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Research Article

FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLET OF DOMPERIDONE MALEATE

Yuwaraj Dilipsingh Dixit*, Pravin Babarao Suruse, Umesh Dhaniram Shivhare

Sharad Pawar College of Pharmacy, Wanadongri, Hingna Road, Nagpur - 441 110, (MS), India.

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*Corresponding author
Yuwaraj Dilipsingh Dixit

Email:
yuvi_dixit@yahoo.co.in

ABSTRACT

The objective of the present study was to develop and evaluate mucoadhesive dosage form of Domperidone maleate. It is an antiemetic synthetic benzimidazole compound that acts as a dopamine D2 receptor antagonist. Mucoadhesive Domperidone maleate tablet formulation was prepared by direct compression method. The formulation F3 containing (Carbopol 940 + sodium alginate) was found to be best among all the formulation batches because of its consistent release rate for 7 h and extent of drug release was 94.44%. Graphical treatment of the formulation F3 to Higuchi's equation showed that the drug release was diffusion mediated. *In-vitro* permeability study for formulation F3 for 7 h had shown 76.69% drug release. FTIR studies showed no evidence on interaction between drug and polymers.

Key words: Domperidone maleate, Mucoadhesive tablet, antiemetic

INTRODUCTION

The unique environment of the oral cavity offers its potential as a site for drug delivery because of the rich blood supply and direct access to systemic circulation, the oral mucosal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (first-pass effect). Mucoadhesive drug delivery system can improve the effectiveness of a drug by helping to maintain the drug concentration between the effective and toxic levels. The advantages of buccal drug delivery sysyem are localization of the dosage form in specified regions to improve and enhance bioavailability of drugs. Drugs that are absorbed through the mucosal lining of tissue can enter directly into the blood stream and not be inactivated by enzymatic degradation in the gastrointestinal (GI) tract. Inhibiting the dilution of the drug in the body fluids and allowing targeting of drug at specific site. Mucoadhesive drug delivery system utilize the property of bioadhesion of certain water soluble polymers which become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time (Rodriguez *et al.,* 2000; Tewes*et al.,* 2006; Hillery*et al.,* 2001; Gavaskar *et al.,* 2010).

Domperidone maleate is a synthetic benzimidazole compound that act as a dopamine receptor antagonist. Its localization outside the blood brain barrier and antiemetic properties has made it a useful adjunct in the therapy for Parkinsonism disease. Domperidone maleate undergoes first-pass and gut wall metabolism. Through hydroxylation and oxidative N-dealkylation, domperidone is metabolized to hydroxyl domperidone and 2, 3-dihydro-2-oxo-1-H-benizimidazole-1-Propionic acid respectively. The systemic bioavailability of Domperidone maleate is 15% following oral administration as it extensively metabolized in liver. The low bioavailability is due to the first-pass hepatic and intestinal metabolism (Martindale and Sweetman, 2002; *Indian Pharmacopoeia*, 2007).

Therefore, the objective of present study was to prolong the drug plasma half-life and avoid first- pass hepatic metabolism of Domperidone maleate by formulating Mucoadhesive dosage form.

METHODOLOGY

Materials

Domeperidone maleate was obtained as a gift sample from Vasudha Pharma Chemical, Hyderabad. Carbapol-940 was obtained as a gift

sample from SD Fine Chemicals Ltd. Mumbai. Sodium alginate, HPMC-K4M, SCMC, Magnesium stearate were purchased from Otto Chem. Ltd. Mumbai and Sodium hydroxide, Potassium dihydrogen phosphate were procured from Qualigens Fine Chemicals, New Mumbai. All other excipients used in the study were of Analytical reagent grade.

Formulation of mucoadhesive buccal tablet

Domperidone maleate tablets formulations were prepared by direct compression using a concave faced single punch tableting machine. Each tablet contained a constant amount of Domperidone maleate (20 mg) and Magnesium stearate (1 mg) and varying composition of buccal bioadhesive polymer mixture of Carbopol 940 and Sodium alginate or carbopol 940 and HPMC-K4M or Carbopol 940 and SCMC.

Accurately weighed quantities of polymers are homogenously mixed with Domperidone maleate. Then Magnesium stearate was added in it and mixed continuously for 10 min. The machine was adjusted to produce tablets of approximate weight of 150 mg. Composition of formulation batches containing different polymers (mgs) are given in table I.

Evaluation of physico-chemical properties

Weight variation test

Twenty tablets were selected at random, individually weighed in a single pan electronic balance and the average weight was calculated. The uniformity of the weight was determined according to USP specification Menon *et al.,* 2011.

Thickness

The thickness of a tablet is only dimensional variable related to the compression process. The thickness of tablets was carried out using Vernier calliper (Menon *et al.,* 2011).

Hardness test

The Monsanto hardness tester was used to measure the hardness of tablets. Five tablets from each batch were used for hardness test and results were expressed in kg/cm^2 (Menon *et al.,* 2011)

Friability test

Friability Test was performed in Roche type Friabilator apparatus, where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets at a distance of six inches with each revolution. The tablets are then dusted and reweighed.[8]

Drug content

Accurately weighed quantity of tablet powder equivalent to 100 mg of the drug was transferred into a 100 mL volumetric flask. Phosphate buffer pH 6.8 was added in it to make up the volume upto 100 mL. The resulting solution was sonicated for 5 min and then filtered through 0.45 μ filter paper. Dilutions were made with phosphate buffer pH 6.8 to obtain a solution containing 50 μg/mL of the drug. The drug content was determined by measuring the absorbance of the resulting solution spectrophotometrically at 284 nm.

Surface pH

The surface pH of the tablets 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 buccal mucosa, it was our attempt to keep the surface pH as close to neutral as possible. The tablets were allowed to swell by keeping then in contact to 1.0 mL of distilled water for 2 h in specially fabricated glass tube. The surface pH was noted bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min (Miyazaki *et al.,* 1995).

***In-vitro* swelling studies**

Domperidone maleate buccal (n=7) tablets from each formulations were weight individually (designed as W1) and placed separately in petri dishes containing 4 mL of phosphate buffer (6.8) solution. At regular intervals (1, 2, 3, 4, 5, 6 and 7 h), the tablets were removed from the petridish and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W_2) and swelling index (SI) was calculated using the formula (Kasshapa *et al.,* 2004).

$$SI = \frac{W_2 - W_1}{W_1}$$

Where,

SI = Swelling Index

W_2 = Weight of tablet after swelling

W_1 = Weight of tablet before swelling

In-vitro mucoadhesion strength

Mucoadhesion strength of tablet was measured with porcine buccal mucosa using a modified 2-arm balance. Porcine buccal mucosa was obtained from a local slaughter house and stored in phosphate buffer pH 6.8 upon collection. The experiments were performed within 3 h of procurement of the mucosa. The porcine buccal mucosa was fixed to the stainless steel piece with cynoacrylate adhesive and then placed in a beaker. Phosphate buffer pH 6.8 was added into the beaker up to the upper surface of the buccal mucosa to maintain buccal mucosal viability during the experiments. The tablet was attached to the upper clamp of the apparatus and then the beaker was raised slowly until contact between porcine buccal mucosa and tablet was established. A preload of 50 g was placed on the clamp for 5 min (preload time) to establish adhesion bonding between tablet and porcine buccal mucosa. The preload and preload time were kept constant for all the formulation. After completion of the preload time, preload was removed from the clamp and water was then added in the beaker from the burette at a constant rate of 100 drops/min. The addition of water was stopped when tablet was detached from porcine buccal mucosa. The weight of water required to detach tablet from buccal mucosa was noted as mucoadhesive strength, and these experiments were repeated with fresh mucosa in an identical manner (Kasshapa *et al.,* 2004; Emami *et al.,* 2008).

Drug-polymer interaction study

The FTIR technique was used for the identification of pure drug Domperidone maleate and various polymers like Carbopol 940, Sodium alginate, Hydroxypropyl methyl-cellulose K4M, Sodium carboxy methylcellulose and best formulation batch F3, containing physical mixture were identified and determine to check the interaction of drug and the polymer in the formulation by using Perkin Elmer Furrier transform infrared spectrometer by KBr pellets (Disc Method).

In-vitro drug release studies

In-vitro drug release study of mucoadhesive tablets of Domperidone maleate was carried out using USP type I apparatus (Paddle method) at 50 rpm. Medium used for release rate study was 500 mL phosphate buffer solution pH 6.8. The assembly was maintained at 37±0.5º C during the course of study. 5 mL sample was withdrawn, at regular time interval of 1 h upto 7 h and replaced with 5 mL of fresh dissolution medium. The amount of drug released was determined by spectrophoto-metrically at 284 nm (Nakhat *et al.,* 2008; Singh *et al.,* 2006).

In-vitro drug permeation studies

Only the mucoadhesive tablets, which gave the optimum release in 7 h and appropriate mucoadhesive strength, were subjected to the permeation studies. The permeation of Domperidone maleate through porcine buccal membrane was carried out using modified diffusion cell. The membrane was mounted over a diffusion cell of diameter 2.1 cm and selected matrix tablet placed on the membrane. The membrane were placed between the donar compartment containing 4 mL of 6.8 pH buffer and receptor compartment 15 mL of 6.8 pH buffer, entire surface of membrane was in contact with receptor compartment was agitated with magnetic stirred at approximately 150 rpm and temperature was maintained at 37°. Each sample of 5 mL were withdrawn from the beaker at 1, 2, 3, 4, 5, 6 and 7 h intervals and replaced by equal volumes of fresh 6.8 pH buffer. The concentration of Domperidone maleate in the samples was measured spectrophotometrically at 284 nm (Yamsani *et al.,* 2007; EL-samaligy *et al.,* 2010; Javier *et al.,* 2011; Bayrak *et al.,* 2011).

In-vivo human acceptability studies

The study was conducted on 10 healthy human male volunteers (aged 18-55 years) under the medical supervision of a team of physician and the informed consent was taken

Table I. Composition of formulation batches containing different polymers (mgs)

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Domperidone maleate	20	20	20	20	20	20	20	20	20
Carbopol 940	90	80	70	90	80	70	90	80	70
Sodium alginate	39	49	59	-	-	-	-	-	-
HPMC- K4M	-	-	-	39	49	59	-	-	-
SCMC	-	-	-	-	-	-	39	49	59
Magnesium stearate	1	1	1	1	1	1	1	1	1
Total weight	150	150	150	150	150	150	150	150	150

Table II. Results of physico-chemical properties of tablets

Formulation batches	Weight uniformity (mg)±SD	Thickness (mm) ±SD	Hardness (Kg/cm²)	Friability (%)	Drug content (%)	Surface pH	Swelling index in (7h)	Muccoadhesive strength (gms)
F_1	150.8±0.78	3.10±0.06	4.5	0.56	98.88	6.2	3.072	48.36
F_2	150.8±0.78	3.10±0.06	4.0	0.59	98.57	6.8	2.559	45.20
F_3	151.1±0.92	3.11±0.02	3.5	0.79	99.62	6.9	2.433	41.09
F_4	150.5±0.91	3.12±0.02	4.5	0.45	98.51	6.5	3.673	49.32
F_5	151.5±0.81	3.12±0.02	4.5	0.59	99.25	6.7	3.205	42.20
F_6	152.0±1.96	3.12±0.02	4.0	0.75	98.56	7.1	2.933	40.13
F_7	152.6±2.21	3.13±0.04	4.5	0.45	98.85	6.9	3.403	43.18
F_8	151.3±1.19	3.13±0.08	4.0	0.53	98.69	7.2	2.673	37.25
F_9	151.2±1.08	3.16±0.04	4.0	0.70	99.24	7.3	2.202	35.64

from all volunteers before conducting the study. Food was prohibited from 0.5 h before the study until its conclusion. Volunteers were given mucoadhesive tablet and instructed to press the tablet against the buccal mucosa for 1 min. A questionnaire was given, to volunteers to score the parameters such as irritancy, comfort, taste, dry mouth, salivation and dislodgement of the tablet during the study and heaviness of the system at the place of attachment (Kasshapa *et al.,* 2004).

Drug release kinetics for the various formulation batches

The *in-vitro* drug release data of Domperidone maleate mucoadhesive tablets for all formulation were proceeds for regression analysis by using MS-excel statistical function.

Table III. Result of *In-vitro* drug release studies

Sr. No	Formulation code	Cumulative % drug release in 7 h
1	F1	76.85
2	F2	87.03
3	F3	94.44
4	F4	57.40
5	F5	65.74
6	F6	72.22
7	F7	69.44
8	F8	73.14
9	F9	86.11

Table IV. Result of *In-vitro* permeation study

Sr. No	Time (h)	Cumulative % drug release
1	0	0
2	1	10.83
3	2	19.47
4	3	27.52
5	4	39.33
6	5	49.50
7	6	62.36
8	7	76.69

RESULTS AND DISCUSSION

Physico-chemical properties

All the formulations were varied from 150.8 to 152.6 mg with minimum standard deviation values indicate that the uniform distribution of polymer and drug in the tablets. The tablets varied from 3.10 to 3.16 mm in thickness with minimum standard deviation values; it assumed that the tablets show uniformity in thickness. The hardness of the tablets was found to be 3.5 to 4.5 kg/cm^2. The hardness is slightly lower than that of the oral tablets; this will be aid in the better absorption of moisture and swelling. Handling will not affect the tablet integrity. The hardness of mucoadhesive tablets varied although compression force was constant. This may be due to the increased concentration of the polymer in the formulations. The friability of the tablets was found to be 0.45 to 0.79 %. Friability was found to inversely proportional to the polymer concentration. This may be due to the more adhesive property of carbopol 940. Drug content in the tablets were within the limit of 98.51 to 99.62 %. As an acidic or alkaline surface pH may cause irritation to the buccal mucosa, the buccal tablets are formulated to have surface pH as close to neutral as possible within salivary pH. The surface pH of all the formulations was close to neutral pH and hence, these formulations may not cause any irritation in the buccal cavity. The formulations containing higher amount of Carbopol-940 showed higher pH because carbopol 940 is acidic in nature. Appropriate swelling behavior of a mucoadhesive tablet is the essential property for uniform and prolonged release of drug and effective mucoadhesion. The swelling index was higher in formulation F4 i.e 3.673 in 7 h. The formulation having higher amount of carbopol 940 shows more swelling index, this may be due to more hydrophilic nature of Carbopol 940. The mucoadhesive strength of the formulations was found to be a function of the concentration of the polymer. Among the formulations, those containing higher concentration of Carbopol 940 exhibited maximum mucoadhesive strength. The mucoadhesive strength of formulation F4 was

Table V. Response of healthy human male volunteers to various parameters

Sr. No.	Criteria	Volunteer's response (%)
1	**Irritation**	
	a) None	100
	b) Slight	-
	c) Moderate	-
	d) Severe	-
2	**Taste**	
	a) Normal	70
	b) Slightly unpleasant	30
	c) Very unpleasant	-
	d) Pleasant	-
	e) Very pleasant	-
3	**Comfort**	
	a) Very comfortable	-
	b) Comfortable	70
	c) Slightly uncomfortable	30
	d) Moderately uncomfortable	-
	e) Severely uncomfortable	-
4	**Dryness of mouth**	
	a) None	80
	b) Slight	10
	c) Moderate	10
	d) Severe	-
5	**Salivary secretion**	
	a) None	10
	b) Slight	80
	c) Moderate	10
	d) Severe	-
6	**Heaviness of tablet at the place of attachment**	
	a) None	90
	b) Slight	10
	c) Moderate	-
	d) Severe	-
7	**Dislodgement of the system during study**	
	a) No	100
	b) Yes	-

higher (49.32 gms) and less in F9 (35.64 gms). Wetting, interpenetration, and mechanical interlocking between mucus and polymer are the successive stages of mucoadhesion. The strength of mucoadhesion is affected by various factors such as molecular weight of polymers, contact time with mucus, swelling rate of the polymer, and the biological membrane used in the study. The higher mucoadhesion of carbopol 940 and HPMC-K4M (F4, F5 and F6) may be due to the ionization of carbopol 940 at salivary pH which leads to improved attachment of the device to mucosal surface. The superior quality of Carbopol 940 as bioadhesive polymer as compared to HPMC K4M and SCMC has also been revealed in other studies. The results of physico-chemical evaluation of Domperidone maleate muco-adhesive tablets are tabulated in table II.

Table IV. Drug release kinetics for the various formulation batches

Formulation code	*In-vitro* drug release	Zero order drug release	Higuchis regression
F1	76.85	0.9957	0.9535
F2	87.30	0.97.95	0.9919
F3	94.44	0.9498	0.9928
F4	57.40	0.9592	0.9984
F5	65.74	0.9318	0.9962
F6	72.22	0.9522	0.9958
F7	69.44	0.9917	0.9565
F8	73.14	0.9800	0.9561
F9	86.11	0.9931	0.9687

In-vitro drug release

The formulation F1, F2, F3, F4, F5, F6, F7, F8 and F9 showed 76.85%, 87.03%, 94.44%, 57.40%, 65.74%, 72.22%, 69.44%, 73.14%, and 86.11% drug release respectively. The maximum drug release was shown by formulation F3. The releases of drug from the tablets were depending on the proportion of the carbopol 940. The release rate is decreased with increasing the polymer concentration Carbopol 940, indicating the retardant effect of the polymer carbopol 940 on the drug release. Among the nine formulations the F3 shows maximum drug release i.e. 94.44%, due to high concentration of sodium alginate. According to the graph of square root of Time Vs Cumulative % drug release was maximum from formulation F4 i.e. 99.84 fallow matrix diffusion. The results of *In-vitro* drug release are shown in table III.

In-vitro permeation study

The *in-vitro* permeation study was carried for formulation F3 on porcine buccal mucosa. The *in-vitro* drug permeation was 76.69% for 7 h. The in-vitro drug permeation data further proceed for regression coefficient using MS-excel statistical program. The R^2 value for formulation F3 was 99.63 it shows zero order release. According to the Higuchis plot all the formulation shows matrix diffusion drug release pattern.

Drug -polymer interaction study

IR spectral studies for the identification of pure Domperidone maleate, Carbopol 940, Sodium alginate, HPMC-K4M, SCMC and optimum physical mixture of F3 (Domperidone maleate + Carbopol 940+ Sodium alginate) shows no interaction between them, it indicate that the drug is compactable with polymer it gives better formulation hence it was formulate.

In-Vivo human acceptability studies

Comfortability of the mucoadhesive system in the oral cavity is an important concern in the buccal drug delivery. Based on the results it can conclude that the mucoadhesive tablet of Domperidone maleate would be comfortably placed in the human oral cavity.

Drug release kinetics

Graphical treatment of the formulation F3 to Higuchi's equation has shown the drug release was diffusion mediated (Table VI).

CONCLUSION

The formulation F3 containing (Carbopol 940+sodium alginate) was found to be best among all the formulation batches because of its consistent release rate for 7 h and extent of drug release was 94.44%. Graphical treatment of the formulation F3 to Higuchis equation has shown the drug release was diffusion mediated. *In-vitro* permeability study for formulation F3 for 7 h has shown drug release 76.69%. Comfortability of the mucoadhesive system in the oral cavity is an important concern in the buccal drug delivery. Based on the results it can conclude that the mucoadhesive tablets of Domperidone maleate would be comfortably placed in the human oral

cavity. Hence the formulation F3 achieved the objectives of the present study as avoiding first pass metabolism, reduced the side effect due to the higher dosing frequency, Prolong the drug plasma half-life and improve the patient compliance.

As extension of the work for pharmacokinetic studies, *in-vivo* studies on animal and controlled clinical studies on human being can be carried out in the future.

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