is robust. The observed results of content uniformity indicated that the drug was uniformly dispersed (Table - 1). Mouth dissolving time of the film was found in the range of 7-10 seconds (Table - 1). Taste of the film was evaluated by the panel of three experts, and the taste was found very well (Table – 2).

In vitro drug release studies were performed by using solutions of different pH as dissolution medium and measuring the drug concentration by HPLC at 217 nm (Table - 3). The film was charged for stability. Table 4 shows six months of accelerated stability & twelve months room temperature stability data. The data indicates that all critical quality attributes of the drug product fall well within the proposed stability specifications. There is no physical or chemical change indicating that the formulation would maintain its efficacy and quality throughout its proposed shelf life.

Table 5 and Figure - 2, a comparative dissolution profile of the reference (Aripiprazole mouth dissolving film) and the test product (conventional Aripiprazole tablet); indicate a good in vitro equivalence between the test and the reference product. The value of the difference factor (F1) 2.1 (between 0-15); and similarity factor (F2) 80.4 (above 50) indicates excellent equivalence in performance between the developed test products and the reference innovator product. Thereby, the *in vitro* values as observed above provide a high degree of assurance towards prospective *in vivo* therapeutic equivalence.

Table I: Physiochemical Evaluation of Aripiprazole Mouth dissolving films

FC[1]	Surface pH ± S.D.	Swelling % ± S.D.	TH[2] (mm) ± S.D.	FE[3] ± S.D.	Weight (mg) ± S.D.	DC[4] (mg) ± S.D.	PML[5] ± S.D.	PMA[6] ± S.D.	MDT[7] (sec.)
F-1	6.66 ± 0.151	69.6 ± 0.55	0.203 ± 0.013	318.43 ± 1.52	59.2 ± 0.38	98.0 ± 1.6	1.24 ± 0.01	2.84 ± 0.01	10
F-2	6.78 ± 0.122	65.3 ± 0.75	0.205 ± 0.023	301.28 ± 2.78	58.8 ± 0.56	98.5 ± 1.4	1.11 ± 0.13	3.14 ± 0.07	07
F-3	6.75 ± 0.131	69.9 ± 0.75	0.193 ± 0.016	298.61 ± 3.14	59.1 ± 0.48	99.1 ± 1.6	1.18 ± 0.10	2.32 ± 0.02	09

[1] Formulation Code; [2] Thickness; [3] Folding Endurance; [4] Drug Content; [5] Percent Moisture Loss; [6] Percent Moisture Absorption; [7] Mouth Dissolution Time.

Table II: Taste Evaluation of Aripiprazole Mouth dissolving films

Formulation Code	Expert I	Expert II	Expert III
F-1	Excellent	Very good	Excellent
F-2	Very good	Excellent	Very good
F-3	Good	Good	Very good

Table III: In Vitro Release study of Aripiprazole in different medium

Study time (min)	% of Drug Release in Phosphate buffer (pH 6.8)	% of Drug Release in Acetate buffer (pH 4.5)	% of Drug Release in 0.1N HCL (pH 1.2)	% of Drug Release in 0.01N HCL (pH 2.0)
00	00	00	00	00
5	3.8	22.6	58.6	90.4
10	6.3	38.1	67.7	96.1
15	6.8	47.5	70.2	101.1
30	7.9	60.1	75.2	102.1
45	8.7	65.2	78.8	102.7

Table IV: Accelerated and RT stability studies data

Parameters	Accelerated Stability (40^0 C / 75% RH) at 1,3 and 6 Months	Room Temperature (25^0 C / 60% RH) at 0,1,3,6, and 12 Months
Description and physical appearance	Complies	Complies
Surface pH (6.0 – 7.5)	All values are in between 6.5 – 7.0	All values are in between 6.5 – 7.0
Percentage moisture loss (PML)	All values are in between 1.0 – 1.5	All values are in between 1.0 – 1.5
Percentage moisture absorption (PMA)	All values are in between 2.0 – 4.0	All values are in between 2.0 – 4.0
Assay (90-110%)	All values are in between 99.1-100.4%	All values are in between 97.8-102.8%
Dissolution (75% Q in 15 minutes)	All comply at S1 stage (USP)	All comply at S1 stage (USP)
Mouth dissolving time (NMT 3 minutes)	All values are in between 10 -20 seconds	All values are in between 10 – 20 seconds
Total degradation product (NMT 1.0%)	All values are in between 0.04 – 0.13	All values are in between 0.05 – 0.10

Table V: Comparative dissolution of test and reference product

Medium	**:** 0.01 N HCl
Volume	**:** 900 ml, 37 ± 0.5^0C
Apparatus	**:** USP-II (Paddle type)
RPM	**:** 60

Time (min)	**0**	**5**	**10**	**15**	**30**	**45**
% Reference	0.0	90.7	98.7	100.5	101.3	102.8
%Test	0.0	92.8	98.5	98.6	98.3	98.9
f1	2.1					
f2	80.4					

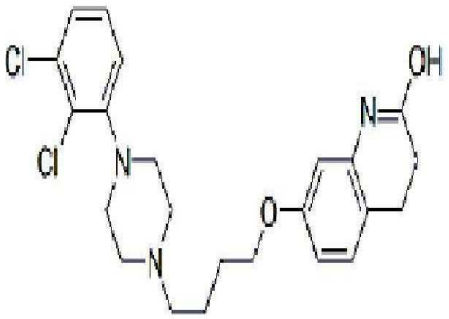

Figure 1

Figure.1. Chemical structure of the drug Aripiprazole

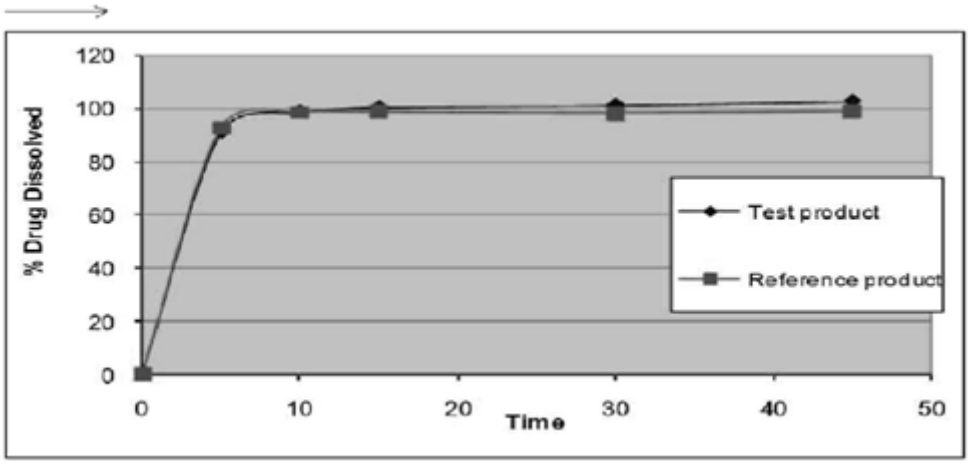

Figure 2: Comparative dissolution of Test and Reference product

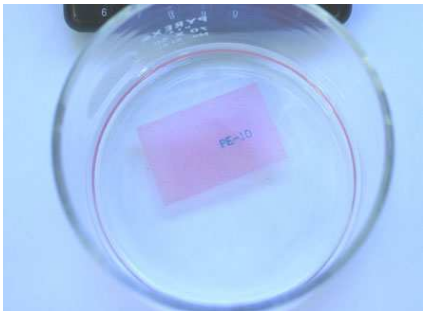

Figure 3: Swelling % determination

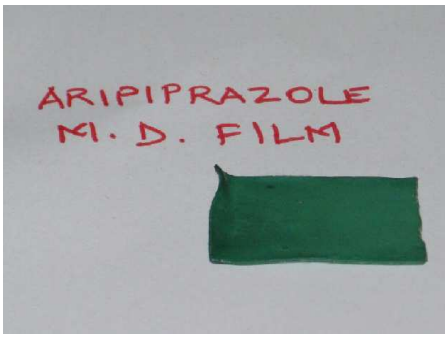

Figure 4: Mouth Dissolving Film of Aripiprazole

CONCLUSION

The mouth dissolving film of Aripiprazole was prepared by the method of solvent evaporation, using hydroxy propyl methyl cellulose (HPMC) - 3 cps and PEG-1000. The prepared film was evaluated for different parameters and the results was found to be promising ensuring safe, bioequivalent and effective dosage form, which can be reproduced with a robust manufacturing process. From the results obtained by this study it can be concluded that the Aripiprazole given in form of mouth dissolving matrix films should be advantageous for patients suffering from psychosis, providing better patient compliance and effective mode of treatment in a disguised manner.

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