

FORMULATION, DEVELOPMENT OF FAST DISSOLVING SUBLINGUAL WAFERS OF AN ANTIEMETIC DRUG USING FILM FORMER

Jayesh Kelodiya, Sunil Kumar Shah, C. K. Tyagi, Prabhakar Budholiya*

College of Pharmacy, Sri Satya Sai University of Technology & Medical Sciences, Sehore (M.P.)

*Corresponding Author's E mail: prabhakarbudholiya@gmail.com

Received 22 July 2021; Revised 11 Aug. 2021; Accepted 18 Aug. 2021, Available online 10 Oct. 2021.



Cite this article as: Kelodiya J, Shah SK, Tyagi CK, Budholiya P. Formulation, Development of Fast Dissolving Sublingual Wafers of an Antiemetic Drug Using Film Former. Asian Journal of Pharmaceutical Education and Research. 2021; 10(4): 71-78.

<https://dx.doi.org/10.38164/AJPER/10.4.2021.71-78>

ABSTRACT

The aim of the present research work is development and characterization of fast dissolving oral Wafers of Meclizine hydrochloride. Meclizine hydrochloride containing fast dissolving wafers were fabricated by the solvent casting method. Drug content was analyzed by UV-Visible spectrophotometer at 232 nm. The percentage drug content was between $95.65 \pm 0.23\%$ and $99.12 \pm 0.61\%$, which proved uniform drug distribution within the Meclizine hydrochloride wafers. All preparations absorb moisture at a very fast rate and they disintegrate as soon as they come in contact with water. The formulated Meclizine hydrochloride wafers showed a disintegration time in the range of 6 ± 1 - 15 ± 1 sec. Formulation F7 showed the least disintegration time of 6 ± 1 sec. Formulations containing only Xanthan gum, Gelatin and Gum acacia showed highest disintegration time of 15 ± 1 sec seconds. The *in vitro* drug release studies were carried out on formulated Meclizine hydrochloride wafers formulation F7. The drug release data showed a drug release of 36.65%, 48.89%, 64.56%, 72.32%, 85.65% and 98.15% 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.

Keywords: Meclizine hydrochloride, Fast dissolving oral wafers, Xanthan gum, Gelatin and Gum acacia.

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 forms¹. 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 features³⁻⁴.

Fast dissolving wafers are a new arising oral dosage forms used by patients world widely. These dosage forms can be used even in acute condition for getting instant relief ⁵. Fast dissolving wafers have gained vast attention on the market because of its various advantages along with an extended shelf life of 2-3 years ⁶. These oral sublingual wafers are nothing but a thin oral strip which when place in the sublingual cavity dissolves immediately due to presence of saliva in the mouth by releasing medicament within short span of time⁷. Sublingual wafers seem to be highly advantageous dosage form during travelling as it does not need water for engulfment⁸. Even rapid onset of action is achieved as this dosage form is highly efficient in avoiding first pass metabolism. Wafers are administered sublingually to improve the onset of action, lower the dose and enhance efficacy of the medicament⁹, it is more stable, durable and quicker dissolving than other conventional dosage forms, an oral wafer helps to enhance bioavailability of the drug¹⁰, improves dosing accuracy i.e., single unit dosage form¹¹, has the potential to allow the use of bitter tasting drug into the formulation and improves patient compliance ¹²⁻¹³. Benign prostatic hyperplasia is a condition in which there is enlargement of prostate gland without malignancy. The bladder wall thickens and loses the ability to empty completely. The aim of the present research work is development and characterization of fast dissolving oral Wafers of Meclizine hydrochloride.

MATERIAL AND METHODS

Material

Meclizine was obtained as a gift sample from pharmaceutical company. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All the chemicals used in this work were of analytical grade.

Methods

Formulation development of oral wafers of Meclizine hydrochloride

Drug (Meclizine hydrochloride) containing fast dissolving wafers were fabricated by the solvent casting method. The optimized amount of polymers was dissolved in 5ml of water and stirred continuously for 1 hour, optimized amount of Plasticizer and drug were dissolved in 95% ethanol and then added to the polymeric solution, the optimized amount of drug was dissolved in 2ml of water and kept on sonication for proper dispersion. Polymeric solution was stirred for 30 min using magnetic stirrer and was kept in undisturbed condition till the entrapped air bubbles were removed. The aqueous solution was casted in a glass moulds having 2.5 x 2.5 cm * 10 wafers area and was dried at controlled room temperature (25°-30°C, 45 %RH) as well as at increased temperature (microwave oven). The wafers took approximately 48 hr to dry at controlled room temperature. The dried wafers were carefully removed from the glass plates and were cut into size required for testing. The wafers were stored in air tight plastic bags till further use.

Table 1: Formulation of oral wafers of Meclizine hydrochloride

Name of ingredients (mg for 12 strips)	F1	F2	F3	F4	F5	F6	F7	F8	F9
API	120	120	120	120	120	120	120	120	120
Xanthan gum	100	200	300	100	200	300	100	200	300
Gelatin	50	100	150	50	100	150	-	-	-
Gum acacia	25	50	75	-	-	-	25	50	75
Pullulan	-	-	-	25	50	75	25	50	75
Methyl Paraben	20	20	20	20	20	20	20	20	20
Aspartame	20	20	20	20	20	20	20	20	20
Citric acid	50	50	50	50	50	50	50	50	50
DM water qs to (ml)	30	30	30	30	30	30	30	30	30

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm
- No. of 2.5 x 2.5 cm² wafers present whole plate = 12
- Each wafers contains 10 mg of drug.
- 12 no. of wafers contains mg of drug? = 10×12 = 120mg
- The amount of drug added in each plate was approximately equal to 120mg.

Evaluation of prepared wafers

Thickness

Three random wafers were selected from each batch and the thickness was measured at three different places using a vernier caliper¹⁴.

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 vivo¹⁵⁻¹⁶. 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 endurance¹⁷.

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 weight¹⁸⁻¹⁹

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

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 232nm²⁰.

Disintegrating time

The most important criteria of present work are to that dosage form should be dissolved within few seconds²¹. The incorporation of polymers to minimizes the disintegrating time. *In vitro* disintegration time was determined by placing the wafer in a petridish containing 10ml 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)²². The dissolution studies were carried out at $37 \pm 0.5^\circ\text{C}$; with stirring speed of 50 rpm in 900 ml phosphate buffer (pH 6.8). Wafers size required for dose delivery ($2.5 \times 2.5 \text{ cm}^2$) was used. Five 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 $0.45 \mu\text{m}$ membrane filter and the concentration of the dissolved Meclizine hydrochloride was determined using UV-Visible spectrophotometer at 232nm. The results were presented as an average of three such concentrations.

RESULTS AND DISCUSSION

The Thickness of formulated Meclizine hydrochloride was varied between $75 \pm 4 \mu\text{m}$ to $86 \pm 3 \mu\text{m}$ due to different amount of polymers used for formulation development. The formulated Meclizine hydrochloride wafers were subjected to weight variation test and the wafers showed a weight variation between $98 \pm 6 \text{ mg}$ - $124 \pm 3 \text{ mg}$ Table 2. This was determined by repeatedly folding one wafer 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. The maximum folding endurance indicates the elasticity of formulation. As the formulation is rigid can be break easily. In formulated all the Meclizine hydrochloride wafers the value of folding endurance was found more than 100, and maximum value of Meclizine hydrochloride wafers was found in formulation F7 (220 ± 6).

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 6.4 ± 0.2 - 6.9 ± 0.2 . Thus, it can be considered that the Meclizine hydrochloride wafers will cause no irritation in the oral cavity table 3.

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 1.05 ± 0.14 - 1.35 ± 0.15 . Thus, it can be considered that the formulation F7 of the Meclizine hydrochloride showed minimum moisture content among all formulations.

Drug content was analyzed by UV-Visible spectrophotometer at 232 nm. The percentage drug content was between $95.65 \pm 0.23\%$ and $99.12 \pm 0.61\%$ as shown in Table 3, which proved uniform drug distribution within the Meclizine hydrochloride wafers.

All preparations absorb moisture at a very fast rate and they disintegrate as soon as they come in contact with water. The formulated Meclizine hydrochloride wafers showed a disintegration time in the range of 6 ± 1 – 15 ± 1 sec table 3. Formulation F7 showed the least disintegration time of 6 ± 1 sec. Formulations containing only Xanthan gum, Gelatin and Gum acacia showed highest disintegration time of 15 ± 1 sec seconds.

The *in vitro* drug release studies were carried out on formulated Meclizine hydrochloride wafers formulation F7. The drug release data showed a drug release of 36.65%, 48.89%, 64.56%, 72.32%, 85.65% and 98.15% 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 table 4.

Table 2: Results of evaluation of prepared wafers

Formulation code	General Appearance	Thickness* in μm	Weight* mg
F1	Translucent	80 ± 2	110 ± 5
F2	Translucent	84 ± 1	115 ± 3
F3	Translucent	86 ± 3	119 ± 4
F4	Translucent	78 ± 2	112 ± 2
F5	Translucent	80 ± 3	118 ± 4
F6	Translucent	82 ± 1	124 ± 3
F7	Translucent	75 ± 4	98 ± 6
F8	Translucent	78 ± 2	102 ± 2
F9	Translucent	81 ± 3	105 ± 4

*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	110 ± 5	6.4 ± 0.1	1.21 ± 0.23
F2	125 ± 4	6.5 ± 0.2	1.12 ± 0.14
F3	142 ± 3	6.4 ± 0.2	1.14 ± 0.25
F4	133 ± 4	6.7 ± 0.3	1.32 ± 0.14
F5	148 ± 5	6.4 ± 0.2	1.14 ± 0.32
F6	165 ± 8	6.5 ± 0.1	1.16 ± 0.14

F7	220±6	6.8±0.4	1.05±0.14
F8	185±5	6.9±0.2	1.22±0.22
F9	192±4	6.7±0.1	1.35±0.15

Table 4: Drug content analysis and disintegrating time

Formulation code	Drug content analysis (%)	Disintegrating time (Sec.)
F1	98.65±0.45	12±2
F2	95.65±0.23	15±1
F3	98.78±0.14	14±2
F4	97.96±0.56	8±2
F5	97.45±0.65	9±2
F6	98.85±0.74	9±2
F7	99.12±0.61	6±1
F8	98.78±0.41	10±2
F9	99.05±0.32	12±2

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

S. No.	Time (Sec.)	Percentage cumulative drug release
1.	60	36.65
2.	120	48.89
3.	180	64.56
4.	240	72.32
5.	300	85.65
6.	360	98.15

Conclusion

Meclizine hydrochloride is an anti-emetic drug with 25% of systemic oral bioavailability. The main objective of the studies described was to develop fast dissolving sublingual wafers of Meclizine hydrochloride, with enhanced oral bioavailability for the treatment of motion sickness. Thus a fast releasing sublingual wafers of Meclizine hydrochloride for the rapid and effective drug delivery with improved bio availability was successfully developed.

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