Available Online through
www.ijpbs.com (or) www.ijpbsonline.com

IJPBS |Volume 3| Issue 1 |JAN-MAR |2013|153-161

Research Article

Pharmaceutical Sciences

# PREPARATION AND EVALUATION OF FAST DISSOLVING ORAL THIN FILM OF CAFFEINE

FARHANA SULTANA*[1], MOHAMMAD ARAFAT[2], SAIFUL I. PATHAN[3]

[1] State university of Bangladesh

[2] The University of Asia Pacific

[3] State university of Bangladesh

*Corresponding Author Email: farhana_sultana_2005@yahoo.com

## ABSTRACT

*The objective of this research was to prepare fast dissolving oral thin film (FDOTF) containing caffeine. Fast dissolving oral thin films of caffeine anhydrous were prepared using HPMC-2910 (15cps), sodium alginate and kollicoat® IR white in various proportions. Total nine formulations were prepared and conducted various physicochemical evaluations including FTIR and in vitro dissolution studies .From the trinocular microscopic images it appears that kollicoat® IR white is more porous which may be due to the characteristic behavior of graft copolymer and was reflected in its lowest disintegration time (12sec.)and its cumulative percent release was 99.86% within 240seconds. Films in formulation F1 prepared with HPMC were very flexible, smooth and its in vitro disintegration time was 13 seconds. Its cumulative percent drug release was 100% within 120 seconds which is remarkable in comparison to other formulations.*

## KEY WORDS

*Cumulative percent drug release, FDOTF, HPMC, In vitro disintegration time, Kollicoat® IR*

## INTRODUCTION

Rapidly dissolving or quick dissolving dosage forms have acquired great importance in the pharmaceutical industry due [1][2][3] to their unique properties and advantages. They undergo disintegration in the salivary fluids of the oral cavity within a minute, where they release the active pharmaceutical ingredient. The major amount of the active pharmaceutical ingredient is swallowed orally with the saliva where subsequent absorption takes place in the gastro-intestinal tract.[4], [5] The rapidly dissolving dosage forms are referred by various names by researchers like quick disintegrating, orally disintegrating, mouth dissolve or melt in mouth dosage forms.[2][4][5]

Fast dissolving oral thin film drug delivery system is solid dosage form which dissolves in a short period of time when placed in the mouth without drinking water or chewing. These are also called fast dissolving oral thin films, Buccal films/ strips, Oral strips, Oral wafer. FDOTFs are the most advanced form of oral solid dosage form due to more flexibility and comfort. It improve the efficacy of APIs by dissolving within minute or seconds in oral cavity after the contact with saliva without chewing and no need of water for administration. It gives quick absorption and instant bioavailability of drugs due to high blood flow and permeability of oral mucosa is 4-1000 times greater than that of skin [6][7]. FDOFs are useful in patients such as pediatric, geriatrics, bedridden, emetic patients,

diarrhoea, sudden episode of allergic attacks, or coughing for those who have an active life style. It is also useful whether local action desired such as local anesthetic for toothaches, oral ulcers, cold sores or teething. [8] The OTFs place as an alternative in the market due to the consumer's preference for a fast-dissolving product over conventional tablets / capsules. The oral thin-film technology is still in the beginning stages and has bright future ahead because it fulfils all the need of patients. Eventually, film formulations having drug/s will be commercially launched using the OTF technology [9].

## MATERIALS AND METHODS

### MATERIALS

Caffeine anhydrous was gift sample from Bio-pharma Ltd., Bangladesh. Sucralose was obtained from Drug International Ltd., Bangladesh as a gift sample, Glycerine was received as a gift sample from uniliver, Bangladesh Ltd., HPMC was purchased from MERCK, India, Kollicoat® IR white was purchased from BASF, Germany, Sodium alginate& Sodium starch glycolate was purchased from Loba chemie, India. All other chemicals and reagents used were analytical grade. Distilled water was used in this study.

Preparation of fast dissolving oral thin film of caffeine anhydrous

The **Table 1** shows the detailed composition of the oral thin film of caffeine anhydrous formulations which were used in the present study.

**Calculation of drug quantity:**

For 20cm x15cm glass rectangular plate, the total area of the plate is 20cmx15cm=300 $cm^2$

Size of the individual film is 3x2 $cm^2$ i.e. 6 $cm^2$

So, theoretically total number of film will be 300/6=50

The total quantity of drug should be taken for 20x15 $cm^2$ Plate will be (50x10)=500 mg.

**Table 1 Composition of various caffeine fast dissolving oral thin film formulations**

| Ingredients | Formulation Code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| Caffeine anhydrous (mg) | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| HPMC 2910, 15cps (mg) | 1500 | 2000 | 2500 | - | - | - | - | - | - |
| Sodium alginate (mg) | - | - | - | 750 | 750 | 750 | - | - | - |
| Sodium starch glycolate (mg) | - | - | - | 750 | 1000 | 1250 | - | - | - |
| Kollicoat® IR white(mg) | - | - | - | - | - | - | 1500 | 2000 | 2500 |
| Citric acid anhydrous (mg) | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |
| Glycerin (ml) | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Sucralose (mg) | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| Ethanol 96% (ml) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Purified water (ml) | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

**PREPARATION OF FAST DISSOLVING ORAL THIN FILM OF CAFFEINE** [10] [11]

**Base film solution:**

**Drug solution:**

Polymer was dispersed in a measured quantity of solvent (mixture of water and ethanol 96%).

It involves the addition of all the ingredients except for base film solution. Initially the drug was added in a solvent. To this solution all other excipients were added with continuous stirring. At last plasticizer (glycerin) was added to this homogenous solution. To the base solution the drug solution was added slowly with a care to eliminate air entrapment. The final film solution was casted on glass plate. The casted films were dried in oven at 60°C for three hours or until dryness. The duration of drying depended on the properties of each polymer. Individual films were prepared by cutting the films into strips of regular dimension of 2cm x 3cm with a stainless steel cutter. The samples were packed in a high density polyethylene sheet, sealed and stored in desiccators at room temperature.

**EVALUATION OF FAST DISSOLVING ORAL THIN FILM OF CAFFEINE**

**Variation of film mass** [12]

The mass of the films was determined by using analytical balance**.** When manufacturing the oral films,the film solutions were cast into sheets and then cut into smaller strips of 6 $cm^2$ (3cm×2 cm). Oral films were cut from different sheets and the variability between the respective polymers as well as the variability between the polymers were investigated.The results are shown in **Table 2**.

**Table 2: Evaluation of the caffeine fast dissolving oral thin films**

| Code | #Thickness (mm) | *Mass uniformity (mg) | # Content uniformity (mg) | #D.T.(Secs) |
|---|---|---|---|---|
| F1 | 0.048 | 52.10±1.20 | 10.06±0.206 | 13 |
| F2 | 0.111 | 82.8±1.23 | 9.9±0.56 | 20 |
| F3 | 0.188 | 110.6±1.43 | 9.87±0.25 | 45 |
| F4 | 0.92 | 86.6±0.88 | 9.75±0.12 | 33 |
| F5 | 0.96 | 91.52±1.24 | 9.80±0.025 | 25 |
| F6 | 0.101 | 95.91±1.76 | 9.83±0.049 | 22 |
| F7 | 0.06 | 60.4±0.74 | 9.98±0.35 | 12 |
| F8 | 0.076 | 86.55±1.28 | 9.99±0.044 | 16 |
| F9 | 0.087 | 106.25±2.09 | 10±0.13 | 27 |

*All the values are expressed as mean± SD, n=10. #All the values are expressed as mean ± SD, n=3.D.T.= Disintegration time in seconds.

**Thickness** [13]

The thickness of film was measured by micrometer screw gauge at different strategic locations. Each film was measured at 5 positions (center and four corners) and the mean thickness was calculated. This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of dose in the film. The results are shown in **Table 2**.

**Folding endurance** [14]

Folding endurance is determined by- repeated folding of the film at the same place till the film breaks. The number of times the film is folded without breaking is computed as the folding

endurance value. The value is given in results and discussion.

**pH value** [12]

The pH value was determined by dissolving one oral film in 2 ml distilled water and measuring the pH of the obtained solution. The pH was measured by using pH paper**.** Differences were expected because various polymers were used as well as the addition of API.

**Disintegration testing** [16]

In vitro disintegration time was determined visually in a glass beaker of 25 ml distilled water with swirling every 10 seconds. The disintegration time is the time when the film starts to break or disintegrates. The results are shown in **Table 2**.

**Assay** [15]

The assay was performed to ensure the drug loading onto each film. This test was performed by dissolving a 6 $cm^2$ area of film in 50 ml of pH 6.8 phosphate buffer with stirring. The resultant solution was filtered using a whatman filter paper, and the filtrate was diluted to 100 ml with the same buffer in a volumetric flask. Then 1 ml of the filtrate was further diluted to 10ml with buffer. This solution was analyzed using a spectrophotometer at 272 nm.

**Content uniformity**

The content uniformity test was used to ensure that every film contains the intended amount of drug substance with little variation among films within a patch. Three pieces, each 6 $cm^2$ (3 ×2 cm), were cut from the whole patch, and assayed for drug content. Same procedure was repeated for all the nine batches. The results are shown in **Table 2**.

**In vitro dissolution** [12]

The in vitro drug release study of film was carried out using a USP 23 type 2 rotating paddle dissolution test apparatus. 250ml of phosphate buffer (pH 6.8) was used, and maintained at 37±5°C while the basket was set at 50 rpm. A film sample of 6 $cm^2$ (3 cm×2 cm) was fixed onto the specially designed SS disk with the help of cyanoacrylate adhesive. The disk was put at the bottom of the dissolution vessel so that the patch remained on the upper side of the disk. Five milliliters of samples were taken at a interval of 60 sec., and the same amount was replaced with fresh buffer. The withdrawn samples were filtered through whatman filter paper and then 1ml of the filtered sample was further diluted to 10ml of the same medium and analyzed using a spectrophotometer at a wavelength of 272 nm. The cumulative percentage release for different formulations was calculated. The relationship between time and percentage release were plotted. The results of in- vitro dissolution studies of all formulations were shown in **Figure 1**.

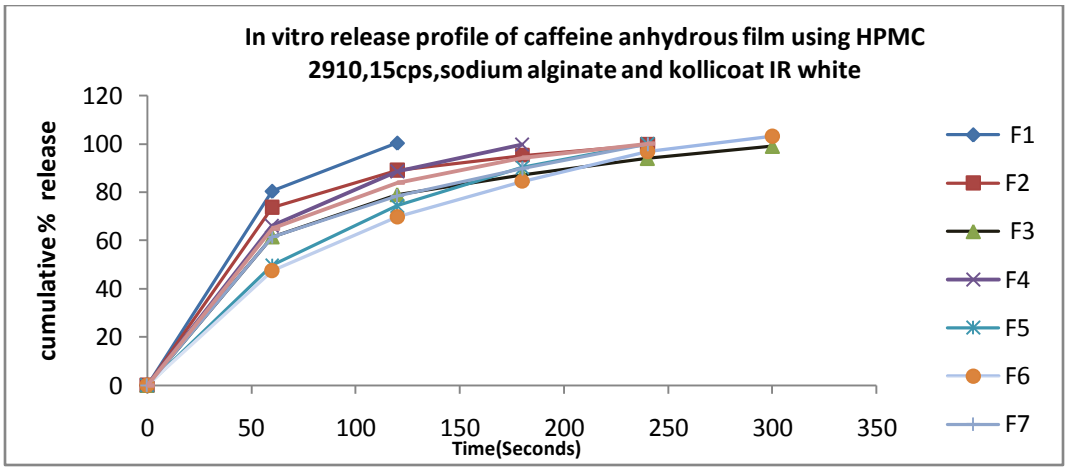



**Figure 1: In vitro drug release profile of fast dissolving oral thin film of caffeine**

**FT-IR solid sample preparation**

**Sample preparation for FTIR, Shimadzu, Japan**

13mm KBr discs were prepared by grinding different sample (2mg) each with KBr (200mg) and then compressing the whole into discs using hydraulic press.Finally, the disk was inserted into the IR sample holder. Then run the spectrum.

**Sample run for FTIR, Nicolet iS5, USA**

For solid sample, 2mg of the sample was entered into the sampling accessories and got the spectrum.

## RESULTS AND DISCUSSION

In the present study, fast dissolving oral thin films of caffeine anhydrous were prepared successfully by using different polymer such as hydroxy propyl methyl cellulose(HPMC) 2910 15cps, kollicoat® IR white, and sodium alginate as film former using solvent casting method. Total nine formulations were prepared. Hydroxy propyl methyl cellulose 2910 (15cps) was used as film former in formulation F1-F3, whereas sodium alginate in the formulation F4-F6,and kollicoat® IR white was used in formulation F7-F9, in various proportion. Mixture of water and ethanol 96% (1:1) was used as solvent .The drying time was 3 hour.

The films were evaluated for various properties including thickness, mass uniformity, pH, folding endurance, drug content uniformity, drug content, cumulative percent release as well as drug –excipients interaction. The mass of the films of all batches were between 50mg to 120mg. A very low standard deviation (1.5 to 2.5%) value indicates that the method used was reproducible and consistent.

The folding endurance of the all the batches were F1(230), F2(250), F3(300), F4(280), F5(250), F6(230), F7(220), F8(240),F9(280).Batch with higher amount of HPMC (F3) scores higher folding endurance than the batch with lower HPMC (F1).Drug content of all the films were between 9.75mg to 10.06mg. The results are shown in **Table 2**.The results of weight and drug content uniformity test showed that the film was homogenous and drug was also uniformly distributed in the films. Films were having thickness adequate for handling and use. The disintegration times of the films were evaluated using phosphate buffer (pH6.8).

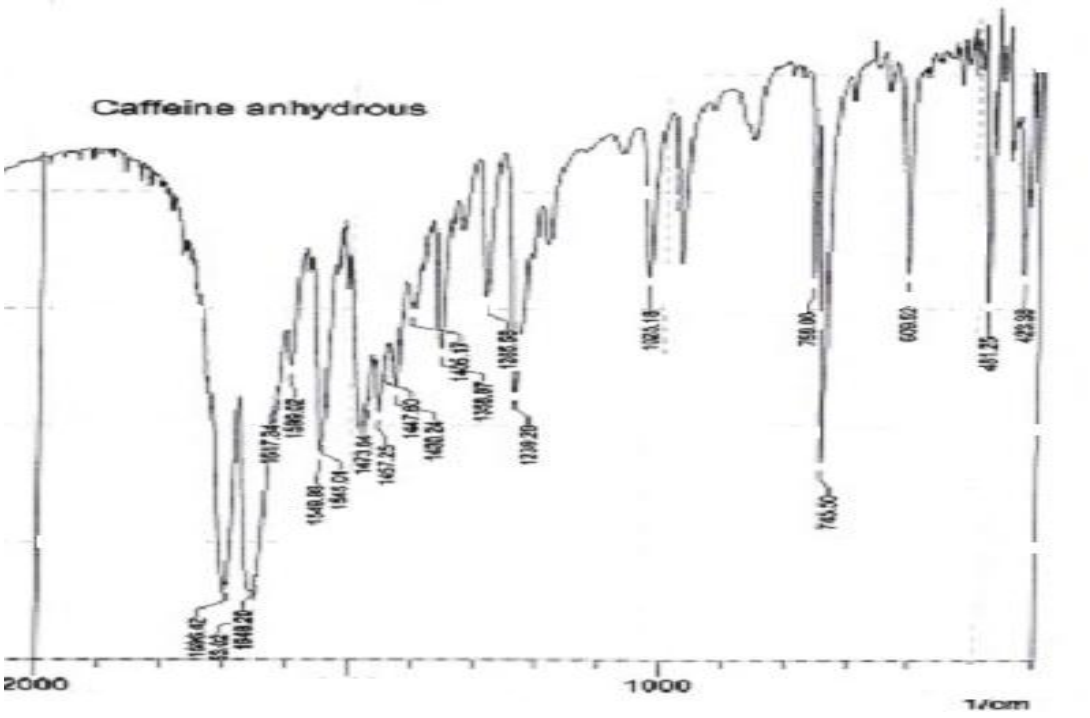
The appearance of the film formulations F1 to F3 by visual inspection was totally homogenous, flexible and both side smooth surface,F4 to F6 was homogenous, flexible and both side smooth surface,F7-F9 was homogenous, flexible and one side smooth surface.

**FT-IR study:**

It appears from the FTIR Spectrum that the combination in formulation F1-F3 (caffeine anhydrous + HPMC) and formulation F7-F9 (caffeine anhydrous +kollicoat IR white ) showed better results when compared to the characteristic peak values of the pure drug (caffeine anhydrous ) while combination in formulation F4-F6 (caffeine anhydrous + sodium alginate + sodium starch glycolate) showed significant changes in the peak

**Trinocular microscopic images**

Images of the caffeine anhydrous films were taken and evaluated. The surface of the film and distribution of polymer and drug within the films were examined. From the images below, it appears that more porous images were found from the kollicoat ®IR white containing film(F7) which may be due to the characteristic behavior of graft copolymer and reflected in its lowest disintegration time (12sec.). On the other hand, hydroxy propyl methyl cellulose containing film (F1) is also porous and showed less disintegration time (13sec) and smooth surface as well.



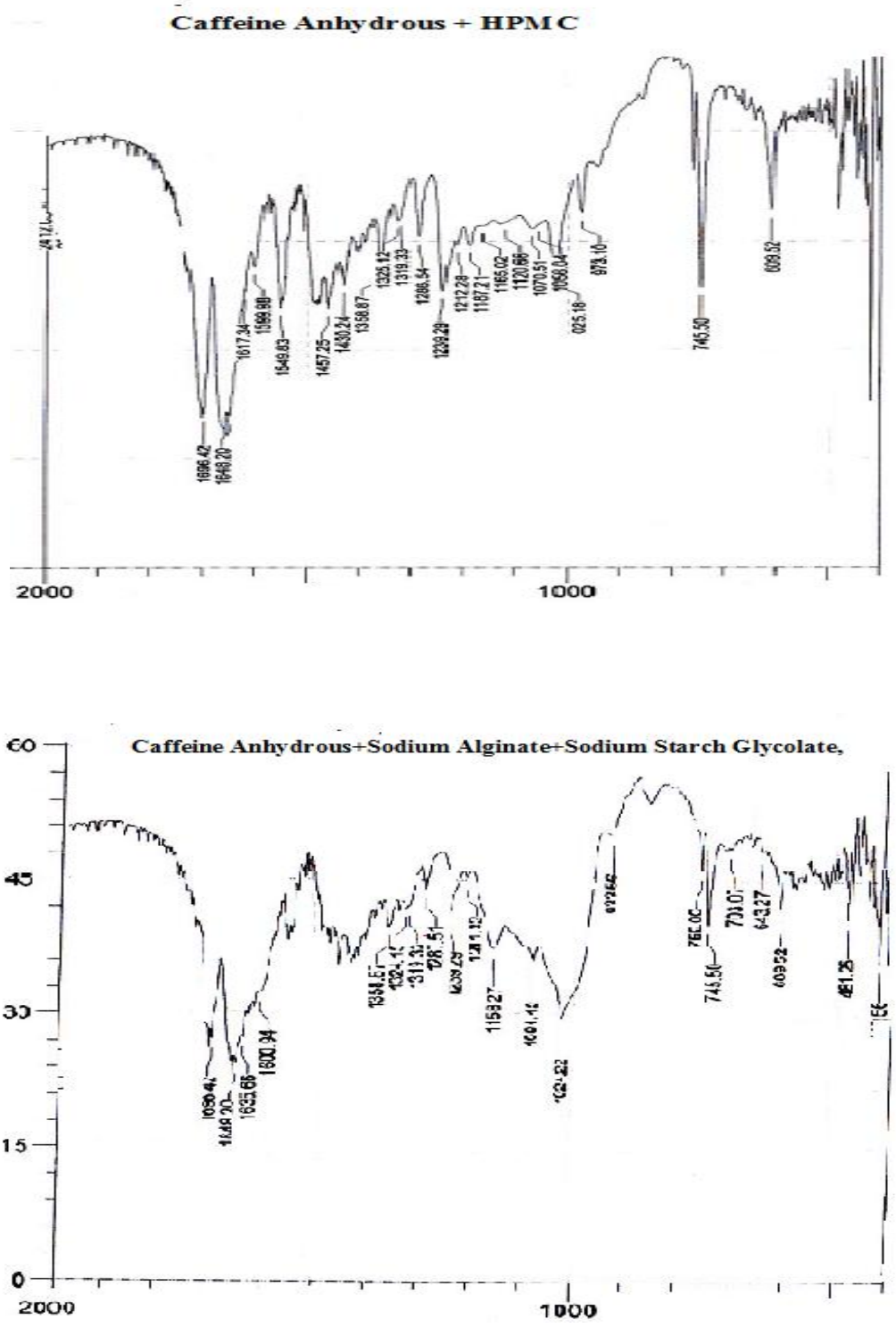



**Figure 2: FT-IR spectrum (FTIR , Shimadzu, Japan) of caffeine anhydrous , caffeine anhydrous +HPMC(F1-F3), caffeine anhydrous+ sodium alginate+ sodium starch glycolate(F4-F6).**

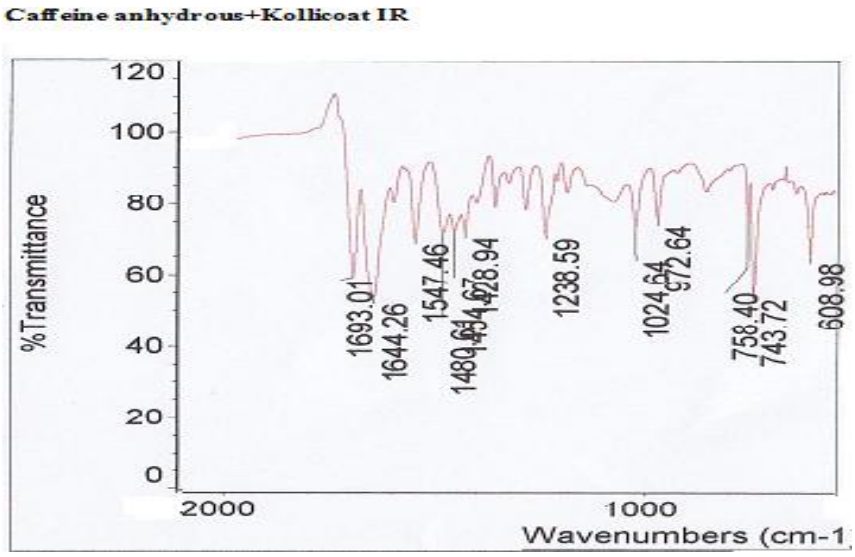
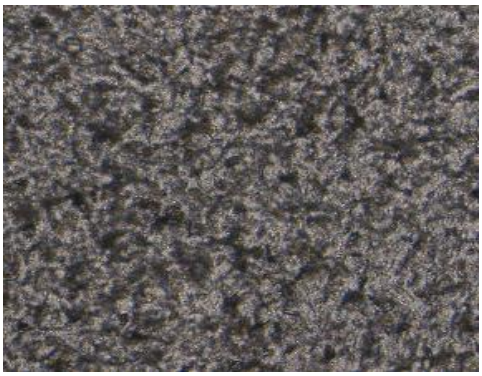
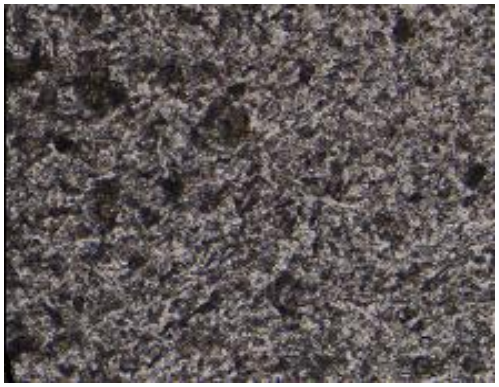



**Figure 3: FT-IR spectrum (FTIR, ID5ATR, Nicolet iS5, USA) of caffeine anhydrous + kollicoat® IR white (F7-F9)**



**HPMC containing caffeine film**

**Sodium alginate containing caffeine film**



**Kollicoat® IR (white) containing caffeine film**

**Figure 4: Trinocular microscopic images (Magnification:40) of HPMC containing caffeine anhydrous film, sodium alginate containing caffeine anhydrous film, kollicoat® IR containing caffeine anhydrous film.**

## CONCLUSION

Fast dissolving oral thin films are intended for the application in the oral cavity and they are an innovative and promising dosage form especially for use in pediatrics and geriatrics. The in vitro studies have shown that this is a potential drug delivery system for caffeine anhydrous with a considerably good physicochemical characteristics and release profile. Based on the above evaluations it is quite evident that the prepared fast dissolving oral thin film of caffeine anhydrous containing film forming agent hydroxyl propyl methyl cellulose (F1) is the best choice which provides faster release of drug within short time.

Future studies are warranted to confirm these results including stability and DSC and other in vivo studies.

## ACKNOWLEDGEMENT

The authors are sincerely thankful to State university of Bangladesh, department of pharmacy, Dhaka, Bangladesh for providing us infrastructure facilities and moral support to carry out this research work.

## REFERENCES

1. Renuka Mishra and Avani Amin*,Formulation and Characterization of Rapidly Dissolving Films of Cetirizine hydrochloride using Pullulan as a Film Forming Agent, Ind J Pharm Edu Res, Jan-Mar, 2011/ Vol 45/ Issue 1,
2. Liang AC, Chen LH. Fast Dissolving Intraoral Drug Delivery Systems. Exp. Opin. Ther. Patents 2001;11(6):981–6
3. Borsadia S, O'Halloran D, Osborne JL. Quick Dissolving Films-A Novel Approach to Drug Delivery. Drug Delivery Technology 2003; 3(3):63-66.
4. Klancke J. Dissolution Testing of Orally Disintegrating Tablets. Dissolution Technologies 2003;10(2):6–8.
5. Parakh SR, Gothoskar AV. Review of Mouth Dissolving Tablet Technologies. Pharm Tech 2003; 27(11):92–100
6. M.D. Nehal Siddiqui, Garima Garg and Pramod Kumar Sharma,A Short Review on "A Novel Approach in Oral Fast Dissolving Drug Delivery System and Their Patents", Advances in Biological Research 5 (6): 291-303, 2011
7. Galey, W.R., H.K. Lonsdale and S. Nacht, 1976. The in vitro permeability of skin and buccal mucosa to selected drugs and tritiated water. J. Investigative.
8. M.D. Nehal Siddiqui, Garima Garg and Pramod Kumar Sharma,A Short Review on "A Novel Approach in Oral Fast Dissolving Drug Delivery System and Their Patents", Advances in Biological Research 5 (6): 291-303, 2011
9. Oral Thin Films," in Orally Disintegrating Tablet and FilmTechnologies, 4th ed. (Technology Catalysts International, Falls Church, VA, 2006), pp: 18-31..
10. Sumitha Ch, Karuna Sree N, Divya B, Madhavi K, Vimal Kumar Varma M, Charbe NN. Int J Chem Research 2009; 1(2): 24-27.
11. Kiran Kumar S*, Senthil Kumar S, Sundaramoorthy K, Shanmugam S and Vetrichelvan T, Research Journal of Pharmaceutical, Biological and Chemical Sciences ,Formulation and *In-vitro* evaluation of rizatriptan benzoate rapimelt tablets and oral thin films – A novel approach, 2011 ,Volume 2 Issue 2 ,108
12. Preparation and evaluation of fast dissolving oral thin film for pediatric use, heinrich heine universitate dusseldorf, M. Pharm dissertation (modified
13. NA Nafee; NA Boraie; FA Ismail; LM Mortada. *Acta Pharm* 2003, 53, 199-212.
14. VK Devi, S Saisivam, GR Maria, PU Deepti. *Drug Dev. Ind. Pharm*, 2003, 29, 495–503.
15. R Patel, N Shardul, J Patel, A Baria. *Arch Pharm Sci & Res*, 2009, 1(2), 212 – 217.
16. Shivani Singh*, Satyam Gangwar Garima Garg, Vipin Garg, P. K Sharma,Formulation and evaluation of rapidlydisintegrating film of Levocetrizin

***Corresponding Author:**
***Farhana Sultana****
*State university of Bangladesh*
*Email:farhana_sultana_2005@yahoo.com,*
*Mobile no: +08801726020159*