DEVELOPMENT AND EVALUATION OF FAST DISSOLVING THIN FILMS OF ARIPIPRAZOLE

Abstract:

In the current pharmaceutical research fast dissolving filmsare playing an important role. In the present research, five different rapidly dissolving films of Aripiprazole were prepared successfully by using different polymer such as hydroxypropyl methyl cellulose (HPMC-E5 LV), polyvinyl pyrollidone by means of solvent casting method. Citric acid as saliva stimulating agent, mannitol as sweetening agent and menthol was used as flavoring agent. Aripiprazole, is an atypical antipsychotic. It is recommended and primarily used in the treatment of schizophrenia and bipolar disorder.

The prepared films were evaluated for different parameters including thickness, mass uniformity, pH, folding endurance, drug content uniformity, cumulative percent release, in-vitro dissolution test and accelerated stability studies. In-vitro dissolutionstudies were performed dissolution guidelines for about 30 minutes. For analyzing the mechanism of drug release kinetics of the films, the data obtained were fitted to various kinetic equations of zero order, first order, Higuchi model and Korsmeyer-Peppas model. On the basis of different evaluated parameters formulation of batch F4 was found to be optimum formulation. The optimized formulation F4 was evaluated for the stability studies at 40^0 C, 75% RH for 45 days. From the evaluation, it was found that there is no significant change in appearance, pH, foldingendurance, drug content, *in vitro* disintegration and percentage drug release.

Keywords: Fast dissolving thin films, Aripiprazole, first pass metabolism, bioavailability, *In-vitro* dissolution studies, release kinetics.

Introduction:

At present scenario there are so many advanced drugdelivery system for administration of various drugs through various route, but the oral route is considered as the most convenient and the preferred route of administration because of low-cost and ease of administration increases the patient compliance[1]. More than 70% of drugs are available in the market in the form of oral drug delivery system. Dysphagia (difficulty in swallowing) is commonly found in pediatric and geriatric patients thus they tend to avoid taking oral solid dosage preparations like tablets and capsules due to fear of choking or suffocation due to physical obstruction[2].

Ultra thin postage stamp size (2x3 cm) fast dissolving oral thin-film is a novel approach, useful for such types of patients[3]. These films consist of hydrophilic polymers, which rapidly disintegrate or dissolve within a few seconds after coming in contact of saliva to release the drug without need of water or chewing. Since the mucosa ishighly enriched with blood supply, it provided quick absorption and instant bioavailability of drugs. It is suitable for the drugs that undergoes high first pass metabolism[4].

Aripiprazole is a phenylpiperazine is effective for the treatment of acute manic episodes of bipolar disorder in adults, children, and adolescents. It is insoluble in water and has a partition co-efficient of 4.537[5]. Aripiprazole is an effective add-on treatment for major depressive disorder; however, there is a greater rate of side effects such as weight gain and movement disorders. Due to presence of sweet taste and flavors drugs can be delivered just like a mouth freshener rather than a medicine. All these facts make Aripiprazole an ideal candidate to prepare and evaluate as fast dissolving thin films.

Materials and Methods:

Materials:

HPMC E-5 LV and Polyvinyl pyrollidone were obtained from Amexco Pharmaceutical Company, Lagos, Nigeria. Propylene glycol and Citric acid were obtained from Emzor Pharmaceuticals Limited, Lagos, Nigeria. Mannitol and menthol were obtained from Food and Pharma Nig. Limited, Lagos, Nigeria.

Development of mouth dissolving film of Aripiprazole by solvent casting method-

The casting solution was prepared by mixing polymer solutionwith drug, sweetener (Mannitol) and flavor (menthol) and saliva stimulating agent (citric acid) as shown in table 1. All excipients were added with continuous stirring. The resulting solution was deaerated by sonication, then poured into appropriate moulds and dried to obtain the films. The casted films were dried in oven at 60°C for three hours or until dryness. The final dosage form was cut into strips (2×2 cm) with a stainless steel cutter. The samples were packed in a high density polyethylene sheet, sealed and stored in desiccators at room temperature[8].

Evaluation of mouth dissolving films

1. Thickness:

Five Aripiprazole films of each formulation were taken and the filmthickness was measured by using micrometer screw gauge (Glutfield Nigeria Limited, Nigeria) at different strategic locations (5 locations). Mean thickness and standard deviation were calculated[9].

2. Weight variation test:

For weight variation test, 10 Aripiprazole films of every formulation were randomly selected and weighed individually to determine the average weight and standard deviation was also calculated[10].

3. Folding endurance

It is expressed as the number of folds required for developingvisible cracks or breaking any given film. This gives an indication of brittleness or flexibility of the film. A 2x2 cm strip was subjected to this test by folding the film at the same point repeatedly several times until a visible crack was observed[11].

4. Drug content:

The Aripiprazole films were tested for content uniformity. Films of 2.25 cm^2 were cut and placed in a 100 ml volumetric flask and dissolved in methanol and the volume was made up to 100 ml. Solution was suitably diluted. The absorbance of the solution was measured at 217 nm[12].

5. Surface pH of films:

If the pH of the film is too acidic or alkaline, it may cause irritation. So it is important to determine surface pH of the film. Surface pH of the film shouldbe neutral i.e., 7 or should be close to 7. The Aripiprazole film to be tested was placed in a test tube and was moistened with 1.0 ml of distilled water and kept for 30 second. The pH was noted by pH meter (Finlab Nigeria Limited, Nigeria) after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1 min. The average of three determinations for each of the formulation was taken and standard deviation was also calculated[13].

6. Percentage moisture loss:

For moisture content test, three Aripiprazole films of each formulation were taken. Initially, these selected films were weighed accurately and kept in desiccator containing fused anhydrous calcium chloride[14]. After 3 days, films were removed,weighed and percentage moisture loss was calculated using the formula-

% Moisture loss=(Final weight-Initial weight)/(Initial weight) x100

7. Tensile strength:

Tensile strength of the Aripiprazole films was checked by Universal Tensile Strength Testing Machine (LS5, Lloyd Instruments Limited, UK) equipped with a 500 N load cell. Test was

conducted under normal laboratory conditions. The film of 400 mm^2 was randomly selected. The lower clamp was held stationary and the film was pulled apart by the upper clamp at a speed of 50 mm/min. The force of the film at the point,when the film broke was recorded[15]. The experiment was performed in triplicate and average values were reported.
The tensile strength at break valuewas calculated using formula:

Tensile strength= (Force at break (N))/(Initial cross section area)

8. Disintegration time:

This test is carried out using the disintegration apparatus. Three Aripiprazole films from each formulation were taken and performed disintegration testby placing the films in the cylindrical glass tube of disintegration apparatus containing 6.8 pH phosphate buffer. The time at which film disintegrated is noted. Mean and standard deviation were calculated. Normally disintegration time for fast dissolving oral films is 5-30 seconds[16].

9. In vitro dissolution test

The dissolution test on Aripiprazole films was performed using the USP apparatus II (Finlab Nigeria, Limited, Nigeria). The dissolution test was performedusing the 500 ml of simulated saliva solution, which consist of pH 6.8 phosphate buffer as dissolution medium. The temperature of the medium was maintained at 37± 0.5°C. Theapparatus was set at 50 rpm. A film sample of $4cm^2$ (2cm × 2cm) was cut and placed in the basket. 5 ml of samples were withdrawn at an interval of 2 minutes for 16 minutes and the same amount of the dissolution medium was replaced with fresh phosphate buffer at the same time in order to maintain the sink condition throughout the dissolution medium. The withdrawn samples were filtered using Whatmann filter paper. Appropriate dilutions were made to the withdrawn sample and were analyzed through UV spectrophotometer at a wavelength of 217 nm. The dissolutionstudy was performed in triplicates and the average value of percentage release was taken[17].

10. Accelerated stability studies:

The stability studies on Aripiprazole films were conducted according to ICH guidelines to investigate the effect of temperature, relative humidity on drug in formulation. Final optimized formulation of batch F4 was subjected to aggravated conditions oftemperature and relative humidity by wrapping it in aluminum foil and packaging it in glass container. The films were kept in stability chamber, at 40 ± 2^0 C temperature and 75 ± 5% RH for 45 days. After it, films were tested for thickness, weight variation, folding endurance, disintegration time, % drug content, and in-vitro drug release[18].

Table 1: Composition of oral thin films containingAripiprazole

Ingredients	Code			
	F1	F2	F3	F4
Aripiprazole	120	120	120	120
HPMC-E5 LV (mg)	25	50	75	100
Polyvinyl pyrollidone (mg)	50	-	100	-
Citric acid (mg)	4	4	4	4
Propylene glycol (ml)	0.25	0.2	0.25	0.2
Mannitol (mg)	10	10	10	10
Menthol (mg)	10	10	10	10
Citric acid (mg)	200	200	200	200
Purified Water (ml)	20	20	20	20

Table 2: Evaluation of physicochemical parameters of Aripiprazole films

Code	Thickness (mm)	Weight uniformity (mg)	Surface pH	% Drug content	Moisture content loss (%)	Folding endurance	Tensile strength (mPa)	Disintegration time (Sec.)
F1	0.15 ± 0.1 4	41.3 ± 0.68	6.38 ± 0.02	96.6± 0.28	8.41 ± 0.29	183 ± 1.02	3.67± 0.08	19± 0.48
F2	0.17 ± 0.23	43.2± 0.57	6.43 ± 0.03	96.51± 0.03	7.52 ± 0.25	187 ± 1.45	2.84± 0.09	21 ± 0.49
F3	0.19 ± 0.13	45.5 ± 0.16	6.74 ± 0.04	98.48± 0.48	6.82 ± 0.25	226 ± 2.03	3.83± 0.11	22 ± 0.51
F4	0.20 ± 0.09	47.6 ± 0.83	6.52 ± 0.03	99.89± 0.82	5.63 ± 0.73	232 ± 1.94	4.23± 0.06	24 ± 0.52

Table 3: Statistical analysis of Aripiprazole films

Code	Zero order		First order		Higuchi Plot		Hixon-Crowell		Korsmeyer- Peppas		
	K_0	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2	K_{KP}	R^2	N
F1	5.6328	0.9765	0.1754	0.8963	24.321	0.9331	0.1883	0.8917	1.9471	0.8854	0.2361
F2	6.7891	0.9647	0.1867	0.9158	25.413	0.9473	0.1741	0.8764	2.4628	0.8637	0.3114
F3	7.0215	0.8971	0.1843	0.8951	23.541	0.9234	0.2265	0.9331	1.8243	0.9146	0.2941
F4	6.9874	0.8558	0.2043	0.8862	25.338	0.9148	0.2345	0.9486	2.3781	0.8965	0.3252

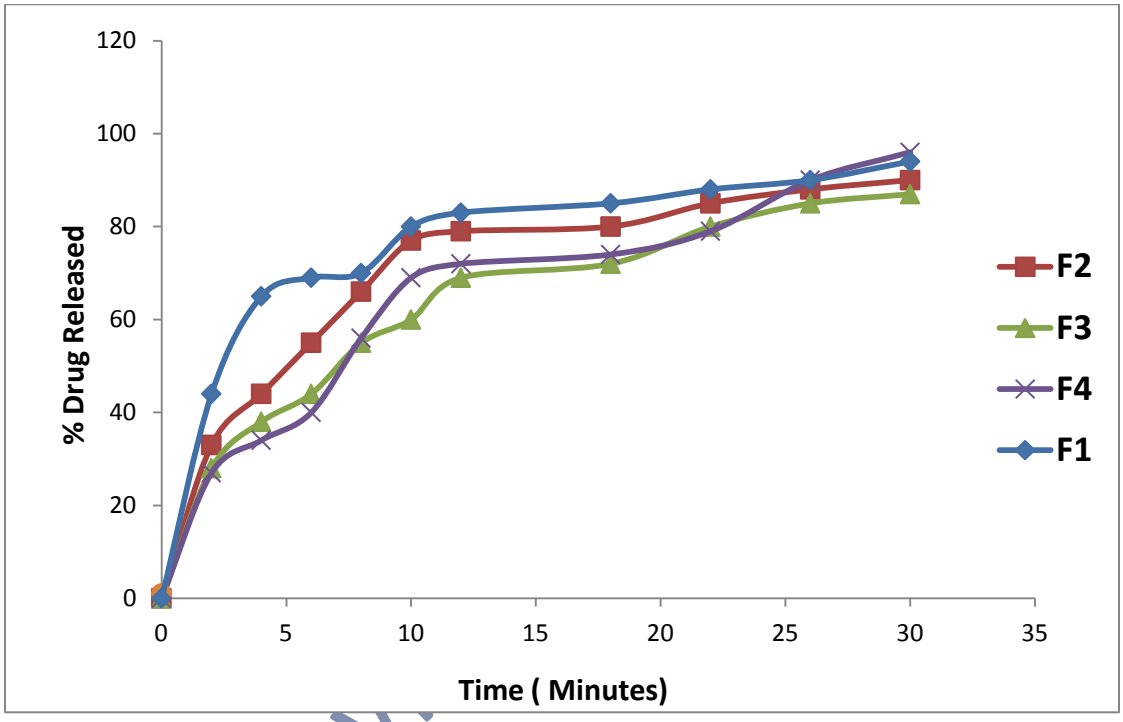

Figure 1: In-vitro dissolution profile of Aripiprazole films

Table 4: Stability study of Aripiprazole films of batch F4

S. N.	Parameter	Initial	After 45 days at 40^0 C, 75% RH
1.	Thickness	0.20 ± 0.09	0.17±006
2.	Weight variation	47.6 ± 0.83	47.1±0.25
3.	Folding endurance	232 ± 1.94	229± 0.58
4.	Disintegration Time	24 ± 0.52	22±0.64
5.	% Drug content	99.89± 0.82	98.86± 0.08
6.	Surface pH	6.52 ± 0.03	6.32± 0.11
7.	In-vitro drug release	95.48% in 30 min	95.37% in 30 min

RESULTS AND DISCUSSIONS

In the present study, fast dissolving oral thin films of Aripiprazole were prepared successfully by using different polymer such as hydroxypropyl methyl cellulose (HPMC-E5 LV), polyvinyl pyrollidone using solvent casting method. Total fiveformulations were prepared. Formulations were totally homogenous, flexible with smooth surface both sides.

The films were evaluated for various properties including thickness, mass uniformity, pH, folding endurance, drug content uniformity, cumulative percent release, in-vitro dissolution test and accelerated stability studies.

It was found that as the concentration of the polymer increases the flexibility of the film decreases. Films with very low concentration of polymer were sticky and brittle in nature. The films with optimum concentration of polymer were found to have good, flexible film forming property.

The thicknesses of the films were found to be from 0.15 ± 0.1 4 mm to 0.20 ± 0.09 mm. The thicknesses of the films were found to increase with increase in concentration of the polymer.

The weight variations of the samples were found to be in the range 41.3 ± 0.68 to 47.6 ± 0.83mg. It was observed that slight increase in the weight of films was due to increase in concentration of the polymer.

The folding endurance of the film was found to be inthe range 183 ± 1.02 to 232 ± 1.94. The folding endurance was found to increases with increase in concentration of the polymer. The tensile strength of the prepared films was found to lie in between 2.84± 0.09 to 4.23± 0.06 Kg/mm^2.Tensile strength was found to increase with increase in concentration of polymer. The pH of the films was found to be in the range between 6.38 ± 0.02 to 6.74 ± 0.04.

Drug content of the films with all polymers was found to be in the range of 96.51± 0.03 to 99.89± 0.82%. Estimation of drug content indicated that the drug is uniformly distributed throughout the film for most of the films evidenced by the low values of standard deviation. The disintegration time of the films were found to be from 19± 0.48 to 24 ± 0.52seconds. It was observed that disintegration time of a film increases with increase in concentration of the polymer.

It was observed that the drug release was found to decrease with increase in concentration of polymer. It indicates that increase in level of polymer, resultsin formation of high viscous gel layer caused by more intimate contact between the particles of polymers resulting in decreased

mobility of drug particles in swollen matrices, finally leading to decreased release rate. Formulation of batch F4 has shown maximum release 95.48% in 30 minutes. For analyzing the mechanism of drug release kinetics of the films, the data obtained were fitted to various kinetic equations of zero order, first order, Higuchi model and Korsmeyer-Peppas model. The regression coefficient was calculated. regression coefficients are summarized in table No. 4. The optimized formulation F4 was evaluated for the stability studies. Formulations were stored at 40^0 C, 75% RH for 45 days. From the evaluation, it was found that there is no significant change in appearance, pH, foldingendurance, drug content, in vitro disintegration and percentage drug release.

Conclusion:

Fast dissolving oral thin films for oral cavity are an innovative and promising dosage form especially for use in pediatrics and geriatrics or others have difficulty of swallowing. The results have shown that the HPMC-E5 LV is a good film former. In combination with PG, it has shown promising fast drug release within 30 min. Successful formulation of Aripiprazole mouth dissolving films may prevent first pass metabolism to a large possible extent. However to verify this fact there is need of in-vivo study using Aripiprazole films.

On the basis of different evaluated parameters formulation of batch F4 was found to be optimum formulation. The preparation of films did not require the addition of any disintegrant separately, so this formulation seems to be an attractive alternative toconventional marketed formulations.

Present study concludes that mouth dissolving films is a potential drug delivery system for Aripiprazole with a considerably good physicochemical characteristics and release profile.

References:

1. Nishimura M., Matsuura K, Tsukioka T, Yamashita H, Inagaki N, Sugiyama T, Itoh Y. In vitro and in vivo characteristics of prochlorperazine oral disintegrating film. *Int J Pharmaceutic*s. 2009, 368(1-2): 98-102.
2. Rawda KA, Shabarayal AR and Azharuddin M. Design and evaluation of fast dissolving oral films of granisetron hydrochloride. *Am. J. Pharm. Tech Res*. 2012; 2(6): 591-609.
3. Gade R, Aynampudi A, Makineni A, Murthy TEGK, Rao CB, Nama S. Design and development of pravastatin sodium fast dissolving films from natural mucilage of ocimum bacilicum seeds. *Int J Pharmaceut Res Rev*. 2014; 2(3): 17-27.
4. Kaza R, Prasanna RY, Ravouru N. Design and characterization of fast dissolving films of valsartan. *Turk. J Pharm Sci*. 2014; 11(2): 175-184.
5. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM (September 2013). "Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis". Lancet. 382 (9896): 951–62.
6. Barnes TR (May 2011). "Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology". Journal of Psychopharmacology. 25 (5): 567–620.
7. De Fruyt J, Deschepper E, Audenaert K, Constant E, Floris M, Pitchot W, Sienaert P, Souery D, Claes S (May 2012). "Second generation antipsychotics in the treatment of bipolar depression: a systematic review and meta-analysis". Journal of Psychopharmacology. 26 (5): 603–17.

8. Kai Bin Liew, Yvonne Tze Fung Tan, Kok K Khiang Peh. Characterization of oral disintegrating film containing donepazil for the alzhemier disease. *AAPS PharmSciTech*. 2012; 13:134-42.
9. Dinge A, Nagarsenker M. Formulation and evaluation of fast dissolving films for delivery of triclosan to the oral cavity. AAPS Pharm Sci Tech. 2008; 9(2): 349-56.
10. Chen MJ, Tirol G, Bass C, Corniello CM, Watson G, Sanchez I. Castable Edible Pharmaceutical Films. *Drug Del Tech*. 2008; 8(6): 35-41.
11. Francesco C, Irma EC, Paola M, Susanna B, Francesca S, Chiara GMG, Luisa M. Nicotine fast dissolving films made of maltodextrins: A feasibility study. American Assoc Pharm Sci Pharm Sci Tech. 2010, 11 (4), 1511-1517.
12. Yasmeen R, Firoz, Y, Chandra Mouli, Vikram A, Mahitha B. Preparation and evaluation of oral fast dissolving films of citalopram hydrobromide, Int J Bioph. 2012, 2, 103- 106.
13. Barnhart S D, Sloboda M S, The future of dissolvable films, *Drug Deliv Technol*. 2007, 7, 34-37.
14. Juluru NS. Fast Dissolving Oral Films: A Review. *Int J Advan Pharm Bio Chem*. 2013; 2(1): 108-112.
15. Sayed HA, Mahmoud ELB, Mohamed AI. Design, formulation and characterization of fast dissolving films containing dextromethorphan. Dig J Nanomater Biostruct. 2014, 9: 133-141.
16. Marzia A, Tasneem F, Pathan SI. Formulation and evaluation of swellable oral thin film of metoclopramide hydrochloride. Bangladesh Pharmaceutical J. 2014; 17(1): 102-112.
17. Yoshifumi M, Takashi I, Kofuji K, Nishida N, Kamaguchi R. Preparation of fast dissolving films for oral dosage from natural polysaccharides. Materials. 2010; *3*: 4291-4299.
18. El-Nabarawi MA, Makky AM, ElSetouhy DA, Abd Elmonem RA, Jasti BA. Development and Characterization of Ketorolac Tromethamine (Kt) Orobuccal Films. *Int J Pharm Pharm Sci*. 2012; 4(4): 186-193.