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DESIGN AND DEVELOPMENT OF *MORINGA OLEIFERA* GUM BASED BUCCAL ADHESIVE TABLETS

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ABSTRACT

The objective of the present study was to study the naturally available Moringa oleifera gum (MG) as drug carrier and mucoadhesive component in buccal delivery using Ondansetron hydrochloride as a model drug. Amounts of MG and Carbopol 934P (CP) were taken as the formulation variables. Direct compression technique was employed for the preparation of buccal tablets using ethyl cellulose as backing layer. The prepared tablets were tested for pre and post-compressional parameter with study the effect of formulation variables on bioadhesive strength and in-vitro drug dissolution study. The hardness, friability, weight variation, drug content, surface pH, mucoadhesive strength, in vitro drug release profiles were uniform and reproducible. Surface pH study of tablets indicated that the all formulations are suitable for buccal environment. However the MG and CP markedly affected the mucoadhesion strength and the release profile. Mucoadhesive strength and drug release was found to be a function of amount of polymers. As amount of polymers increases mucoadhesive strength increases and drug release decreases. The formulation variables were found to be significant for mucoadhesion and release properties (P< 0.05). The study indicates that the MG has sufficient mucoadhesive property for buccal application.

KEYWORDS: *Moringa oleifera gum, mucoadhesion, in- vitro dissolution.*

INTRODUCTION

In recent years, there have been important developments in different dosage forms for existing and newly designed drugs and natural products, and semi-synthetic as well as synthetic excipients often need to be used for a variety of purposes. Gums and mucilages are widely used natural materials for conventional and novel dosage forms. These natural materials have advantages over synthetic ones since they are chemically inert, nontoxic, less expensive, biodegradable, and widely available. They can also be modified in different ways to obtain tailor-made materials for drug delivery systems and thus can compete with the available synthetic excipients [1, 2]. Despite the advantages, they have certain disadvantages like microbial contamination, batch-to-batch variation, isolation and purification. Natural polymers have many applications as excipients in dosage form design and manufacture of solid matrix systems, implants, films, beads, microparticles, nanoparticles, inhalable, injectable systems, as well as liquid formulations [3, 4].

Moringa oleifera gum (MG) is a natural polymer derived from bark of *Moringa oleifera* (Family: Moringaceae). The root yields an essential oil, which is very pungent and has a very offensive order. The bark contains a white crystalline alkaloid, two resins, an organic acid, mucilage and ash. The MG contains about galactose 41.5%, arabinose 26.9%, xylose 25.9%, rhamnose 5.6% and trace amount of uronic acid [5]. The stem of the tree exudes a gum which is initially white in colour but changes to reddish brown to brownish black on exposure [6].

The present investigation was aimed at using the inexpensive, naturally and abundantly available MG as drug carrier and mucoadhesive component in buccal delivery using Ondansetron hydrochloride as a model drug. Ondansetron hydrochloride is a potent antiemetic and is effective in the treatment of nausea and vomiting associated with cancer therapy, pregnancy, migraine, etc [7].

MATERIALS AND METHODS

Ondansetron hydrochloride (ODH) was obtained as a gift sample by IPCA Laboratories Pvt. Ltd., Mumbai. Moringa gum was procured from Local Area. Directly compressible lactose (DCL), Carbopol 934P (CP), Magnesium Stearate (MS) and Ethyl cellulose (EC) were purchased from Rajesh Chemicals, Mumbai. All other chemicals used in study were of analytical grade.

Methods:

Methods of purification of MG:

The gum was collected from incisions of trees. The gum was dried and crushed by using mortar and pestle. It is passed through sieve # 80. Dried gum was stirred in distilled water (300 ml) for 4-5 hours at room temperature. The supernant layer was obtained by centrifugation. The residue was washed with water; this procedure was repeated for three times. Finally the supernant layer was made up to 500 ml and treated with twice the volume of acetone by continuous stirring. The precipitate material was washed with water and dried at 50-60 ^{0}C under vacuum by using rotary evaporator [8, 9].

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Analytical Method Development:

Preparation of stock solution:

Accurately weighed quantity of 10 mg ODH was transferred to a 100 ml volumetric flask. Then approximately 50 ml of phosphate buffer solution (PBS) of pH 6.8 was added and resulting solution was sonicated for 5 min. Further required quantity of PBS pH 6.8 was used to adjust volume of solution to 100 ml.

Preparation of serial dilution:

From the stock solution, aliquots of 1 to 10 ml were transferred to the 10 ml volumetric flask and final volume was made to 10ml with PBS pH 6.8 to get 2-20 µg/ml concentration respectively. Finally the absorbances of prepared solutions were measured against blank (PBS pH 6.8) at 310 nm by using UV visible Spectrophotometer (Jasco V-630, Japan) and calibration curve was plotted [10].

Precompression parameters of powder blend:

The two most important attributes for the direct compression formula are good flow and good compressibility. Interparticulate interactions that influence the bulking properties of a powder with powder flow. So, precompression parameters of all formulations blend were conducted for angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio [11].

Preparation of Buccal Adhesive Tablets:

The buccoadhesive tablets were prepared using different polymers in combinations with varying ratios as summarized in Table 1.

Table No. 1: Composition of buccal adhesive tablets

Ingredients (mg)	Formulations					
	F1	F2	F3	F4	F5	F6
ODH	8	8	8	8	8	8
Moringa oleifera gum	16	24	32	-	-	-
Carbopol 934P	-	-	-	16	24	32
DCL	35	27	19	35	27	19
Magnesium Stearate	1	1	1	1	1	1
Ethyl cellulose	20	20	20	20	20	20
Total weight (mg)	**80**	**80**	**80**	**80**	**80**	**80**

All the ingredients in Table 1, were powdered, passed through sieve # 80. This buccal adhesive tablets were prepared by a direct compression method involving two steps. In first step drug, gum and diluents were mixed homogeneously in a double cone blender for 15 minutes in ascending order. Finally lubricant was added and mixed for 5 minutes. The blended powder was then lightly compressed on 6 mm flat faced punch using single punch tablet compression machine (Cadmach, Ahmedabad), at 4 Kg/cm^2 force. Later, upper punch was raised and the ethyl cellulose 20 mg was placed inside the die cavity and subsequently two layers were then compressed at 5-6 Kg/cm^2 force [12].

Evaluation of Buccal Adhesive Tablets:

All formulations were evaluated for uniformity in tablet weight and thickness. Diameter and thickness of tablets were determined by using vernier caliper (Mitutoyo, Japan). Each formulation was also examined for friability using a Roche-type friability apparatus and hardness using a Monsanto-type hardness tester [13].

Determination of Drug Content:

Five tablets from each formulation were powdered individually and a quantity equivalent to 8 mg of ODH was weighed accurately and dissolved into 100 ml phosphate buffer solution (PBS) having pH 6.8. This stock solution was sonicated for 20 min. This resulting solution was further diluted to 10 ml with PBS pH 6.8 for achieve concentration upto 10 µg/ml and analyzed on spectrophotometer (Jasco V-630, Japan) at 310 nm [10].

Stability Study in Human Saliva:

The stability study of optimized formulation was performed in natural human saliva. The saliva was collected from humans (age 18-45years). Buccal adhesive tablets were placed in 5 ml of human saliva and kept for 12 h. At regular time intervals (0, 1, 3, 6, 9 and 12 h), the tablets were examined for physical stability i.e. changes in color and collapsing of the tablets [14].

Surface pH Study:

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may irritate the buccal mucosa, there was aim to keep the surface pH as close to neutral as possible. Buccoadhesive tablets were left to swell in 2 ml distilled water for 2 h. The surface pH of the tablets was determined by means of a pH paper placed on the core surface of the swollen tablet. A mean of three readings was recorded [15].

Determination of mucoadhesive Strength:

The in vitro mucoadhesion studies were conducted using a modification of a bioadhesion test assembly described by Gupta et al. [16] Sheep buccal mucosa was used as the model membrane. The tablet was lowered onto the mucosa under a constant weight of 5 g for a total contact period of 1 min. Mucoadhesive strength was assessed in terms of weight (g) required detaching the tablet from the membrane.

In vitro drug release studies:

Drug release studies (n=3) were conducted for all the formulations using dissolution rate test apparatus (Apparatus 2, Electrolab, TDT-08L, Mumbai). Tablets were supposed to release the drug from one side only; therefore impermeable backing membrane side was fixed to a 2 X 2 cm glass slide with the help of two way adhesive tape. It was then placed in the dissolution apparatus. This study was carried out in PBS pH 6.8 as the dissolution medium at 37±0.5 °C and with stirring speed of 50 rpm [13, 17]. Aliquots of small samples were periodically withdrawn and the sample volume replaced with an equal volume of fresh dissolution medium. The samples were suitably diluted and analyzed spectrophotometrically (Jasco V-630, Japan) at 310 nm. Drug release data was analyzed using PCP Disso V3 software.

Data analysis:

The dissolution profile of all the batches were fitted to Zero order kinetics, First order kinetics, Higuchi, Hixon-Crowell, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release by using a PCP Disso V3 software and the model with the higher correlation coefficient was considered to be the best fit model [18].

RESULTS AND DISCUSSION

The objective of the present study was to study the naturally available *Moringa oleifera* gum as drug carrier and mucoadhesive component in buccal delivery using Ondansetron hydrochloride as a model drug.

Analytical method was developed for the drug and validated. Absorbance maxima were found to be 310 nm, which corresponds to the literature. The results of the study are given in the following Table 2.

The flow properties such as angle of repose, Hausner's ratio, Carr's index, Bulk density and Tapped density are considered as indirect measurements of powder flowability. All parameter values are within the satisfactory limit compared with the standard values shown in Table 3.

Table No. 2: Observations of Analytical method development in a UV spectrophotometer

S. No	Parameters	Observations
1	Absorbance Maximum	310 nm
2	Slope	0.0455
3	Intercept	0.0046
4	Correlation Coefficient (R^2)	0.999

Table No. 3: Rheological properties of powder blend of F1 to F6

Formul-ations	Bulk density	Tapped density	Carr's index	Hausner's Ratio	Angle of Repose (θ)
F1	0.445±0.011	0.522±0.019	13.94±0.52	1.17±0.08	24.02±0.22
F2	0.439±0.018	0.512±0.026	14.24±0.71	1.16±0.011	25.22±0.16
F3	0.478±0.017	0.580±0.023	17.58±0.45	1.21±0.010	27.36±0.15
F4	0.423±0.008	0.512±0.003	17.38±0.745	1.21±0.016	20.75±0.92
F5	0.436±0.008	0.535±0.004	18.50±0.617	1.23±0.012	22.12±0.40
F6	0.422±0.004	0.510±0.005	17.25±0.642	1.21±0.012	22.67±0.62

In all formulations tablet weights varied between 80.2 and 79.7 mg, thickness between 2.03 and 2.13 mm, and hardness between 5.7 and 6.8 kg/cm². The assay for drug content of ODH varied between 97.31 and 98.82 %, and the friability ranged between 0.59 and 0.69 %. Thus, all the physical parameters of the compressed matrices were practically within permissible limits.

Tablets of all the formulations (n = 3) had shown a surface pH values in the range of 5.5-7. As amount of CP was increased surface pH of formulations shifted towards pH 5 but was within the normal range. Thus surface pH test indicated no risk of mucosal damage or irritation to buccal mucosa [19].

The physical stability of buccal adhesive tablets (n = 3) of ODH was examined in natural human saliva and evaluated by their appearance characteristics, such as colour and shape. The tablets of all formulations did not change colour and were not disintegrated for at least 12 h, indicating the satisfactory stability of the drug and buccal devices in the human saliva. Physical properties of the buccal devices such as thickness and diameter increased slightly owing to swelling of the buccal devices in human saliva. But the buccal devices did not collapse in the human saliva until the end of the study, confirming the sufficient strength of the buccal adhesive tablets. These results suggested that the ODH tablets with MG and CP could stabilize the drug in human saliva [20-21].

Table 4 shows significant variation ($P < 0.05$ in each case) in the values of mucoadhesive strength obtained using different ratios of polymers. The figure depicts an increase in bioadhesive strength with an increase in the amount of polymer(s).

Table No. 4: Mucoadhesive strength and Drug release study

Formulations	Mucoadhesive Strength (g)	Cumulative % drug release at 12hr	Release exponent (n)	Best fit model
F1	14.78 ± 0.31	88.746 ± 0.93	0.4928	Matrix
F2	16.12 ± 1.25	84.646 ± 1.41	0.5071	Matrix
F3	18.19 ± 1.36	79.164 ± 1.31	0.5387	Matrix
F4	26.3 ± 0.82	80.904 ± 0.79	0.4533	Matrix
F5	30.7 ± 1.03	72.040 ±1.63	0.5071	Matrix
F6	35.8 ± 0.98	67.145 ± 1.32	0.5437	Matrix

For MG or CP containing tablets, it was observed that with the increase in polymer content there was a decrease in rate of drug release with an increase in CP content in tablets there was increase in bioadhesion. In the current study, the values of release exponent (n), calculated as per Korsmeyer-Peppas equation indicated non-Fickian drug transport mechanism. Fig. 1 and 2 show % release of drug from the formulations containing different amount of polymers. Tablets from both group showed % drug release less than 90% and the highest release from MG group was found to be 88.74% (Fig.1). This is because of higher % hydration of MG, which in turn led to matrix erosion. Tablets from CP group showed a lesser % drug release compared to MG group[12]. The maximum drug release from this group was found to be 80.90% (Fig. 2).

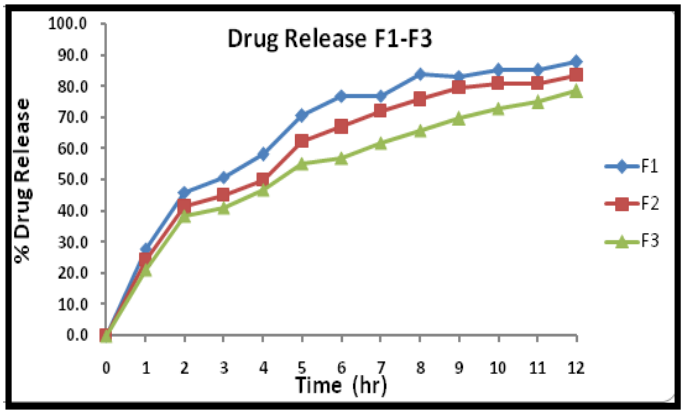

Fig. 1: % Drug Release from the formulations containing MG

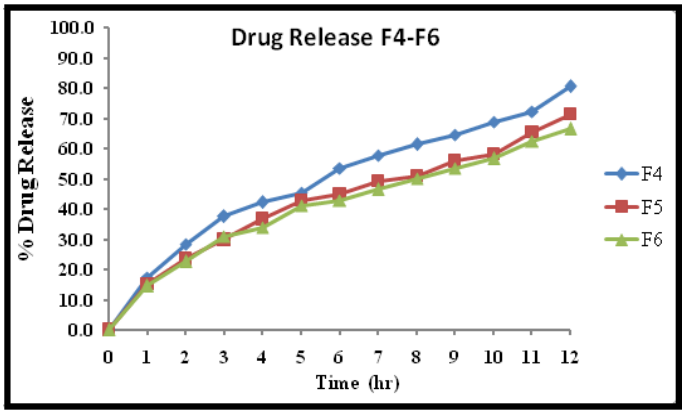

Fig. 2: % Drug Release from the formulations containing CP

CONCLUSIONS

The present study indicated the applicability of natural polymer MG as a buccal adhesive polymer. Buccal adhesive tablets contain MG and CP was developed to a satisfactory level in terms of drug release, Mucoadhesive performance, physicochemical properties and surface pH. Based on the results obtained so far, it was concluded that the objectives of the investigation was fulfilled. Surface pH of all formulations was found to be in the range, which were nearer to the salivary pH. Hence it was assumed that these formulations do not cause any irritation to the mucous layer of the oral cavity. Mucoadhesive strength and drug release was found to be a function of amount of polymers. As amount of polymers increases mucoadhesive strength increases and drug release decreases. The formulation variables were found to be significant for mucoadhesion and release properties ($P< 0.05$). In a nutshell, naturally available *Moringa oleifera* gum (MG) as drug carrier and mucoadhesive component in buccal delivery.

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