Asian Journal of Pharmaceutical Education and Research
Vol -10, Issue-4, October- December 2021
ISSN:2278 7496

RESEARCH ARTICLE Impact Factor: 7.014

FORMULATION, DEVELOPMENT AND EVALUATION OF FAST DISSOLVING SUBLINGUAL WAFERS OF AN ANTIPSYCHOTIC DRUG USING FILM FORMER

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Received 18 Sept. 2021; Revised 22 Sept. 2021; Accepted 25 Sept. 2021, Available online 10 Oct. 2021

Cite this article as: Singh A, Shende S, Singh N. Formulation, Development and Evaluation of Fast Dissolving Sublingual Wafers of an Antipsychotic Drug Using Film Former. Asian Journal of Pharmaceutical Education and Research. 2021; 10(4): 18-26.
https://dx.doi.org/10.38164/AJPER/10.4.2021.18-26

ABSTRACT

In the present study, Fast dissolving sublingual wafers of Olanzapine were prepared by solvent casting technique with a view to enhance patient compliance. Different formulation of fast dissolving wafers was prepared and evaluated for drug and polymer compatibility studies, thickness, weight uniformity, surface pH determination, folding endurance, percentage of moisture content, drug content analysis, disintegrating time, *in vitro* dissolution study and stability studies. Effect of super disintegrants on disintegration time, drug content and in vitro release have been studied. The formulated Olanzapine wafers showed a disintegration time in the range of 9 ± 1- 26 ± 5sec. Formulation F7 showed the least disintegration time of 8 ± 1 sec. Formulations containing only Xanthan Gum, Gelatin and Cross Carmellose Sodium showed minimum disintegration time of 9 ± 1 sec select as optimized formulation.

Keywords: Olanzapine, Fast dissolving sublingual wafers, Xanthan Gum, Gelatin, Cross Carmellose Sodium.

INTRODUCTION

Among the novel drug delivery system, buccal drug delivery is the main and extensive acceptable drug delivery between the other delivery systems. The orally disintegrating tablets are available in the market providing 1 to 2 minute of disintegration time. Among fast dissolving drug delivery systems, oral flash release wafer drug delivery system is an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience in difficulties of swallowing traditional oral solid dosage forms [1]. This technology has been used for local action, rapid release of products and for direct systemic circulation in the oral cavity to release drug in rapid fashion. And also this delivery protect drug from first pass metabolism and improve the dissolution. Oral thin wafer drug delivery systems are solid dosage forms, which dissolve in a short period of time when placed in the mouth without drinking water or chewing. These are also referred as fast dissolving oral wafers, wafers, buccal films/ Oral strips [2].

The mucous membrane permeability provides a convenient route for the systemic delivery of new and existing therapeutic drugs. Different mucosal regions like oral mucosa, nasal, rectal, vaginal, ocular may facilitate bioavailability by avoiding the hepatic metabolism. Transmucosal drug delivery is being considered as an attractive delivery route for new and existing drug compounds, some of which are only available today through parenteral delivery. Among the various sites available for transmucosal drug delivery, the buccal mucosa and the sublingual area are the best-suited sites for local as well as systemic delivery of drugs, due to their physiological features[3].

The buccal mucosal site offers a smooth, immobile surface with high vascular perfusion, in contrast to the sublingual mucosal site, which lacks an immobile mucosal surface. The lack of an immobile surface derives from the fact that the sublingual space is constantly washed by saliva from the sublingual salivary ducts. However, the sublingual mucosal membrane is much thinner (190 μm) than the buccal mucosal membrane (580 μm). The difference in thickness may explain the difference in permeability (Kp) of the mucosal membranes, 579 x 10^{-7} cm/min Vs 973 x 10^{-7} cm/min for the buccal mucosa and floor of the mouth, respectively. When compared to other mucosal areas, the buccal mucosa is more tolerant to potential allergens, with less impact for irreversible damage, and relatively lower enzymatic activity. For compromised patient populations where swallowing is difficult or where a potential choking hazard is present, a buccal delivery device presents an elegant and effective dosage format with improved bioavailability when compared to other oral formats[4.]

Buccal devices offer advantages to care givers for administration, in that the buccal area is easily accessible and generally a well-tolerated site by patients as it does not require swallowing for the device to deliver an efficacious systemic dose with rapid onset. A number of buccal products are emerging for the treatment of chronic conditions, as well as breakthrough treatments for central nervous conditions and pain therapies in the form of oral sprays, buccal films or tablets and sublingual films or wafers. As with transdermal applications, formulators are limited by the ability to deliver higher Molecular Weight (Mw) compounds through buccal mucosal tissue. This is because the buccal and sublingual membranes contain a stratified (multilayered) epithelium that demonstrates differentiation of various cell layers in the form of keratinisation. This is different from the single epithelium cell layer lining the gastro-intestinal tract, thereby resulting in less resistance to permeability [5].

Several approaches can be taken to increase the permeation of a drug through the buccal mucosal membrane. One of these approaches is to improve the bioadhesion properties to increase residence time and drug release of the device in the oral cavity. Modification of the drugs partition coefficient can be used as an approach. A third approach, which is also used in transdermal drug delivery, is to employ the use of chemical permeation enhancers [6].

To improve patient compliance and provide a rapid onset of action. To reduce the extent of hepatic first pass metabolism. To reduce side effects associated with the API by reducing its dose. To enhance the oral bioavailability of molecules. The aim of the present research work is development and characterization of fast dissolving oral wafers of Olanzapine.

MATERIALS AND METHODS

Materials:

Repaglinide was received as a gift sample from Sun Pharmaceutical Industries Limited, Mumbai, India. Hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M) was procured from Meditab Specialities Pvt. Ltd., Satara. Sodium alginate, Gum tragacanth was purchased from S.D fine chemicals, Mumbai., Magnesium stearate, talc were purchased from Mapromax, Life sciences Pvt. Ltd., Dehradun. Other solvents and chemicals used in the research were of LR grade. All the studies were carried in distilled water.

Methods:

Formulation development of sublingual wafers of Olanzapine

Drug (Olanzapine) containing fast dissolving wafers were fabricated by the solvent casting method. Xanthan Gum, Gelatin, Gum Acacia, Cross Carmellose Sodium, Aspartame by solvent casting technique with ice cold distilled water and sublingual wafers were prepared. Drug solution was sonicated for 30 - 45 min to solubilize the drug completely in the solvent. Drug solution was poured into polymeric solution and ethanol was added for alkaline hydrolysis. Both solutions are uniformly mixed to get a homogeneous solution on magnetic stirrer at 250 - 320 rpm. Then this solution was spread on film former by adjusting the desired temperature on glass moulds of 15cm*5 cm^2. Once the wafer sheet was ready, it was cut into desired size of 2.5*2.5 cm^2 cm was dried and The dried wafers were carefully removed from the glass plates and was cut into size required for testing. The wafers were stored in air tight plastic bags till further use [7]. The composition of sublingual wafers is given in Table 1.

Table 1: Selection and optimization of wafers forming agents

Name of ingredients (mg for 12 strips)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Olanzapine	60	60	60	60	60	60	60	60	60
Xanthan gum	50	100	150	50	100	150	50	100	150
Gelatin	25	50	75	25	50	75	-	-	-
Gum acacia	25	50	75	-	-	-	25	50	75
Cross Carmellose Sodium	-	-	-	25	50	75	25	50	75
Methyl Paraben	20	20	20	20	20	20	20	20	20
Aspartame	10	10	10	10	10	10	10	10	10

Citric acid	20	20	20	20	20	20	20	20	20
DM water qs to (ml)	30	30	30	30	30	30	30	30	30

Dose calculations

- Width of the plate = 5 cm
- Length of the plate = 12 cm
- No. of 2.5 x 2.5 cm^2 wafers present whole plate = 12
- Each wafers contains 5 mg of drug.
- 12 no. of wafers contains mg of drug = 5 × 12 = 60 mg

The amount of drug added in each plate was approximately equal to 60 mg.

Evaluation of prepared Wafers [8-10]

Thickness

Three random wafers were selected from each batch and the thickness was measured at three different places using a vernier caliper.

Weight uniformity

For each formulation, three randomly selected patches were used. For weight variation test, 10 wafers from each batch were weighed individually by digital electronic balance and the average weight and relative standard deviation was calculated**.**

Surface pH Determination

The surface pH of fast dissolving wafers was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the oral mucosa, it is important to keep the surface pH as close to neutral as possible. The wafer to be tested was placed in a petridish and was moistened with 0.2 ml of distilled water. The electrode of pH meter (Electronic India) was placed on the surface of wafer to determine the surface pH.

Folding Endurance

This was determined by repeatedly folding one wafers at the same place until it broke. The number of times the wafers could be folded at the same place without breaking cracking gave the value of folding endurance.

Percentage of moisture content

The wafers were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual wafers were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

$$\text{Percentage of Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{x } 100$$

Drug content analysis

The patches (n = 3) of specified area were taken into a 10 ml volumetric flask and dissolved in methanol and volume was made up with 10 ml methanol. Subsequent dilutions were made and analyzed by UV spectrophotometer at 256 nm.

Disintegrating time

The most important criteria of present work are to that dosage form should be dissolved within few seconds. The incorporation of polymers to minimizes the disintegrating time. *In-vitro* disintegration time was determined by placing the wafer in a petridish containing 10 ml distilled water with swirling every 10 sec. The time at which the wafer disintegrated was noted.

***In vitro* dissolution study**

The *in vitro* dissolution test was performed using the USPXXX dissolution apparatus II (Paddle type). The dissolution studies were carried out at 37 ± 0.5 °C; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Wafers size required for dose delivery (2.5 × 2.5 cm^2) was used. 5 ml aliquot of dissolution media was collected at time intervals of 1, 2, 5, 10 and 15 minutes and replaced with equal volumes of phosphate buffer (pH 6.8). The collected samples were filtered through 0.45 µm membrane filter and the concentration of the dissolved Olanzapine was determined using UV-Visible spectrophotometer at 256 nm. The results were presented as an average of three such concentrations.

Stability studies

Stability studies were carried out with optimized formulation which was stored for a period of one, two and three months at 40 ± 2^oC temperature and 75 ± 5 % relative humidity for a period 3 months. The % Assay of formulation was determined by U.V. spectrophotometer using calibration curve method. The % assay of wafers was found to slightly decrease at higher temperature.

RESULTS AND DISCUSSION

Different formulation of fast dissolving wafers was prepared and evaluated for drug and polymer compatibility studies, thickness, weight uniformity, surface pH determination, folding endurance, percentage of moisture content, drug content analysis, disintegrating time, *in vitro* dissolution study and stability studies.

The thickness of formulated Olanzapine was varied between 38 ± 2µm to 48 ± 3µm due to different amount of polymers used for formulation development. The formulated Olanzapine wafers were subjected to weight variation test and the wafers showed a weight variation between 75 ± 2 µm to 98 ±2.

As the formulation is rigid can be break easily. In formulated all the Olanzapine wafers the value of folding endurance was found more than 100, and maximum value of Olanzapine wafers was found in formulation F7 (220 ± 5).

The surface pH of all the formulations were determined in order to investigate the possibility of any kind of side effects in the oral cavity as acidic or alkaline pH is bound to cause irritation in the oral mucosa. The pH of the formulated wafers was found to be in the range of 6.5 ± 0.2-6.8 ± 0.2. Thus, it can be considered that the Olanzapine wafers will cause no irritation in the oral cavity.

The wafers were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual wafers were weighed repeatedly until they showed a constant weight. The moisture content of the formulated wafers was found to be in the range of 1.11 ± 0.36 - 1.75 ± 0.14. Thus, it can be considered that the formulation F7 of the Olanzapine showed minimum moisture content among all formulations.

Drug content was analyzed by UV-Visible spectrophotometer at 256nm. The percentage drug content was between 98.12 ± 0.36% and 99.45 ± 0.32% as shown in Table 7.6, which proved uniform drug distribution within the Olanzapine wafers.

All preparations absorb moisture at a very fast rate and they disintegrate as soon as they come in contact with water. The formulated Olanzapine wafers showed a disintegration time in the range of 9 ± 1- 26 ± 5sec. Formulation F7 showed the least disintegration time of 8 ± 1 sec. Formulations containing only Xanthan Gum, Gelatin and Cross Carmellose Sodium showed minimum disintegration time of 9 ± 1 sec select as optimized formulation.

The *in vitro* drug release studies were carried out on formulated Olanzapine wafers formulation F6. The drug release data showed a drug release of 55.65 ± 0.25 %, 65.58 ± 0.32 %, 78.85 ± 0.36 %, 85.56 ± 0.45 %, 92.23 ± 0.15 % and 99.14 ± 0.23 % respectively at the 60, 120, 180, 240, 300 and 360 sec of study period. This faster release of the drug can be accounted to the optimum ratio of the wafer forming polymers used having both properties of gelation and fast melt. The drug release was found to be much faster than that of the permeation for the same formulations due to the fact that a much larger sink condition was maintained during the drug release studies which lead to a much faster release of the drug into the media.

Minor difference was found between evaluated parameters before and after ageing/storage and all was in acceptable limits. Therefore, formulation remains stable for sufficient time.

Table 2: Results of evaluation of prepared wafers

Formulation code	General Appearance	Thickness (µm)	Weight (mg)
F1	Translucent	38 ± 2	75 ± 2
F2	Translucent	42 ± 2	82 ± 3
F3	Translucent	45 ± 3	89 ± 2
F4	Translucent	39 ± 1	93 ± 2
F5	Translucent	45 ± 2	95 ± 3
F6	Translucent	48 ± 3	98 ± 2
F7	Translucent	40 ± 2	85 ± 2
F8	Translucent	43 ± 2	89 ± 3
F9	Translucent	46 ± 2	93 ± 3

***Average of three determinations (N=3)**

Table 3: Result of surface pH determination, folding endurance, percentage of moisture content

Formulation code	Folding endurance* (Times)	Surface pH determination	Percentage of moisture content*
F1	165 ± 4	6.5 ± 0.2	1.25 ± 0.14
F2	185 ± 6	6.7 ± 0.1	1.45 ± 0.23
F3	175 ± 5	6.8 ± 0.2	1.32 ± 0.25
F4	165 ± 6	6.5 ± 0.2	1.65 ± 0.32
F5	160 ± 5	6.8 ± 0.2	1.75 ± 0.14
F6	175 ± 4	6.6 ± 0.2	1.35 ± 0.25
F7	220 ± 5	6.7 ± 0.3	1.11 ± 0.36
F8	155 ± 2	6.8 ± 0.2	1.32 ± 0.32
F9	183 ± 3	6.5 ± 0.1	1.45 ± 0.23

Table 4: Drug content analysis and disintegrating time

Formulation code	Drug content analysis (%)	Disintegrating time (Sec.)
F1	98.85 ± 0.25	25 ± 3
F2	98.12 ± 0.36	21 ± 2
F3	98.45 ± 0.41	26 ± 5
F4	98.85 ± 0.36	23 ± 4
F5	98.98 ± 0.25	20 ± 6
F6	98.78 ± 0.41	15 ± 2
F7	99.45 ± 0.32	9 ± 1
F8	99.12 ± 0.74	15 ± 3
F9	98.75 ± 0.25	13 ± 4

Table 5: Results of *In-Vitro* release study of optimized formulation F7

S. No.	Time (Sec)	Cumulative drug release (%)
1.	60	55.65 ± 0.25
2.	120	65.58 ± 0.32
3.	180	78.85 ± 0.36
4.	240	85.56 ± 0.45
5.	300	92.23 ± 0.15
6.	360	99.14 ± 0.23

*Average of three reading (n=3)

Table 6: *In-vitro* drug release data for F7

Time (Sec.)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
60	0.70711	-0.301	55.65	1.195	84.35	1.926
120	1	0	65.58	1.349	77.64	1.890
180	1.41421	0.301	78.85	1.602	60.02	1.778
240	2	0.602	85.56	1.746	44.22	1.646
300	2.44949	0.778	92.23	1.845	30.02	1.477
360	2.82843	0.903	99.14	1.897	21.15	1.325

*Average of three reading

Table 7: Regression analysis data of optimized formulation F7

Batch	Zero Order	First Order	Higuchi's Model	Korsmeyers Peppas Equation
		R^2		
F7	0.980	0.835	0.994	0.989

CONCLUSION

Different formulation of fast dissolving wafers was prepared and evaluated for drug and polymer compatibility studies, thickness, weight uniformity, surface pH determination, folding endurance, percentage of moisture content, drug content analysis, disintegrating time, *in vitro* dissolution study and stability studies. Effect of super disintegrants on disintegration time, drug content and in vitro release have been studied. The formulated Olanzapine wafers showed a disintegration time in the range of 9 ± 1- 26 ± 5sec. Formulation F7 showed the least disintegration time of 8 ± 1 sec. Formulations containing

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