International Journal of Pharmaceutics & Drug Research
ISSN: 2347-6346
Available online at http://ijpdr.com

Original Research Article

FORMULATION, DEVELOPMENT AND EVALUATION OF FAST DISSOLVING SUBLINGUAL WAFERS OF PROMETHAZINE HYDROCHLORIDE

Karishma Jaiswal, Ramujagar Singh, Kavita R. Loksh

Oriental College of Pharmacy, Raisen Road, Patel Nagar, Bhopal, Madhya Pradesh 462022, India

***Correspondence Info:**

Karishma Jaiswal,
Oriental College of Pharmacy, Raisen Road, Patel Nagar, Bhopal, Madhya Pradesh 462022, India

Email:
jkarishma216@gmail.com

***Article History:**

Received: 22/10/2020
Revised: 27/10/2020
Accepted: 17/11/2020

ABSTRACT

The purpose of present work was a development of fast dissolving sublingual wafers of promethazine hydrochloride to overcome the limitation of current routes of administration, to provide faster dissolution rate and increase patient compliance, especially for outpatient setting. The wafers were prepared by solvent casting method, using polymers such as gelatin and xanthan gum in different ratios. All films were evaluated for tensile strength, weight variation, thickness, disintegration time, drug content, pH, folding endurance and *in vitro* drug release. Thus stable, porous, uniformly loaded fast disintegrating, taste masked promethazine hydrochloride sublingual wafers with good compatibility and stability was achieved. Satisfactory results were obtained when the wafers were subjected to tests such as uniformity of weight, thickness, surface pH, drug content, disintegration time, moisture content and *in vitro* drug release studies. Films were smooth, acceptable and translucent in colour. For optimized batch, drug content (99.12±0.61%), disintegration time (6±1 sec), dissolution (98.15% in 360 sec) were acceptable. Optimized batch F7, due to its potential to deliver through fast dissolving film, can be developed for clinical use.

Key words: Sublingual wafers, Promethazine hydrochloride, Solvent casting method, Fast dissolving film.

INTRODUCTION:

Researchers throughout the world are focusing intensively on the methods for the development of new drug delivery systems to enhance patient's compliance. Fast dissolving wafers are a new arising oral dosage forms used by patients world widely. Like the emerging trend worldwide, India is also undergoing rapid urbanization, leading to a significant increase in traveling. This has lead to health-related issues like motion sickness, traveler's diarrhea, migraine, *etc*. Motion sickness also known as travel sickness is a condition in which there exists a disagreement between visually perceived movement and the vestibular system's sense of movement.

Nausea, vomiting, dizziness, fatigue, and headache are the most common symptoms of motion sickness (Benson, 1978; Craig, 2002). Promethazine hydrochloride is first-generation anti-histamine of the phenothiazines family. It acts mainly as a strong antagonist of the H1 receptor (antihistamine) and a moderate mACh receptor antagonist; hence it blocks the action of acetylcholine on the receptors (anticholinergic effect), and this explains its benefit in reducing nausea experienced during motion sickness (I.P, 2007).

Oral drug administration is the most accepted route for drug delivery. Among different oral drug delivery systems available, tablets are the most popular. Over the years, we have seen considerable modifications in this highly accepted dosage form. One of them is the development of oro dispersible tablet that rapidly dissolve and disintegrate (Kathawala et al., 2013). The sublingual route is capable of producing a rapid onset of action because of the high permeability and the rich blood supply, thus making it an appropriate route for drugs with short delivery period and frequent dosing regimen. This route overcomes first pass metabolism thus increasing the bioavailabilty of the drug.

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. 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 time. Sublingual wafers seem to be highly advantageous dosage form during travelling as it does not need water for engulfment. 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 medicament, it is more stable, durable and quicker dissolving than other conventional dosage forms, an oral wafer helps to enhance bioavailability of the drug, improves dosing accuracy i.e., single unit dosage form, has the potential to allow the use of bitter tasting drug into the formulation and improves patient compliance (Galgatte et al., 2017).

MATERIALS AND METHODS

Promethazine HCl was purchased from Balaji Drug Suppliers, Ahmedabad, India. Gelatin, Xanthan Gum, Gum acacia, pullulan, methyl paraben, aspartame and citric acid was purchased were obtained from Loba chem. Pvt. Ltd, Mumbai. All other chemicals were of analytical grade and were used without additional purification.

Optimization of formulations

Solvent casting technique

Drug (promethazine hydrochloride) containing fast dissolving wafers were fabricated by the solvent casting method. The optimized amount of HPMC was dissolved in 5ml of water and stirrer 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: Selection and optimization of wafers forming agents

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 was 5 cm, length of the plate was 12 cm and the number of 2.5 x 2.5 cm^2 wafers present in whole plate was 12. Each wafers contains 10 mg of drug *i.e* 12 number of wafers contains 120 mg (10x12) of drug. The amount of drug added in each plate was approximately equal to 120 mg.

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 caliper (Rao et al., 2010).

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 (Anilkumar et al., 2010).

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 (Shalini et al., 2014; Mahesh, 9].

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 (Bhyan et al., 2011).

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 250 nm (Shalini et al., 2014; Mahesh et al., 2014).

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 10ml distilled water with swirling every 10 sec. The time at which the wafer disintegrated was noted (Mahesh et al., 2014; Bhyan et al., 2011).

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. 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 µm membrane filter and the concentration of the dissolved promethazine hydrochloride was determined using UV-Visible spectrophotometer at 250 nm. The results were presented as an average of three such

concentrations (Mahesh et al., 2014; Bhyan et al., 2011).

RESULTS AND DISCUSSION

Films were smooth, translucent, acceptable and white in colour with good integrity. Thin film shows quick disintegration and dissolution. While, thick film takes more time to disintegrate or dissolve. Thickness was measured by using calibrated Vernier calliper and showed thickness in the range of 75±4-86±3 µm. Weights were shown to be minimum within the range of 98±6- 124±3 mg. The outcomes of the results are discussed in the table 2.

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 ±SD)

Folding endurance showed strength and flexibility of film. Folding endurance depends on plasticizer concentration. Folding endurances of all batches are shown in table 2. This data revealed that films were having good mechanical strength with flexibility. The surface pH of the oral dissolving film was determined in order to investigate the possibility of any side effect *in-vivo*. As an

acidic or alkaline pH may cause irritation of the oral mucosa, it was decided to keep the surface pH as close to neutral as possible. Surface pH of a film and pH of an oral cavity (pH 6.8) should be closer. Formulation with pH 6.8 would get dissolved quickly in saliva and would be compatible with it. All batches have shown pH in the range of 6.67 to 6.81 which is closer to 6.8 as shown in table 2. Hence, it would not produce any irritation in a mouth. The percentage moisture absorption test was carried out to check physical stability or integrity of the wafer at humid condition. Percentage moisture content was shown to be minimum within the range of 1.05±0.14-1.35±0.15 mg. The outcomes of the results are discussed in the table 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

*Average of three determinations (n=3 ±SD)

It is a challenging task to get a desired drug content in a film. The drug content was found to be within the range of 95.65±0.23 to 99.12±0.61 indicating uniform distribution of drug in the formulated tablets as per pharmacopial specification. The outcomes of the results are discussed in the table 4.

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

*Average of three determinations (n=3 ±SD)

The maximum drug content and minimum disintegrating time was found in formulation F7 and it was considered as optimized formulation. The optimized formulation F7 among other batches was subjected to further studies. Dissolution study has shown that dissolution rate decreases with increase in polymer concentration and decrease in plasticizer concentration. The possible reason is high polymer concentration results in closer contacts of polymer particles which ultimately turn into formation of a high viscosity gel layer around drug contents. Further, this results into decreased mobility of drug in gel matrices, which leads to decrease in release rate [13].

The comparative *in vitro* release study of optimized formulation F7 is show in table 4. *In vitro* release study may be attributed to faster uptake of water due to porous structure formed. The *in vitro* drug release of all the formulations was made for maximum time period of 10 minutes. Percentage cumulative drug release at the end of 360 sec was found to be 98.15 % at 300 sec, 85.65% respectively 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 were found to be much more 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 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

Promethazine 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 promethazine hydrochloride, with enhanced oral bioavailability for the treatment of motion sickness. Fast dissolving sublingual wafers containing promethazine hydrochloride for treatment of motion sickness were developed by using film former with xanthan gum as polymer. On the basis of the results obtained, formulation F7 was found to be the most acceptable.

Conclusion

So it was concluded that solvent casting technique along with superdisintegrant addition was excellent method in formulation of fast dissolving tablets of promethazine hydrochloride which gives quick relief from emesis. Hence the dosage form developed may be very useful for the treatment of motion sickness, where availability of potable water may be difficult. Due to oral disintegration, geriatric population having difficulty in swallowing conventional tablets may also be benefitted.

References

1. Benson, A. (1978). Medication for motion sickness. Royal Air Force School of Aviation Medicine. 73-75.
2. Craig, S. (2002). Motion sickness: Review of causes and preventive strategies. J of Travel Med. 9: 251-56.
3. Indian Pharmacopoeia. (2007). Promethazine hydrochloride. The Indian Pharmacopoeia Commission, Ghaziabad. 3: 989-90.
4. Kathawala, K.J., Parikh, A.Y., Inamder, B.P., Shah, S.G. (2013). Mouth dissolving tablet: superlative conclusive dosage in solid form for modern age. Pharma Science Monitor. 4(4): 120-126.
5. Galgatte, U.C., Patil, P.P., Chaudhari, P.D. (2017). Development of fast dissolving sublingual wafers by using film former: Optimization and characterization. J Chem Pharma Res. 9(4): 82-91.
6. Rao, N.G.R., Kulkarni, U., Patil, B.S., Gururaj, V. (2010). Formulation and evaluation of fast dissolving tablets of some ayurvedic churnas by vacuum drying technique. Int J Pharm Pharma Sci. 3: 109-111.
7. Anilkumar, J.S., Waghule, A.N., Amol, P., Harinath, N.M. (2010). Development and characterization of oral fast dissolving tablets of nifidipine using camphor as a subliming agent. Res J Pharma Biol Chem Sci. 1(1): 46-50.
8. Shalini, G.C., Karwa, P., Khanum, A., Pandit, V. (2014). A laconic review on fast dissolving sublingual films as propitious dosage form. Drug delivery let. 4(1):49-61
9. Mahesh, A., Shastry, N., Sadanandam, M. (2010). Development of Tastes Masked Fast Disintegrating Film of Levocetirizine Dihydrochloride for Oral Use. Curr Drug Deliv. 1: 21-27.
10. Bhyan, B., Jangra, S., Kaur, M., Singh, H. (2011). Orally Fast Dissolving Films: Innovations in Formulation and Technology. Int J Pharmaceut Sci. 9(2): 50-57.
11. Parul, S., Anoop, K., Pankaj, S., Sharad, V. (2012). Fast disintegrating oral films: A recent trend of drug delivery. Int J Drug Dev Res.4(4):80-94.
12. Jain, R.A., Mundada, A.S. (2015). Formulation, development and optimization of fast dissolving oral film of montelukast sodium. Int J Drug Dev Res. 7:40-6.
13. Jadhav, Y.G., Galgatte, U.C., Chaudhari, P.D. (2018). Over coming poor solubility of dimenhydrinate: Development, optimization and evaluation of fast dissolving oral film. Adv Pharm Bull. 8(4): 721-725.