FORMULATION AND *IN-VITRO* EVALUATION OF FAST DISSOLVING ORAL FILMS OF PROMETHAZINE

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ABSTRACT

INTRODUCTION

Fast disintegrating/dissolving medicine delivery devices are oral films that swiftly disintegrate or adhere in the mouth. It includes the ability to administer systemic medications without having any first-pass effects. A first-generation antihistamine from the phenothiazine family is promethazine HCl. It is effective in treating motion sickness but it has a poor oral bioavailability. The study aims is to formulate promethazine fast dissolving oral film using natural and synthetic polymers and compare the formulations.

MATERIAL AND METHODS

This experimental study was conducted in the Pharmaceutic laboratory of Department of Pharmacy at Universal College of Medical Sciences, Bhairahawa, Nepal from February 2022 to July 2022. Fast dissolving oral films of promethazine were prepared by solvent casting method using polymers and plasticizers in varying concentrations. Weight variation, thickness variation, surface pH, folding endurance, swelling index, disintegration duration, dissolution study and medication content were among the several in vitro assessment criteria that were identified.

RESULTS

When examined for physical characteristics, thickness, weight uniformity, in vitro disintegration time, folding durability, drug content, and an in vitro drug release, films were determined to be adequate. The films of the F2 formulation demonstrated an increased rate of drug dissolution with a drug content of 99.17%, a disintegration time of 38 sec, and a drug release of more than 99% within 16 min.

CONCLUSION

Synthetic polymer (Hydroxypropyl methyl cellulose) showed better result in comparison to natural polymer (Sodium alginate).

KEYWORDS

Promethazine, Fast dissolving oral Film, Solvent casting method.

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INTRODUCTION

The oral route is the most widely used method of drug delivery since it is easy to swallow, pain-free, versatile (able to handle a wide range of medication candidates), and most importantly, patient-compliant. The most glaring drawback of oral dose forms like tablets and capsules is difficulty swallowing, which makes patients less compliant, particularly in the case of children and the elderly, bedridden, and nauseated patients.[1] Oral solid dosage forms, which account for about 60% of all dosage forms, have several issues that can be addressed by the creation of new dosage forms, such as fast dissolving oral films that are free of these issues.

For juvenile and elderly patients who have trouble swallowing standard oral solid dose forms, fast dissolving drug delivery devices were originally created in the late 1970s as an alternative to conventional dosage forms.[2] It provides the same benefits as the oral route, including the capacity to deliver systemic drugs without causing first-pass effects. Fast-dissolving oral films appear to be the most promising of the several oral transmucosal formulations.[3] Oral thin films include polymers, plasticizers, saliva stimulating factor, Superdisintegrants, surfactant, sweeteners, flavor, and coloring agents. Promethazine HCl is a first-generation antihistamine.[4] It primarily acts as a strong antagonist of the H1 receptor and a moderate antagonist of the muscarinic acetyl choline receptor; as a result, it inhibits the activity of acetylcholine on the receptors (anticholinergic effect), which explains its efficacy in minimizing motion sickness, nausea, dizziness, motion sickness, nausea and vomiting.[5] Although the medicine is helpful in the treatment of motion sickness, it has low oral bioavailability due to a large first-pass effect, with about 25% of the drug reaching the systemic circulation. Around one hour before starting the journey, it is prescribed to take as its onset of action is about 20 min.[6]

MATERIAL AND METHODS

Promethazine HCl was provided as a gift sample from Siddhartha Pharmaceuticals Pvt. Ltd, Madhawaliya, Tilottama, Rupandehi, Nepal. All other excipients and equipments were provided by the college laboratory. (Table 1 & 2). Ethical clearance was obtained from Institutional Review Committee having Reference No. UCMS/IRC/038/22 in February 8, 2022.

Table 1. List of Chemicals

S. No.	Ingredients	Function
1.	Promethazine HCl	Active pharmaceutical ingredient
2.	Hydroxypropyl methyl cellulose (HPMC)	Synthetic polymer
3.	Sodium alginate (SA)	Natural polymer
4.	Polyethylene glycol- 400 (PEG-400)	As a plasticizer
5.	Citric acid	Saliva stimulants
6.	Saccharin	Sweetener
7.	Peppermint	As a flavoring agent
8.	Sodium lauryl sulphate (SLS)	Surfactant
9.	Potassium dihydrogen phosphate	Buffer

Table 2. List of Equipments

S. No.	Equipments	Manufacturer
1.	Digital weighing balance	Sartorius
2.	Digital pH meter	Slope
3.	Thermostatic hot plate with magnetic stirrer	Bluefic
4.	Hot air oven	Bluefic
5.	Desiccator	Bluefic
6.	UV visible spectrophotometer	Spectrochem-I
7.	Digital vernier caliper scale	Accurate scientific
8.	Dissolution test apparatus	Accurate scientific

Preparation of standard stock solution of Promethazine HCl

Accurately weighed 25 mg of Promethazine HCl was taken and transferred to 250 ml of the volumetric flask containing a small amount of buffer solution that had pH the same as stimulated saliva (6.8). The drug and buffer solution were mixed well by vigorous shaking and volume was made to 250 ml using the same buffer solution to make the final concentration of 100 µg/ml.

After this serial dilution of standard stock solution of Promethazine HCl was prepared to range from 1-10 µg/ml. Different diluted concentration of solution were prepared by pipetting out 0.1 ml, 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1.0 ml from (100 µg/ml) stock solution to a series of a volumetric flask of 10 ml. volume was adjusted using simulated saliva. The absorbance of each standard stock solution was read out using UV spectrophotometer at 276 nm to obtain a calibration curve. This curve helps to determine the concentration of the unknown sample by comparing the standard stock sample of known concentration.

Preparation of simulated saliva

Accurately weighed disodium hydrogen phosphate 2.382 gm, potassium dihydrogen phosphate 0.19 gm and sodium chloride 8.0 gm were dissolved in 1000 ml beaker with distilled water. pH was adjusted to 6.8 with 0.1 M Hcl.[7]

Preparation of fast dissolving oral films of Promethazine HCl by solvent casting method

In this method, following step was performed: (Table 3)

- The hydrophilic polymer and plasticizer were weighed and dissolved in 10 ml hot distilled water and was stirred for 2 hrs. That was first solution.
- Drug and other ingredients like colorant, surfactant was dissolved in 3-4 ml distilled water to form second solution.
- Sweetener and saliva stimulating agent were dissolved in 10 ml distilled water followed by constant stirring through magnetic stirrer.
- The third solution was prepared by blending second solution in first solution.
- Flavoring agent was added in third solution and kept for 2 hours to remove air bubble and the resultant homogeneous solution was poured into a petri dish.
- Then the films were dried in an oven at 50 o C for 24 h.
- The dried films were wrapped in a butter paper and cut into 2x2 cm^2 area, covered with an aluminum foil and kept in a desiccator.
- Selected films were subjected to different evaluation parameters.[8,9]

Table 3. Formulation of FDOFs of promethazine HCl

S. No.	Ingredients (w/w)	Property	F1	F2	F3	F4	F5	F6	F7	F8
1.	Promethazine HCl (mg)	API	25	25	25	25	25	25	25	25
2.	HPMC (mg)	Synthetic polymer	40	42	44	46	-	-	-	-
3.	Sodium alginate (mg)	Natural Polymer	-	-	-	-	40	42	44	46
4.	PEG (mg)	Plasticizer	12	10	08	06	12	10	08	06
5.	SLS (mg)	Surfactant	6	6	6	6	6	6	6	6
6.	Citric acid (mg)	Saliva stimulating agent	6	6	6	6	6	6	6	6
7.	Sodium saccharin (mg)	Sweetening agent	6	6	6	6	6	6	6	6
8.	Peppermint oil (mg)	Flavoring agent	5	5	5	5	5	5	5	5

Evaluation of fast dissolving oral film

Morphological and organoleptic control

The color, homogeneity, transparency, smell, appearance and texture of the OTFs were examined visually and sensually.[10] Also evaluated for air entrapment, crack, drug precipitation and ease of removal from petri dish.[11]

Uniformity of mass

Twenty randomly selected fast dissolving film of appropriate size were weighed on analytical balance and then average mass and standard deviation (SD) were calculated.

Film thickness variation

The thickness of film was measured by using digital Vernier caliper at different strategic locations. This is essential to determine uniformity in the thickness of the film as this is directly related to the accuracy of dose in the film.[12]

Folding endurance

The folding endurance is expressed as the number of folds (number of times the film is folded at the same place) required to break the specimen or to develop visible cracks.[13]

Surface pH test

Each batch's film (2x2 cm2) were placed on a closed petri-plate containing 5 ml of distilled water at room temperature, and the surface pH were measured with a digital pH meter.[14]

In-vitro disintegration studies

In vitro disintegration time was determined visually in glass beaker of 25 ml distilled water with swirling every 10 seconds. Disintegration test also performed by petri dish method. In this method, 10ml of distilled water was placed in petri dish and then oral film of desired size was placed in petri dish. After that, time required for complete disintegration was noted.[15]

In-vitro dissolution studies

A dissolution equipment was used to conduct in vitro drug release test on the Fast dissolving oral Films (USP Type II paddle). A UV-visible spectrophotometer set to 276 nm was used to measure the absorbance of the diluted filtrates.[16]

Content uniformity/Drug content

One sheet of film from each formulation was dissolved in simulated salivary fluid at pH 6.8 in a flask of 30 ml and shaken for certain time to get homogenous solution. According to USP standards, the contents of preparation should lay between the limits of 98-101%. The results were expressed as a mean of three determination of each formulation and mean was calculated. The drug content was calculated using a standard calibration curve of Promethazine HCl at wavelength 276 nm.[17]

RESULTS

Morphological and organoleptic control

F1, F2, F3 and F4 were found to be homogenous, uniform and less transparent with API. F5, F6, F7 and F8 were found to be non-homogenous, non-uniform and poorly transparent with API.

Film thickness variation

Thickness of film ranged from the minimum of F2 formulation (0.1728±0.0262) to the maximum of F4 (0.1022 ±0.00577) formulation containing synthetic polymer. Thickness of film containing natural polymer was found to be more (ranged from 0.2132±0.053 to 0.2566±0.024) than film containing synthetic polymer. (Table 4)

Surface pH

The surface pH of the strips was ranged from 6.77±0.02 to 6.8±0.045. There will not be any kind of irritation to the mucosal lining of the oral cavity, since the surface pH of films was found to be around neutral.[18] (Table 4)

Folding endurance

Folding endurance of all formulation was determined and found that formulation containing higher concentration of PEG were flexible and of plastic nature. Films with relatively lesser concentration of PEG revealed that it was not enough to plasticize the film and the films were found to be more brittle and fragmented easily. Folding endurance was found in ranged from 91 to 349 which was similar as reported by RA Jain et, al.[19] (Table 4)

Disintegration time

The disintegration time for different formulation was mentioned in the Figure 2. Among different formulation the minimum DT was observed in F2 formulation (38 seconds) and the maximum DT was observed in F8 formulation (62 seconds). (Table 4)

Content uniformity

Content uniformity was determined and results showed in between limits i.e. 98% to 101% of synthetic polymer containing formulation (98.47% to 99.90%). (Table 4)

Dissolution study

Drug concentration was determined spectrophotometrically at 276 nm using calibration curve. Drug release in percentage was determined by using absorbance. (Table 5)

In-vitro evaluation of formulation

Table 4. Evaluation parameters of formulation

Formulation	Weight variation (g)	Thickness variation (mm)	Surface epH	Folding endurance	Disintegration (seconds)	Content iniformity (%)
F1	0.0978±0.0061	0.183±0.0387	6.78±0.03	349	42	98.76
F2	0.0998±0.0055	0.1728±0.0262	6.78±0.055	331	38	99.90
F3	0.1011±0.00599	0.2036±0.036	6.8±0.045	311	44	98.47
F4	0.1022 ±0.00577	0.2052±0.0217	6.79±0.03	295	47	99.14
F5	0.1055±0.0567	0.2132±0.053	6.77±0.02	190	41	98.28
F6	0.1081±0.029	0.2432±0.034	6.75±0.04	151	48	95.81
F7	0.1101±0.051	0.2511±0.022	6.78±0.03	121	55	103.61
F8	0.1114±0.058	0.2566±0.024	6.77±0.05	91	62	104.63

Table 5. Drug release in percentage

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
2	62.48	63.51	59.57	56.22	48.34	51.94	46.46	40.2
4	68.23	70.03	64.20	62.74	56.14	59.06	53.06	47.91
6	83.22	81.51	75.77	73.28	60.51	62.23	60.85	54.17
8	84.77	87	81.85	81.85	66.94	68.23	66.68	58.88
10	87.68	90.68	84.6	85.2	71.74	72.00	70.71	63.60
12	92.14	94.8	90.68	89.14	78.08	76.71	74.4	70.03
14	97.37	98.65	96.86	97.02	84.94	83.66	82.63	79.03
16	98.74	99.17	98.83	98.14	91.11	91.46	89.06	86.23

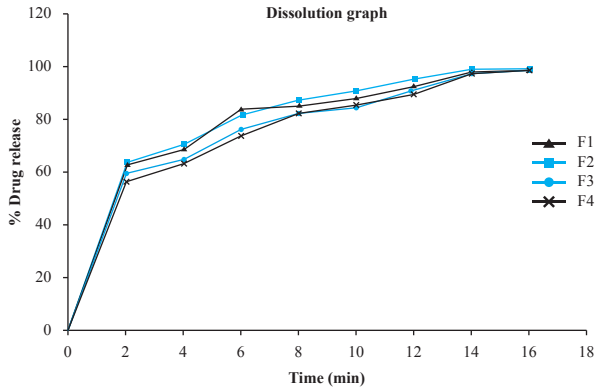

Figure 1. Comparative dissolution graph of formulations containing synthetic polymer

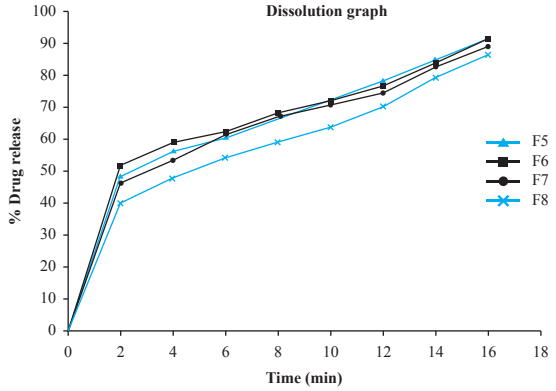

Figure 2. Comparative dissolution graph of formulations containing natural polymer

DISCUSSION

Different batches of Fast dissolving oral films were successfully prepared by solvent casting method. Higher concentration of polymer results in increments of thickness of film. Thickness of film was found in ranged from 0.183mm to 0.256 mm which was better with the results found by A. Hussain et. al. (i.e. ranged from 0.22mm to 0.29mm).[20] Formulation F1 had minimum weight (0.0978±0.0061) and formulation F4 had maximum weight (0.1022 ±0.00577). Formulation F5, F6, F7 and F8 had significant weight variation (0.1055 to 0.1114 gm) due to agglomeration and poor film forming property of natural polymer. Formulation containing concentration of plasticizers less than 10% was not enough to plasticize the films because the formed films were somewhat brittle in nature.[21]

Formulation containing synthetic polymer was found to be good in appearance because HPMC is a good polymer to form film.[22] From this study, it can be observed that the concentration of plasticizer is directly proportional to folding endurance. It means if concentration of plasticizer increases then folding endurance also increases due to elasticity nature of plasticizer. Formulation containing natural polymer had varied content uniformity (98.28 to 104.63%) due to uneven and non-uniform distribution.

The disintegration time of formulation containing SA (natural polymer) was prolonged due to poor film forming property and high viscosity of SA than the HPMC. Formulation containing HPMC (synthetic polymer) revealed lesser disintegration time in comparison of formulation containing natural polymer. Plasticizer enhanced the disintegration time by facilitating the penetration of fluids into the film, since plasticizer alter the densely packed chains of HPMC texture by forming a polymer structure. Similar results were also found by Manar Adnan Tamer et, al.[23] Formulation containing synthetic polymers showed release more than 80% within 10 min which showed better release. The release pattern of film containing natural polymer was found that release of more than 80% within 14 min as shown in Figure 1 and Figure 2.

Synthetic polymer showed better release than natural polymer which is due to more viscous nature of natural polymer that hindered the release of the drug. In the comparison of among all formulation, formulation F2 showed best release of 99.17 % within 16 min. As concentration of polymer increases, the drug release was found to be decreased according to above results. This may be because a larger concentration of polymer produces a gel layer of high consistency as a result of intimate interactions between HPMC particle, which reduces the movement of drug particles in swelling lattices and lowers the dissolution rate.[24] It was also found that when the concentration of plasticizer was decreased, the rate of drug release pattern was also decreased. The increase in the rate of drug release could be found by the ability of hydrophilic plasticizer to promote the dissolution by creating pores for the drug to diffuse out of the films and enhance the release of the drug. There was direct relationship between the drug release and concentration of plasticizer.[25]

CONCLUSION

It was concluded that the developed oral films of different formulations show promising results. Formulation containing synthetic polymer showed better results in comparison to natural polymer. The release of drug found to have indirect relation with the polymer concentration and direct relation with the plasticizer concentration.

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CONFLICT OF INTEREST

None

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