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Formulation and *In Vitro* Evaluation of Fast Dissolving Sublingual Films of Agomelatine

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Abstract
Oral trans mucosal drug delivery is considered to be an important alternative to the per oral route for the systemic administration of drugs, as it considered the most convenient, easy, safest route of administration. Oral mucosa has rich vasculization, offers better permeability to many drugs and it act as an excellent site for the absorption of drugs. Fast dissolving oral film (FDOF) is used as a novel approach, as it dissolves rapidly in mouth and directly reaches to the systemic circulation. Oral film technology fulfills all the requirements of potential solid dosage form. The aim of this study is to formulate and evaluate the (FDOF) of an antidepressant drug (Agomelatine) and improved bioavailability of drugs as compared to conventional solid oral dosage forms. Oral films were prepared by using HPMC (Hydroxy Propyl Methyl Cellulose-E3 and E-5), Ethanol, Dichloromethane, Tween 80, combination of two polymers and other excipients. Films were prepared by the solvent casting method. Films were evaluated for mechanical properties, Morphology study, swelling properties, disintegration time, and *In-vitro* drug release. F10 formulation shows maximum *In- vitro* drug release 96.92±1.42, following first order kinetics (r^2 =0.9915). The release exponent 'n' was found to be for F10 is 0.4487, which appears to indicate a Fickian diffusion and may indicate that the drug release was controlled by first order release.

Keywords
Agomelatine, Sublingual film, HPMC E3 and E5, *In-vitro* dissolution studies etc.

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INTRODUCTION
Recently Fast dissolving technology have been emerging out as a new drug delivery system that provides a very convenient means of taking medications and supplements[1]. Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to conventional dosage forms for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms. The buccal cavity is an attractive route of administration for Systemic drug delivery. Oral mucosa has a rich vascularization and offers higher permeability to many drugs. It has been well known that after buccal and sublingual administration drug solutes are rapidly absorbed in to the reticulated vein and are then drained into the systemic circulation[2]. The concept of Fast Dissolving Drug Delivery System emerged from the desire to provide patient with a conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common

problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients[3]. Agomelatine is (BCS class II drug) a melatonergic, an antidepressant drug. The half-life of Agomelatine is 2-3 hr. The drug is orally administered as 25 mg tablets (Agoprex). The conventional dosage forms exhibit low systemic bioavailability ~5% due to first pass metabolism. Hence there is a need to develop a dosage form that can bypass first pass metabolism and enhance the bioavailability.

Following oral administration, Agomelatine is well absorbed by oral route and undergoes substantial first-pass metabolism; the systemic bioavailability of Agomelatine less than 5 percentage which was described earlier. In view of these facts this drug can be considered as a suitable candidate for fast dissolving oral film. In this study, an attempt is made to investigate the feasibility of fast dissolving oral films as a medium for the fast delivery of Agomelatine with better bioavailability and enhanced patient compliance.

MATERIAL AND METHODS

Agomelatine was purchased from Jackson Laboratories Pvt Ltd, Amritsar, India. HPMC-E3 and E5, Tween 80 were purchase from Central drug house Dichloromethane and Aspartame were obtained as a gift sample from Ranbaxy Pvt Ltd, Gurgaon. Organic solvents used were of analytical grade and other chemicals of Laboratory grade.

Preparation of Agomelatine Sublingual film formulations F1-F12[4]

Drug (Agomelatine) containing fast dissolving films were fabricated by the solvent casting method. The optimized amount of polymer was dissolved in 10ml of 1:1 ratio of ethanol and dichloromethane and stirrer continuously for 1 hour, optimized amount of sweetener, and Plasticizer were dissolved in 95% ethanol and then added to the polymeric solution Then the optimized amount of drug was dissolved in the above polymeric solution and kept on sonication for proper dispersion. Then drug-polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The above mixture solution was casted in a plastic Petri dish having 75 cm^2 surface area and was dried at controlled room temperature (25°-30°C, 45% RH) as well as at increased temperature (microwave oven). The film took approximately 48 hours to dry at controlled room temperature. The dried film was carefully removed from the Petri dish and was cut into size required for testing. The films were stored in air tight plastic bags till further use. Same procedure was being followed for the preparation of HPMC-E3 films, HPMC-E5 films as alone and combination of HPMC E3:E5 (1:1 ratio) and HPMC-E3: HPMC-E5 (1:2 ratio). The composition of drug loaded film is shown in table no 01.

Table: 01 Formulation of fast dissolving sublingual films of Agolmelatine F1-F12

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
	1:4	1:5	1:6	1:4	1:5	1:6	1:4	1:5	1:6	1:4	1:5	1:6
Agomelatine (mg)	188	188	188	188	188	188	188	188	188	188	188	188
HPMC E3 (mg)	752	940	1128	….	….	….	376	470	564	250	314	376
HPMC E5 (mg)	….	….	….	752	940	1128	376	470	564	502	626	752
Ethanol(ml)	10	10	10	10	10	10	10	10	10	10	10	10
Dichloromethane (ml)	10	10	10	10	10	10	10	10	10	10	10	10
Tween 80 (%w/w)	20	20	20	20	20	20	20	20	20	20	20	20
Aspartame	50	50	50	50	50	50	50	50	50	50	50	50

Evaluation of prepared fast dissolving sublingual films

Film Thickness and Weight Variation[5, 6]

The thickness of each of 10 film of each type of formulation was measured using a micrometer screw gauge6 and the average was determined and the individual weight each of 10 samples of each formulation was determined. The average weight was calculated and recorded.

Hydration Study (water uptake/ swelling study) [7, 8]

The film sample was weighed and placed on a pre-weighed stainless steel wire mesh. The wire mesh was then submerged in a petri-dish containing 20 ml distilled water. Increase in weight of the film was determined at regular time intervals until a constant weight was obtained.

The hydration ratio of the film was calculated using following formula-

Hydration ratio = Wt -W0/ W0

Where Wt = weight of film at time t and

W0 = weight of film at zero time

Measurement of Mechanical Properties [9, 10]

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters tensile strength, elastic modulus, % strain, and load at yield. The mechanical properties of the film give idea about to what extent the film can withstand the force or stress during processing, packaging, transport and handling. The desirable characteristics of film are moderate tensile strength, low elastic modulus, high % strain and high load at yield. From the above study, the polymer should give soft but tough film.

Percent Elongation[11]

The prepared film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force till the film was broken.

The percent elongation was calculated by using formula-(mm-2) as given below

Percent elongation = L1/ L0 X 100

Where L1= increase in the length, L0 = Initial length

Tensile Strength

Film strip of dimension 2 X 2 cm2 and free from air bubbles or physical imperfections was held between two clamps positioned at a distance of 3 cm apart. A cardboard was attached on the surface of the clamp via a double sided tape to prevent the film from being cut by the grooves of the clamp. During measurement, the strips were pulled at the bottom clamp by adding weights in pan till the film breaks14. The force was measured and recorded.

Tensile strength (kg/cm2) = Force at Break/ Initial cross sectional area of the film (cm2)

Folding Endurance[12]

This parameter was determined by repeatedly folding one film at the same place till it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance were recorded.

Surface pH

The surface pH of the films was determined in order to investigate the possible side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the oral mucosa. The film to be tested was placed in a petri dish and was moistened with 0.5 ml of distilled water and kept for 1 h. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1.0 min.15. The average of three determinations were recorded.

Compatibility studies

The drug-polymer compatibility was confirmed by taking IR spectrum of drug, polymer and physical mixture of drug-polymer proved that the excipients were compatible with the Agomelatine as shown in figure: 01

Determination of Drug Content[13]

The drug content and content uniformity test was performed to ensure uniform distribution of drug.

Five film units (2 cm x 2 cm) were cut from the four corners and the central part of the film (n=3). Each film unit was placed in 100 ml of distilled water. Samples of 10 ml were withdrawn and diluted with 25 ml of methyl orange (1%w/v) and extracted with chloroform (3x7.5 ml), and then the volume of sample was made up to 50 ml with sodium acetate solution. The solutions were filtered and analyzed at 236nm in a UV-Visible Spectrophotometer (Model UV-1700, Pharma spec, UV-Visible Spectrophotometer and Shimadzu, Japan). The average of five films was taken as the content of drug in one film. The concentration of Agomelatine (in µg/ml) was calculated using standard calibration curve of Agomelatine.

In vitro Disintegration time (Chen MJ et al, 2006)

The disintegration time is the time when a film starts to break or disintegrate. The *in vitro* disintegration of fast-dissolving films was determined visually in a glass dish of 25 ml distilled water with swirling every 10 s. and disintegration time was measured.

***In-vitro* Dissolution studies (Cilurzo F, et al, 2008)**

The *in vitro* dissolution test was carried out in a USP II paddle dissolution apparatus. Samples of Agomelatine-loaded films were equivalently containing 10 mg (4cm2) was cut and placed in Dissolution media. The dissolution medium consisted of 300 ml freshly deionized simulated saliva (pH 6.8), maintained at 37 ± 1 ^{0}C and stirred at 100 rpm. Samples of 10 ml were withdrawn at predetermined time intervals & replaced with fresh medium. The samples were diluted with 25 ml of methyl orange (1%w/v) and extracted with chloroform (3x7.5 ml), and then the volume of sample was made up to 50 ml with sodium acetate solution. The solution was filtered using What man filter Paper. The absorbance was taken at 236 nm against blank UV spectrophotometer (UV1700, Shimadzu, Japans) results are shown in figure: 02 and 03.

RESULTS AND DISCUSSION

Evaluation of Prepared Films

From the results of the tests for physical characterization conducted, it is observed that the Weight and thickness of all film samples was uniform within each formulation. Films formulated from

HPMC-E3 were shown poor mechanical properties, whereas those prepared from HPMC-E5 were slightly rough in texture, less flexible and translucent. While the film prepared from combination of HPMC-E3: E5 (1:1 ratios) and HPMC-E3: E5 (1:2 ratios) were smooth in texture, flexible and slightly translucent. All film formulations exhibited good folding endurance exceeding 500, except F1- F3 containing HPMC-E3 formulation indicating that they are poor and less flexible.

Weight variation varies from 56.21±1.02 to 69.50±0.67mg. The weight of the films increased with the increase in the concentration of polymers. The formulations prepared by using HPMC E3 were shown results in the range of 56.21±1.02 (F_1) to 66.82±0.54 (F_3). The formulations prepared by using HPMC E5 were shown results in the range of 58.52±0.64 (F_4) to 69.50±0.67 (F_6). The formulations prepared by using combination of polymers (HPMC E3 and HPMC E5) were shown results in the range of 57.12±0.54 (F_7) to 68.14±0.55 (F_{12}).

All the film formulations of Agomelatine containing polymers show uniform drug content as found to be 95.43±0.88 to 98.19±0.81 in all the formulations (F1-F12). The measurement of Swelling Index indicates that maximum swelling takes place in the formulations containing lower proportions HPMC E3 namely F1, moderate and desirable proportions by the combinations of HPMC E3 to E5 namely F10, and the least in those containing HPMC- E5 as alone F6. Because of as the concentrations of HPMC polymer increases, decreases the swelling behavior of same polymer in each formulations and therefore subject to lesser swelling upon hydration. It was also observed that films containing the low level of hydrophilic polymers disintegrated very fast. The presence of the desirable level of polymer, HPMC E3 seems to increase the surface wettability and swelling of the films. The rank order of swelling index from films was found to be HPMC E3 > combinations of HPMC > HPMC- E5 as alone.

The percentage elongation of the formulations prepared by using HPMC E3 were shown results in the range of 5.32±0.056 (F_1) to 6.32±0.042 (F_3). The formulations prepared by using HPMC E5 were shown results in the range of 7.45±0.035 (F_4) to 9.23±0.069 (F_6). The formulations prepared by using combination of polymers (HPMC E3 and HPMC E5) were shown results in the range of 6.14±0.071 (F_7) to 8.95±0.082 (F_{12}).

The tensile strength (kg/sq.cm^2) of the formulations prepared by using HPMC E3 were shown results in the range of 0.78±0.022 (F_1) to 1.02±0.052 (F_3). The formulations prepared by using HPMC E5 were shown results in the range of 1.13±0.021 (F_4) to 1.82±0.054 (F_6). The formulations prepared by using combination of polymers (HPMC E3 and HPMC E5) were shown results in the range of 1.16±0.048 (F_7) to 1.75±0.063 (F_{12}).

The folding endurance of the formulations prepared by using HPMC E3 were shown results in the range of 101.6±0.461 (F_1) to 115.8±0.594 (F_3). The formulations prepared by using HPMC E5 were shown results in the range of 123.1±0.683 (F_4) to 138.2±0.422 (F_6). The formulations prepared by using combination of polymers (HPMC E3 and HPMC E5) were shown results in the range of 116.8±0.658 (F_7) to136.4±1.060 (F_{12}).

Surface pH

An acidic or alkaline pH of administered dosage forms can irritate the buccal mucosa. The measured surface pH was found to be close to neutral in all the formulations ranging from 6.4±0.13- 6.6±0.16. Which means that they have less potential to irritate the buccal mucosa and therefore they should be fairly comfortable.

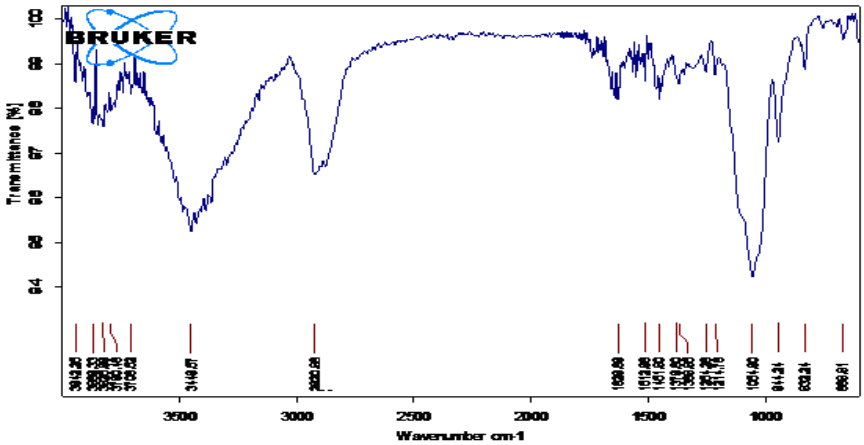

Figure 01: FT-IR characteristic peaks of optimized formulation F10 with HPMC E3and HPMC E5

The IR spectrum of Agomelatine pure drug exhibited peaks at 648, 696, 733, 755, 830, 904, 1027, 1132, 1181, 1212, 1249, 1360, 1433, 1532, 1625, 3248, 3537. Formulation with HPMC E3 and HPMC E5 combination exhibited peaks at 665, 699, 754, 831, 944, 1054, 1214, 1253, 1347, 1369, 1457, 1558, 1653, 3446, and 3669 etc.

From the FT-IR studies, it was observed that the peaks of Agomelatine were detected and identified in the spectrum of Agomelatine with formulation confirming that there was no interaction of Agomelatine with polymers and excipients.

Disintegration time of the formulations prepared by using HPMC E3 were shown results in the range of 38.6± 0.72 (F_1) to 50.5±1.12 (F_3). The formulations prepared by using HPMC E5 were shown results in the range of 42.5±0.56 (F_4) to 59.3± 0.57 (F_6). The formulations prepared by using combination of polymers (HPMC E3 and HPMC E5) were shown results in the range of 40.3±1.15 (F_7) to 58.5±0.63 (F_{12}).

***In vitro* drug release studies**

In vitro drug release studies in simulated saliva show more than 85 % release of Agomelatine from all film formulations, *i.e.*, HPMC E3 contains F1-F3 was found (94.43±1.14 to 90.74±0.79), HPMC E5 contains F4-F7 was (92.03±1.09 to 87.82±0.62), combinations of HPMC E3 1:1 E5 ratio contains F7-F9 was (95.42±0.87 to 90.48±0.74), and HPMC E3 1:2 E5 ratio contains F9-F12 was found to be (96.92±1.42 to 89.01±0.76), within 20 minutes with F10 showing a maximum percentage drug release of 96.92±1.42 percentage. This could be attributed to the higher rate and extent of swelling of the larger proportion of the hydrophilic polymer, because low level of HPMC E3 and E5 in F10. As the polymer concentration was increased the rate of drug release was decreased, this might be due to the increase level of polymer results in formation of high viscosity gel layer caused by more intimate contact between the particles of HPMC results in decreased mobility of drug particles in swollen matrices, which leads to decrease in release rate slightly.

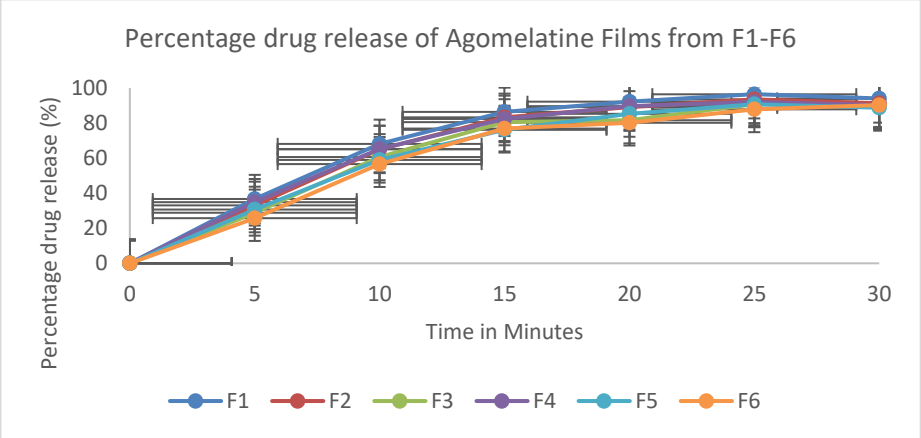

Figure: 02 *In-vitro* drug release profile of Agomelatine Films contains HPMC E3 and E5 (F1-F6)

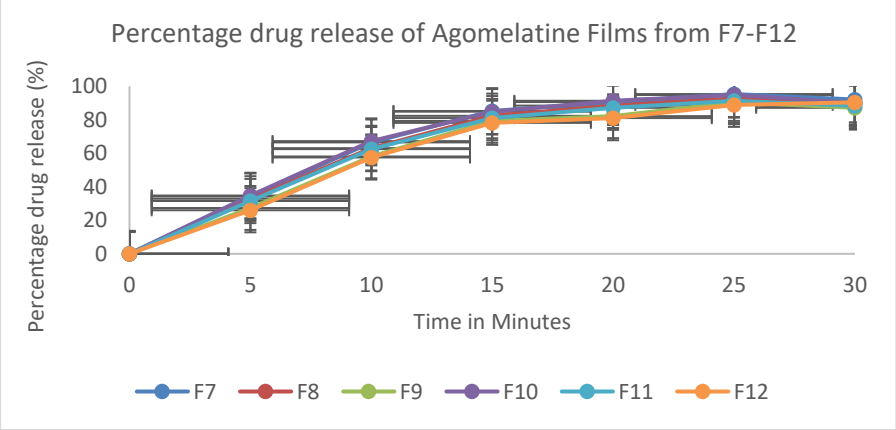

Figure: 03 *In-vitro* drug release profile of Agomelatine Films contains combinations of HPMC E3 and E5 (F7-F12)

Kinetic analysis of *In-vitro* release data

In order to determine the release mechanism that provides the best description to the pattern of drug release, the *in vitro* release data were fitted to zero order, first-order, Hixson Crowell equation and Higuchi matrix model. The release data were also kinetically analyzed 15 using the Korsmeyer–Peppas model. The release exponent (n) describing the mechanism of drug release from the matrices was calculated by regression analysis using the following equation.

Mt/ M_ = Ktn

Where Mt/M_ is the fraction of drug released.

When the release data were fitted to Koresmeyer-Peppas release model and interpretation of release exponent values (n) enlightens in understanding the release mechanism from the dosage form19. Release exponent (n) 0.5 Fickian diffusion; 0.5< n <1.0 Non-Fickian diffusion; n=1 Case-II transport; n=1 > Super Case-II transport. After undergoing the release model for all the formulations the in vitro drug release of the optimized formulation F10 was best explained by first order, as the plots showed the highest linearity (r2 = 0.9915), followed by Korsmeyer peppas (r2=0.9771), Higuchi (r2 = 0.9602) and then zero order (r2 = 0.8676). The corresponding plot (ln Mt/MP vs ln time) for the Korsmeyer-Peppas equation of the optimized formulation F10 indicated good linearity for F10 formulation. The release exponent 'n' was found to be for F10 is 0.4487, which appears to indicate Fickian diffusion and may indicate that the drug release was controlled by first order release.

Stability studies

When the oral film preparation was stored in an aluminum package under normal condition or in a chamber controlled at 40°C and 75% in humidity for 4–13 weeks, no apparent changes in the Agomelatine content, form or color of preparations were observed. The contents of Agomelatine were fairly stable ranging from 95.63± to 101.7% during 13 weeks after storage at 30°C and 60% humidity (normal condition), or from 98.0% to 100.4% during the same periods after storage at 40°C and 75% RH humidity (accelerated condition).

CONCLUSION

This study shows that it is possible to formulate fast dissolving films of Agomelatine with the intention of obtaining better therapeutic efficiency with increasing bioavailability and improving patient compliance. Plasticizer used Tween 80 resulted in better films in respect to physicochemical parameter like tensile strength, percentage elongation, folding endurance and flexibility. Aspartame used as a sweetener will successfully mask the bitter taste of the drug Agomelatine. Formulation F10 shows minimum disintegration and dissolution time in comparison to other formulation. F10 was the best formulation showed 96.92±1.42 percentage drug release in 20 min. Data obtained from correlation coefficient and slope values revealed that drug release from formulation followed first order kinetics. *In vitro* stability evaluation of optimized formulation F10 with different environmental conditions, confirms the potential of films for longer storage.

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