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Development and Evaluation of Orally Fast Dissolving Film of Agomelatine

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Abstract : Orally Fast dissolving film (OFDF) is a dosage form which placed in the oral cavity, quickly gets hydrated, sticks onto the site of application and then disintegrates to release the drug. Agomelatine is an antidepressant also used for mood disorders such as anxiety and obsessive compulsive disorder. Fast dissolving films of Agomelatine were prepared by solvent casting technique. HPMC E-15 was selected as polymer because of its good water solubility. Polyvinyl pyrrolidone K-30(PVP K-30) as superdisintegrant and polyvinyl alcohol as film forming agent. Mannitol as sweetner and saliva stimulating agent used in the formulation. The compatibility of the drug in the formulation was confirmed by FTIR studies. A various concentration of polymers was used in order to optimize API concentration of the new dosage form. The orally fast dissolving film was characterized for weight, thickness, folding endurance, tensile strength and dissolution using *In-vitro* experimentations. The effect of PVA and PVP K-30 on drug release profile and film forming properties was investigated. Estimation of drug content of films was performed and the results were satisfactory. *In-vitro* dissolution studies revealed higher drug release from formulation F6 batch.
Key words : Orally fast dissolving film, Agomelatine, PVP K-30, PVA, Antidepressant.

Introduction

Oral route is the most preferred route for the delivery of the drugs till date as it bears various advantages over the other route of drug administration, but oral drug delivery systems still need some advancements to be made because of their some drawbacks related to particular class of patients which includes geriatric, paediatric and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms. Even with the fast dissolving tablets there exists a fear of choking due to its tablet type appearance. Orally fast dissolving film is new drug delivery system for the oral delivery of the drugs. It was developed on the basis of technology of the transdermal patch[2]. Orally fast dissolving film rapidly disintegrates and dissolves to release the medication for oromucosal and intragastric absorption. Agomelatine is a new agent with a unique pharmacological outline, as it is the first melatonergic antidepressant. It has potential role in the treatment of patients with major depressive disorder (MDD). Agomelatine is a chemical compound that is structurally closely related to melatonin. Agomelatine has a new pharmacological mechanism of action, which combines melatonin MT1 and MT2 agonist properties with a serotonin 5-HT2C antagonist effect[3]. Agomelatine was rapidly and well absorbed oral administration. Because of its action upon

the melatonin receptors, agomelatine shows a marked improvement in sleep quality. The aim of present work was to improve patient compliance by avoid spitting of the medication by the patients, ensure faster drug delivery for mood disorders, avoid severe gastric irritation and diarrhea caused by agomelatine and mask the bitter taste of drug.

Materials and Methods

Agomelatine was obtained as a gift sample from Enaltec Labs, Mumbai. HPMC E-15 was procured from LOBA CHEME, Mumbai, PVP K-30 obtained from Evonik, Kolkata. Mannitol from Research Lab Fine Chem Industry, Mumbai, and PVA was obtained from Reliance Cellulose.

Formulation of Orally Fast Dissolving Films

Orally fast dissolving films of Agomelatine were prepared by solvent casting technique using film forming polymer. In this method, three portions were made. In first portion the drug was dissolved in sufficient quantity of Ethanol, and in second portion weighed amount of PVP K-30, HPMC E-15 and mannitol were added in methanol[8]. In third portion, the weighed quantity of PVA was dissolved in sufficient amount of distilled water with continuous stirring on magnetic stirrer[4]. Now, this third portion was mixed with shaking in above two portions. At last calculated amount of PEG400 and flavours were added to this drug polymeric solution. This solution was mixed thoroughly to obtain homogeneous solution. Methanol was finally added to make up the final volume. The homogeneous solution was put in to mould prepared from aluminium or glass (size 4-5 $cm^{2)}$ and dried at 40-50^0 C. The optimization of batch was carried out by 3^2 full factorial designs. Different formulation codes were assigned to all batches containing ratios of PVA and PVP K-30[10].

Table 1. Formulation of Orally fast dissolving films of Agomelatine

Composition / Form. Code	Agomelatine (mg)	Polyvinylpyrr-olidone K-30 (mg)	Polyvinyl alcohol (mg)	Hydroxypr-opylmethylcellulose E-15 (mg)	Mannitol (mg)
F1	25	10	15	10	4
F2	25	15	15	10	4
F3	25	20	15	10	4
F4	25	10	20	10	4
F5	25	15	20	10	4
F6	25	20	20	10	4
F7	25	10	25	10	4
F8	25	15	25	10	4
F9	25	20	25	10	4

Evaluation of Orally Fast Dissolving Films

Weight variation

Weight variation is studied by individually weighing 10 randomly selected filmstrips and calculating the average weight should not deviate significantly from average weight. According to specifications given in I.P.2007 for 30 mg film standard deviation should not more than 10 %[20].

Film thickness

The thickness of the drug loaded films was measured with the help of micrometer screw gauge at different strategic locations like four corners and centre of the each film. Mean SD is calculated. The standard range for film thickness should not be less than 5 %. This is essential to assure uniformity in the thickness of the film as this was directly related to the accuracy of dose[6].

Surface pH

The film formulation has to be kept in the oral cavity, pH of the saliva ranging from 5.5-7.5. So, to dissolve and solubilise the drug in saliva present in the oral cavity the pH of film should keep near to neutral. Since acidic or alkaline pH may leads to irritation to the buccal mucosa. The surface pH of the film is calculated in order to investigate any side effects *in vivo*. A combined pH electrode was used for this purpose. The film preparation to be tested was placed in nesseler cylinder and was slightly moistened with o.5 ml distilled water introduced drop wise. The pH is measured by bringing the electrode in contact with the surface of the oral film and allowing equilibrating for 1 min. The study performed on three films of each formulation and mean ±SD calculated[5].

Folding endurance

It is measured manually for the prepared oral film. A film was repeatedly folded at the same place till until it breaks. The number of times the film could be folded at the same place without breaking gave the value of folding endurance. This test should be performed on three films of each formulation and mean ±SD calculated[7].

Drug content

The films were tested for content uniformity. Films of size 4 cm^2 is placed in 100 ml volumetric flask and dissolved in methanol, volume is made upto 100 ml with methanol (100µg/ml). Samples were suitably diluted by using methanol. The absorbance of the solution wasmeasured at 230 nm in UV spectrophotometer. The acceptance value (AV) of the preparation 85-115%[8].

***In-vitro* disintegration time**

In vitro disintegration time was determined visually in a glass dish of 25 ml distilled water with swirling every 10 seconds. The test was performed in triplicate for each formulation. The disintegration is the time when film breaks or disintegrates. Superdisintegrants should be incorporated in the film formulation to improve disintegration rate. All the films were subjected to disintegration test and results obtained. In Indian pharmacopoeia limits for disintegration is 1-3 min for fast dissolving dosage forms[9].

***In-vitro* dissolution studies**

The in vitro dissolution study was carried out in freshly prepared deionised simulated saliva solution pH 6.8 phosphate buffer using USP paddle apparatus at 37±0.5^oC. Percent drug release was calculated for each formulation. Samples were withdrawn at every 1 min time interval within 5 min dissolution study. Samples were diluted by 6.8 phosphate buffer solution and analysed by UV-Visible spectrophotometer[5].

Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. Tensile testing of the film was determined with digital tensile tester, which consists of two load cell grips[10]. The lower one is fixed and upper one is movable. The test film of specific size was fixed between cell grips and force was gradually applied till the film breaks[21]. Tensile strength is calculated by Formula;

$$\text{Tensile strength} = \frac{\text{Force at break}}{\text{Initial cross sectional area of film in } mm^2}$$

Percent elongation

It is calculated by the distance travelled by pointer before the break of the film on the graph paper. When stress is applied, a film strip sample stretches and this is referred to as strain. Strainis basically the deformation of film strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases[17]. It is calculated as;

$$\% \text{ Elongation} = \frac{\text{Increase in length}}{\text{Original Length}} \times 100$$

Result And Discussion

Thickness of the film:

The thickness of the drug loaded films F-1 to F-9 formulations was measured with the help of micrometer screw gauge at different strategic locations like four corners and centre of the each films. Mean SD is calculated. Film thickness should be controlled within a ± 5 % variation of standard value. This is essential to assure uniformity in the thickness of the film as this is directly related to the accuracy of doseand other mechanical properties of the film.Thickness of a single film varies from 0.61±0.01 to 0.65±0.02 mm. The results are reported in the Table 2.

Weight variation of film :

The weight of each filmstrip is taken on Electronic analytical balance and the weight variation is calculated as mean SD. Weight variation varies from 25.67±1.87 to 29.03± 0.60. The results are given in the Table 2.

Folding endurance of the films:

The number of times the film fold until it breaks is reported. The studies reflex the influence of concentration of PVA in the formulation. As the concentration of PVA is increased, folding endurance is also increased. Formulation F3 shows the largest folding endurance. Folding endurance of all Agomelatine films are reported in Table 2.

Surface pH:

The film formulations have to be kept in the oral cavity, pH of saliva ranging from 5.5-7.5. So, to dissolve and solubilize the drug in the saliva present in the oral cavity the pH of the film should keep near to neutral. If it is acidic it can leads to irritation of the buccal mucosa. Surface pH of all Agomelatine fast dissolving films are reported in Table 2. Surface pH of the formulations does not show considerable variations in pH. All formulations show acceptable pH range 6.3-6.8. This study also reflects the influence of concentration of PVA in the formulation. As there is increase in proportion of PVA, pH of the formulation also increases as PVA is more alkaline than PVP.

Formulation code	Average thickenss (mm) Mean± S.D	Average weight (mg) Mean± S.D	Folding Endurance Mean± S.D	Surface pH Mean± S.D	Disintegration Time Mean± S.D	%Drug content	Average Tensile Strength Mean ± S.D	Percent Elongation At break Mean± S.D
F1	0.61±0.01	25.67±1.87	181±3.4	6.3±0.2	230 ±1.8	90.16 ±1.2	1.20±0.2	37.04±0.91
F2	0.61±0..01	28.7±0.20	183±2.3	6.3±0.2	200±2.1	92.00 ±0.4	1.12±0.02	37.56±1.0
F3	0.65±0.02	28.72±0.50	187±3.4	6.6±0.1	180±2.1	94.25 ±1.5	1.14±0.02	35.50±0.76
F4	0.64±0.02	28.59±0.50	184±2.6	6.7±0.1	210±1.2	91.16 ±2.1	1.12±0.03	37.09±0.56
F5	0.63±0.02	29.03±0.60	182±2.0	6.8±0.07	220±1.9	95.66 ±2.9	1.16±0.02	35.86±0.32
F6	0.65±0.02	27.84±0.80	182±2.0	6.6±0.1	170±1.7	98.16 ±1.0	1.17±0.03	36.37±0.31
F7	0.64±0.02	27.77±0.90	183±2.3	6.6±0.1	190±1.2	92.33±1.7	1.20±0.01	35.47±0.31
F8	0.63±0.01	28.43±0.30	183±2.3	6.7±0.1	200±1.6	94.75 ±2.4	1.20±0.01	38.27±0.22
F9	0.64±0.02	28.45±0.30	182±2.0	6.7±0.1	230±1.9	90.25 ±2.2	1.16±0.01	32.76±0.51

***In-vitro* Disintegration Test:**

In-vitro disintegration time is determined visually in a glass dish of 25 ml distilled water with swirling every 10 seconds. The disintegration is the time when film breaks or disintegrates. Superdisintegrants should be incorporated in the film formulation to improve disintegration rate. PVP is incorporated as a superdisintegrant. All the films were subjected to disintegration test and results obtained. In Indian pharmacopoeia limits for disintegration are 1-3 min. The *In-vitro* disintegration time of all Agomelatine films are reported in Table 2.

Drug content

Drug content of optimized batches are calculated by using film containing 5 mg of Agomelatine.Three trials from each formulation are analyzed spectrophotometrically. The mean value and standard deviation of all the formulations are calculated. The drug content ranging from 90.16±2.2 to 98.16±1.0.The results indicated that in all the formulations the drug content is uniform.The studies also show that uniformity of content is within the specifications range 85-115%.The results are as shown in Table 2.

Tensile strength:

Mechanical properties of the films are evaluated using Instron TA.XT2 texture analyzer equipment equipped with a 50 N load cell. Films are held between two clamps positioned between 3 cm. During measurement the strips were pulled at the rate of 2mm/sec. From the results it clears that when the concentration of the polymer increases, the tensile strength of the film also increases. The formulation F1 shows the maximum tensile strength. Presence of PEG 400 as a plasticizer imparts the flexibility to the Polymers. Tensile strength measures the ability of the film to with stand rupture. The Formulation F3 shows the maximum strength 1.20±0.2, shown in Table 2. This might be due to formation of strong hydrogen bonds between polymer and plasticizer thereby imparting flexibility to withstand rupture, but formulation F7 & F8 also shows comparable tensile strength as compared to F1 formulation.

Percentage elongation of the films:

The film of 03 inch X 10 mm was taken for the studies. Percentage elongation was found to be increased as increase in concentration of polymer in the film. Data is reported in Table 10.

***In-vitro* Drug release study:**

In-vitro dissolution study shows maximum release i.e. 94.01% for F6 formulation this could be attributed to higher concentration of PVP and lower concentration of PVA in the formulation. *In-vitro* drug release data is shown in Table 3.

Table 3: *In-vitro* drug release study of all formulations

Time in Min	Cumulative drug release (%) ±SD								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	50.98 **±1.0**	63.49 **±0.3**	56.51 **±0.3**	80.94 **±0.3**	52.31 **±1.0**	83.26 **±0.6**	80.36 **±0.6**	69.19 **±0.8**	70.23 **±0.9**
2	57.03 **±0.2**	65.69 **±0.3**	64.37 **±0.2**	82.42 **±0.7**	61.25 **±0.9**	89.23 **±1.0**	70.29 **±1.3**	70.19 **±0.9**	73.14 **±0.6**
3	63.99 **±1.4**	68.09 **±0.2**	67.97 **±0.3**	83.35 **±0.9**	68.13 **±0.9**	91.93 **±1.0**	67.9 **±0.2**	75.68 **±0.8**	78.03 **±1.8**
4	69.01 **±1.3**	70.92 **±0.4**	71.78 **±0.3**	84.60 **±1.2**	72.61 **±1.0**	93.16 **±1.4**	71.07 **±1.0**	78.40 **±1.7**	80.20 **±0.8**
5	72.86 **±1.1**	74.65 **±0.3**	74.90 **±1.4**	85.21 **±0.8**	89.36 **±0.7**	94.01 **±0.5**	78.80 **±1.0**	81.90 **±1.1**	82.26 **±0.4**

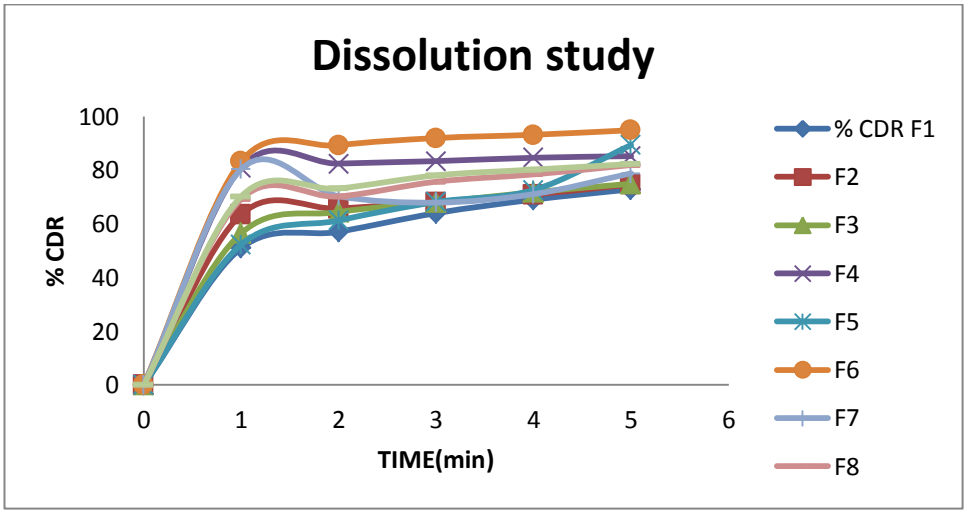

Fig.No. 1: Comparative Evaluation of *in-vitro* drug release study of formulation

Optimization

Statistics was applied to the results obtained from general factorial design in which two independent variables varied namely polyvinyl pyrrolidone (X1) and polyvinyl alcohol (X2) and their effect is recorded on dependent variable namely % drug release (Y1).Evaluation and interpretation of research findings are almost important and the p-value serves a valuable purpose in these findings. Table 11 shows ANOVA for the dependent variable % drug release. The values of X_1 and X_2 were found to be significant at $p < 0.05$, hence confirmed the significant effect of both the variables on the selected responses. Variable caused significant change in the responses. From this data optimum concentration of polyvinyl pyrrolidone10 mg and polyvinyl alcohol 15 mg was found.

Table 4. ANOVA for % drug release (Y1).

Source	Degree of Freedom	F value	P-value	Inference
Model	5	18.12	0.0189	Significant
A-PVP K-30	1	7.69	*0.0694*	
B-PVA	1	*15.57*	*0.0290*	

std.dev. = 2.12
R-Squared = 0.9680

The Variance Inflation Factor (VIF) measured how much the variance of that model coefficient was inflated by the lack of orthogonality in the design and was calculated for % drug release. It was found to be near to one which indicating good estimation of the coefficient. Similarly Ri-squared was near to zero which led to good model. The values of Prob>F were less than 0.0003,

which indicated model terms were significant. The linear model obtained from the regression analysis used to build a 3-D graph's in which the responses were represented by curvature surface as a function of independent variables. The relationship between the response and independent variables can be directly visualized from the response surface plots. The response surface plots were generated using Design Expert 8.0.4 software presented in figure. 21 to observe the effects of independent variables on the response studied % drug release. From response surface 3 level factorial design was chosen using linear design mode. The range was set from minimum 75.26 to maximum 100.91. The 9 run was performed for the response % drug release and model was found to be linear.

The perturbation plot

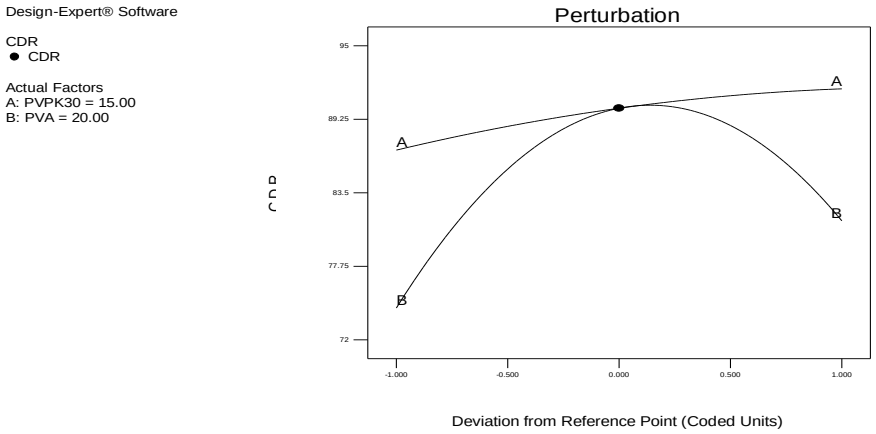

Fig.No.2: Perturbation plot

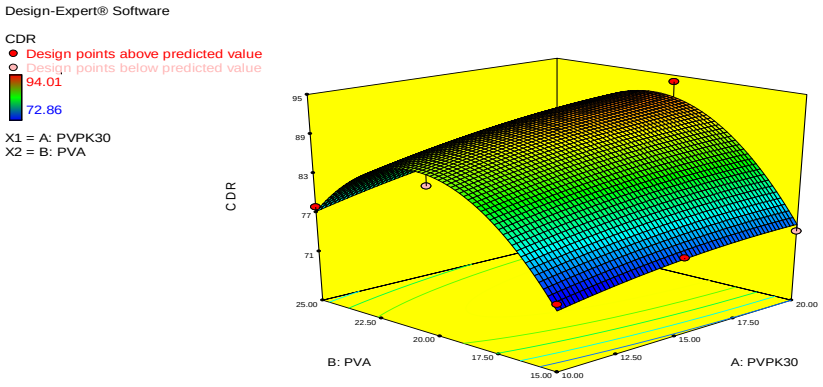

Fig.No.3: Surface Response plot showing effect of polyvinyl pyrrolidone K-30 and polyvinyl alcoholon release

Stability studies[16]:

Accelerated stability study

Table 5: Stability data for F6 formulation

Sr. No	Observations	Before Accelerated Stability Testing	After Accelerated Stability Testing		
			30 days	60 days	90 days
1	Drug content	**98.16%**	**98.12%**	**98.05%**	**98.00%**
2	Visual appearance (Colour changes)	**Light yellow**	**Light yellow**	**Light yellow**	**Light yellow**
3	pH	**6.6**	**6.6**	**7.0**	**7.2**
4	Disintegration time	**20 Sec**	**24 Sec**	**28 Sec**	**35 Sec**

Formulation F6 at 40^{o}C temperature is found to be stable upto 3 months. There is no significant change in drug content, visual appearance i.e. change in colour and disintegration time. All films stored at elevated temperature showed slight change in pH, other parameters are found to be unchanged. This change in pH is due to presence of PVA which is alkaline in nature, but it does not affect stability of drug within the film.

Conclusion

The present study indicates a good orally fast dissolving films containing Agomelatine for systemic delivery with an added advantage of faster drug action for mood disorders like anxiety and obsessive compulsive disorder. Finally, it is concluded that the drug release from the Fast dissolving film was increased by using the increased concentration of Superdisintegrant, thus assisting in faster disintegration in the buccal cavity. As the drug having low solubility, fast disintegration may leads to more drug availability for dissolution, resulting in faster absorption in systemic circulation increased systemic availability of drug may leads to quick onset of action which is prerequisite for anti-depressive patient.

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