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FORMULATION AND EVALUATION OF FAST DISSOLVING ORAL FILM OF MESALAZINE

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ABSTRACT

Mesalamine is a derivative of salicylic acid (5-amino salicylic acid [5-ASA]) and also known as mesalazine. Mesalamine is categorized as a BCS class IV drug (low solubility, low permeability) according to the Biopharmaceutics Classification System. It is slightly soluble in water and poorly absorbed following its oral administration (approximately 25%). The aim of present work is to formulate and evaluate fast dissolving oral films of dolasetron mesylate to improve water solubility, dissolution rate, oral bioavailability and reduction of first pass metabolism and increase patient's compliance. The present work deals with the investigations carried out on the preparation and characterization of fast dissolving tablets containing Meclizine with increase its bioavailability. The enhancement of solubility was done in different amount PEG 4000, On the basis of percentage cumulative drug release study it was concluded that solid dispersion is better option in spite of pure drug. Different formulation of Meclizine oral fast dissolving films were prepared and evaluated for Thickness, Weight, folding endurance, disintegration time, tensile strength moisture content and assay. The thickness of the Meclizine OFDFs formulations F1 – F6, developed with HPMC and superdisintegrants (SSG, CCS and CP) were found ranging from 42±4 µm to 62±5µm. From the obtained thickness data it was observed that the thickness of the film was increased by increasing in the concentration of the film former. Hence, the thickness of the film was directly proportional to its film former concentration. Cumulative % drug release was calculated on the basis of drug content of Meclizine present in the respective film. The results obtained in the in vitro drug release for the formulations were tabulated in table. The optimized formulations F-5 show drug release up to 98.85±0.23% at the end of 15min. The initial release of the optimized formulation was

more (25.58±0.45); therefore the onset of action was very quick compare with the innovator product.

KEYWORDS: Mesalazine, Fast dissolving films, Solvent casting method, Superdisintegrants.

INTRODUCTION

Oral route is a most preferred route of drug administration for systemic effect due to its ease of administration, non-invasiveness, adaptability, patient compliance and acceptability (Liang *et al.*, 2001). About 60% of all the formulations are solid dosage form. Tablet is the most preferred dosage form due to ease of manufacturing, transportation and more patient compliance (Habib *et al.*, 2000). Generally geriatric, pediatric, nauseous, bed ridden and non-compliance patients experience difficulties in swallowing the conventional oral dosage form and do not take their medicines as prescribed. It is estimated that 50 % of the population was affected by this problem, which finally results in a higher chance of non-compliance & ineffective therapy (Siddiqui *et al.*, 2011).

The elderly constitute a major portion of today's population mainly because of increased life expectancy of individuals (Brniak *et al.*, 2015). Dysphagia or difficulty in swallowing is common problem, the disorder of dysphagia is associated with many medical conditions including stroke, Parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders including cerebral palsy (Gisel *et al.*, 1994). The most common complaint with tablet is size, fear of chocking followed by surface form and taste. The problem of swallowing tablets is more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water (Avery *et al.*, 2001).

To overcome this Oral fast disintegrating drug delivery systems were developed, these systems were first developed in the late 1970s as an alternative to tablets, capsules and syrups for pediatric & geriatric patients who experience difficulties in swallowing traditional oral solid dosage forms. These dosage forms either dissolve or disintegrate generally within a 3 minute in mouth, without need of water. Oral fast Disintegrating dosage form have started gaining popularity & acceptance as new drug delivery system because they are easy to administer & lead to better patient compliance (Chauhan *et al.*, 2012).

Various bioadhesive mucosal dosage forms have been developed, which includes adhesive tablets, gels, ointments, patches, and more recently the use of polymeric films for buccal

delivery, also known as mouth dissolving films. The surface of buccal cavity comprises of stratified squamous epithelium which is essentially separated from the underlying tissue of lamina propria and submucosa by an undulating basement membrane.

Formulation of fast dissolving buccal film involves material such as strip-forming polymers, plasticizers, active pharmaceutical ingredient, sweetening agents, saliva stimulating agent, flavoring agents, coloring agents, stabilizing and thickening agents, permeation enhancers, and superdisintegrants. All the excipients used in the formulation of fast dissolving film should be approved for use in oral pharmaceutical dosage forms as per regulatory perspectives.

Meclizine, a piperazine-derivative H_1-receptor antagonist similar to buclizine, cyclizine, and hydroxyzine, is used as an antivertigo/antiemetic agent. Meclizine is used in the management of nausea, vomiting, and dizziness associated with motion sickness and vertigo in diseases affecting the vestibular apparatus.

MATERIAL AND METHODS

Material

Meclizine was obtained as a gift sample from pharmaceutical company. HPMC was procured from Qualikems fine chem. Pvt Ltd Vadodhara. PEG400, sodium starch glycolate, croscarmellose sodium was obtained from S.D fine chemicals limited, Mumbai. Citric acid, ethanol was obtained from Loba Chemical Pvt Ltd (Mumbai, India). Hydrochloric acid, KH_2PO_4, NaoH was obtained from S. D. Fine Chem. Ltd., Mumbai. 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

Preparation of solid dispersions

Optimization of drug: polymer ratio

In order to optimize the drug is to polymer ratio, we have prepared the matrices by both i.e. physical mixture method and solid dispersion method.

Physical mixture method: All the ingredients were weighed accurately and passed through sieve no. 85 in order to obtain powder of fine particle size with narrow size distribution. The physical mixture of drug with carrier PEG 4000 was prepared in

different concentration by slightly grinding the drug and carrier in mortar for 2 min. The drug: PEG 4000 ratio which was taken as 1:1, 1:2, and 1:3 respectively. Then the resultant powder was passed through sieve no 60 and was stored in desiccator for 2-6 hrs to carry out further analysis. The prepared physical mixture was subjected to dissolution study. On the basis of percentage cumulative drug release study it was concluded that solid dispersion is better option in spite of pure drug. The study revealed that physical mixture shows a sudden bursting effect and erratic pattern in their release mechanism therefore the solid dispersion was best alternate. In solid dispersion it was found that in 1:1 and 1:2 ratio there was also a bursting effect and at higher polymer ratio i.e. at 1:3 the drug release was truly delayed which can further optimized to get better results. Therefore 1:3 ratios were found to be superior and were used for further evaluation purpose.

Preparation of solid dispersion of Meclizine

For the preparation of Meclizine-PEG 4000 solid dispersion by conventional method, PEG 4000 was weighed and melted at 58°C (± 1°C) and a measured amount of Meclizine was added and stirred. After solidification at room temperature, sample was pulverized with use of a pestle and mortar and sieved through a 400-mm mesh. 400mg of MCZ-PEG 4000 powder (containing 25mg of Meclizine and 75 mg of PEG 4000) was used for further investigations.

Preparation of physical mixture

For the preparation of MCZ-PEG 4000 physical mixture, MCZ and PEG 4000 were weighed and mixed for 5 min with use of a pestle and mortar and sieved through a 400mm mesh (Nokhodchi *et al.,* 2007). MCZ-PEG 4000 - PEG 4000 powder mixture (containing 25mg of MCZ and 75 mg of PEG 4000) was used for further tablet preparation.

Evaluation of dispersion granules

Percentage drug content

For the determination of MCZ content, dispersion granules equivalent to 10 mg of MCZ, were weighed and extracted with 10 ml of methanol by mechanical mixing for 5min followed by centrifugation at 10,000 rpm for 5 min on a centrifuge. The supernant was filtered through 0.45µ membrane filter, and the filtered solutions were suitably diluted and analyzed for MCZ at 232nm using a validated UV spectrophotometric method.

Formulation of oral film of Meclizine

Casting process of fast disintegrating oral film

Various methods are available for casting of oral films. This is fast disintegrating oral film hence on the laboratory scale solvent casting technique was adopted for formulation of films.

Solvent casting technique

Meclizine containing fast dissolving films was fabricated by the solvent casting method (Mahesh *et al.,* 2010). The optimized amount of HPMC was dissolved in 5ml of water and stirrered 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 in sonicator 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^2 10 films area and was dried at controlled room temperature (25°-30°C, 45 %RH) as well as at increased temperature (microwave oven). The film took approximately 48 hr to dry at controlled room temperature. The dried film was carefully removed from the glass plates and was cut into size required for testing. The films were stored in air tight plastic bags till further use.

Table 1: Selection and Optimization of Film Forming Agents.

Name of ingredients (mg for 12 strips)	F1	F2	F3	F4	F5	F6
API Equivalent to 300 (mg)	1200	1200	1200	1200	1200	1200
HPMC	400	600	800	400	600	800
Glycerin	-	-	-	-	-	-
PEG-400	100	100	100	100	100	100
SSG (mg)	100	150	200	-	-	-
CCS (mg)	-	-	-	100	150	200
Aspartame (mg)	25	25	25	25	25	25
Citric acid (mg)	50	50	50	50	50	50
DM water qs to (ml)	30	30	30	30	30	30

HPMC=Hydroxypropyl methylcellulose, PEG 400= Polyethylene glycol 400, SSG= Sodium starch glycolate, CCS =Croscarmellose sodium.

Dose calculations

- Width of the plate = 5cm
- Length of the plate = 12cm

- No. of 2.5 x 2.5 cm^2 films present whole plate = 12
- Each film contains 25 mg of drug.
- 12 no. of films contains mg of drug = 25×12 =300 mg
- The amount of drug added in each plate was approximately equal to 300mg.

Evaluation of prepared film

Thickness

The thickness of films was measured at three different places using a vernier caliper (Lakshmi *et al.*, 2005).

Weight uniformity

For each formulation, three randomly selected films were used. For weight variation test, 10 films from each batch were weighed individually by digital electronic balance and the average weight was calculated.

Folding endurance

This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking cracking gave the value of folding endurance (Patel *et al.*, 2010).

Percentage moisture content

The films were weighed individually and kept in desiccators containing activated silica at room temperature for 24 hrs. Individual films 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.

Drug Content Analysis

The films (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 232nm.

Disintegrating time

The objective of present work is that films should be dissolved within few seconds. Three super disintegrating agent were selected for minimizing the disintegration time.

***In vitro* dissolution study**

The *in vitro* dissolution test was performed using the USP dissolution apparatus II (Paddle with sinker). 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). Film 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 Meclizine was determined using UV-Visible spectrophotometer at 232nm. The results were presented as an average of three such concentrations.

Stability studies

Stability studies were carried out for optimized formulation F3 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 film was found to slightly decrease at higher temperature.

RESULTS AND DISCUSSION

The present work deals with the investigations carried out on the preparation and characterization of fast dissolving tablets containing Meclizine with increase its bioavailability. The enhancement of solubility was done in different amount PEG 4000, On the basis of percentage cumulative drug release study it was concluded that solid dispersion is better option in spite of pure drug. The study revealed that physical mixture shows a sudden bursting effect and erratic pattern in their release mechanism therefore the solid dispersion was best alternate. In solid dispersion it was found that in 1:1 and 1:2 ratio there was also a bursting effect and at higher polymer ratio i.e. at 1:3 the drug release was truly delayed which can further optimized to get better results. Therefore 1:3 ratios were found to be superior and were used for further evaluation purpose.

Different formulation of Meclizine oral fast dissolving films were prepared and evaluated for Thickness, Weight, folding endurance, disintegration time, tensile strength moisture content and assay. The thickness of the Meclizine OFDFs formulations F1 – F6, developed with HPMC and superdisintegrants (SSG, CCS and CP) were found ranging from 42±4 µm to 62±5µm. From the obtained thickness data it was observed that the thickness of the film was

increased by increasing in the concentration of the film former. Hence, the thickness of the film was directly proportional to its film former concentration.

The average weight of the films was measured in triplicate for each film and found in the range from 125±7–165±3mg. Formulations F1-F6 folding endurance was in the range of 136±5-185±4. The observed folding endurance data of the films developed with various viscosities and concentrations of film formers indicated that the increase in viscosities and concentrations of the film lead to increase in the folding endurance of the films. The formulations F1 – F6 developed with different concentrations of SSG, CCS and CP, disintegration time were found in the range of 1.45±0.14 sec to 2.45±0.32sec. The formulations F8 prepared with CCS and CP having different concentrations were ranging from 1.45±0.14sec. The data of disintegration time indicates that increasing the concentrations of polymer along with different viscosities tends to increase the disintegration time.

The formulated OFDFs were evaluated and the % moisture content was calculated. A reduced % moisture content was observed with increase in polymer concentration varying from 1.25±0.25% to 1.58±0.65% w/w for Meclizine films. The Content uniformity was worked out on individual films of 12 samples. A film of size 2.5*2.5cm^2 was cut and kept in 10ml of volumetric flask containing solvent. This was then shaken in a mechanical shaker till it was dissolved to get a homogeneous solution and then filtered. Concentrations the drug content was found in the range of 98.56±0.25-99.11±0.25%. Even though all the formulations drug content within the specification range, Cumulative % drug release was calculated on the basis of drug content of Meclizine present in the respective film. The results obtained in the in vitro drug release for the formulations were tabulated in table. The optimized formulations F-5 show drug release up to 98.85±0.23% at the end of 15min. The initial release of the optimized formulation was more (25.58±0.45); therefore the onset of action was very quick compare with the innovator product.

Evaluation of solid dispersions

Table 2: Percentage cumulative drug release of physical mixture.

S. No.	Time interval (min.)	Percentage cumulative drug release of physical mixture*			
1	**0**	**1:1**	**1:2**	**1:3**	**Pure Drug**
2	30	25.56	29.98	35.65	9.45
3	60	36.65	38.85	42.23	11.23
4	120	45.58	52.23	59.98	14.45
5	240	55.54	63.45	69.94	16.65
6	360	62.23	71.15	73.36	18.89
7	480	65.25	73.32	76.45	20.41

Percentage drug content

Table 3: Results of drug content.

Label claim	Amount found*	Label claim (%)	S.D.	% RSD
25mg	24.95	99.80	0.045	0.038

*****Average of three determination (n=3)

Table 4: Results of Evaluation of prepared Film.

Formulation code	General Appearance	Thickness (µm)	Weight (mg)
F1	Translucent	62±5	165±3
F2	Translucent	58±6	160±4
F3	Translucent	55±5	155±5
F4	Translucent	48±4	145±6
F5	Translucent	45±5	125±7
F6	Translucent	42±4	120±3

(N=3, mean±SD)

Table 5: Result of folding endurance, disintegration time, tensile strength moisture content and assay.

Formulation code	Folding endurance	Disintegration time (min.)	Tensile strength (kg/cm^2)	Moisture Content (%)	Assay (%)
F1	145±3	2.36±0.25	0.65±0.05	1.45±0.32	98.85±0.36
F2	156±4	2.25±0.36	0.47±0.03	1.52±0.25	98.56±0.25
F3	165±3	2.45±0.32	0.58±0.02	1.58±0.65	98.78±0.14
F4	155±2	2.11±0.25	0.63±0.04	1.47±0.14	98.85±0.36
F5	185±4	1.45±0.14	0.74±0.06	1.25±0.25	99.11±0.25
F6	136±5	2.36±0.25	0.62±0.05	1.36±0.36	98.96±0.32

(N=3, mean±SD)

Table 6: Results of Optimized formulation F5.

Name of Ingredients	Composition (mg) Per Strip
API	1200
HPMC K15	600
PEG-400	-
SSG	100
CCS	-
Aspartame	150
Citric acid	25
DM water qs to (ml)	30

Table 7: Results of *in-vitro* release study of optimized formulation F5.

S. No.	Time (Min.)	Cumulative % Drug release
1.	1	25.58±0.45
2.	2	45.65±0.25
3.	5	69.98±0.36
4.	10	78.85±0.25
5.	15	98.85±0.23

(N=3, mean±SD)

Table 8: Characterization of stability study of Optimized Film (F5)

Characteristic	Time (Month)			
	Initial	1 Month	2 Month	3 Month
% Assay*	99.45	99.25	98.85	98.25

(N=3, mean±SD)

CONCLUSION

From the research work it can be inferred that fast-dissolving oral films of drug release are preferable. The films prepared by HPMC, and SSG had shown strong mechanical power, release of narcotics, period for disintegration and analysis of dissolution. F5 formulation is considered the better with less disintegrating time and release in 15 min according to the results obtained. Percent drug release and disintegration time was taken as responses for study which were found within the accepted ranges. Meclizine administered in the form of fast dissolving films will be potential novel drug dosage form for pediatric, geriatric and also for general population by providing faster release and better patient compliance.

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