

APPLICATION OF NOVEL NATURAL MUCOADHESIVE POLYMER IN THE DEVELOPMENT OF PENTOXIFYLLINE MUCOADHESIVE TABLETS

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ABSTRACT

Objective: The present study was planned to develop a mucoadhesive tablet formulation of the drug pentoxifylline using natural mucoadhesive polymer from the plant *Ocimum basilicum* Linn.

Methods: The isolated polymer was used to formulate the mucoadhesive tablets with 3 different concentrations. The tablets were formulated by using direct compression technique and evaluated for various parameters such as thickness, friability, weight variation, hardness, mucoadhesive strength, swelling index by standard methods, and the *in vitro* drug release studies in USP dissolution test apparatus type-II.

Results: The swelling index was indirectly proportional to the polymer concentration and the tablets with a high concentration of polymer showed better mucoadhesive strength (28.5532 ± 0.4660). The *in vitro* drug release showed that the drug release was indirectly proportional to the polymer concentration. The formulation F3 showed the controlled release of drug pentoxifylline (99.84 ± 1.86) for 10 h. The mechanism of drug release was found to be Fickian diffusion and followed the zero-order kinetics, which was proved by its highest linearity (r^2) in all the formulations.

Conclusion: The tablets formulated with the isolated polymer of *Ocimum basilicum* Linn showed the good mucoadhesive mucoadhesive property and it controlled the release of the pentoxifylline.

Keywords: Mucoadhesion, *Ocimum basilicum*, Pentoxifylline

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INTRODUCTION

Naturally acquired mucoadhesive polymers are gaining much attention in the development of various pharmaceutical dosage forms [1]. Bioadhesion, as a state in which two materials, at least one of which being of biological nature are held together for an extended period of time by interfacial forces [2]. It is also defined as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time [3, 4]. Mucoadhesion is an obverse of bioadhesion, which is aimed to target the drugs to a particular mucosal area of the body. The polymers, those are water-soluble and become adhesive during hydration were used to formulate the mucoadhesive dosage forms. The mucoadhesive dosage forms are aimed to target the drug with increased gastric residence time, sustained/controlled release, minimized the first-pass effect and reduced adverse effects [5, 6]. The mucoadhesive polymers selected should be non-toxic, non-irritant, non-absorbable, non-covalent, biocompatible, adhesive and economic in nature [7]. Either natural (gelatin, guar gum and sodium alginate) or synthetic/semi-synthetic (Hydroxypropyl methylcellulose, Carbopol 934 and Sodium carboxy methyl cellulose), may be used alone or in a combination of two or more for the mucoadhesive drug delivery systems [8–12].

Ocimum basilicum Linn. (OBL) is an erect, almost glabrous herb, belonging to the Lamiaceae family, native to Iran, Afghanistan and India, which grows to between 30 and 90 cm high. The leaves are ovate, lanceolate, cucuminate, toothed or entire, glabrous on both surfaces and glandular. When mature, they reach approximately 5 cm in length, excluding the petiole, which is approximately 2 cm long. The upper surface is smooth and lustrous; on the lower surface along the midrib and the petiole short, stiff hairs occur sparingly [13]. It represents an important source of essential oil used in food, pharmaceutical, perfumery and cosmetics industries [14]. Its aromatic leaves are used in fresh or dried forms as a drug in traditional medicine and as a flavoring agent in food and confectionery products as well as beverages [13, 15]. The seeds of OBL are high in fiber (22.6%) and in some regions of Asia like Iran and India, basil seeds are frequently included in beverages and

desserts for aesthetic purposes as well as a source of dietary fiber [16].

Bhosale *et al.* [17] investigated the hydrogel isolated from the seeds of OBL as a binder and proved that it has potential binding and granulating property. Khazaei *et al.* [18] characterized the new biodegradable edible film made from OBL seed gum and revealed that it had a good potential to be used in producing edible films for various food applications. Akbari *et al.* [19] used supercritical carbon dioxide phase inversion technique to dry the seed mucilage to form a nanometric structure and they found the bioadhesive property of seed mucilage was good and many active pharmaceutical compounds might be loaded to the resultant nanometric structure to enhance drug release. Naji-Tabasi *et al.* [20] evaluated the potential of OBL seed gum nanoparticles as an oral delivery system for glutathione, which was fabricated by ion gelling technique and calcium was used as a cross-linking agent. A novel drug delivery system, loaded the drug cephalexin on the OBL seed mucilage coated magnetic nanoparticles was prepared and characterized by Rayegan *et al.* [21].

Even though several advances and researches have been made in the area of mucoadhesion and polymers, still the search for newer mucoadhesives are going on. Plant-derived polymers like mucilage are widely used in the pharmaceutical industry due to their emollient, lack of toxicity, and low cost. So, in this present work, an attempt was made to study the application of novel natural mucoadhesive polymer from the plant *Ocimum basilicum* (MAPOB) in the development of pentoxifylline mucoadhesive tablets concern to the *in vitro* drug release rate.

MATERIALS AND METHODS

Materials

The seeds of *Ocimum basilicum* were purchased from the local vendors of Chennai, Tamilnadu in the month of February 2018. The collected seeds were identified and authenticated by a botanist Dr. S. Balasubramanian, ABS Medicinal garden, Salem. The voucher specimen (OBG-1) was kept in our museum for future reference. Pentoxifylline

was obtained as a gift sample from Shasun Pharmaceuticals, Puducherry. Microcrystalline cellulose and magnesium stearate were purchased from Central Drug House (India). Acetone, diethyl ether and petroleum ether were from Qualigens (India) and sodium hydroxide from E-Merck (India). All the chemicals used were of analytical grade.

Methods

Isolation of MAPOB

Three batches of MAPOB was prepared on a laboratory scale by the method of Rao *et al.* [22]. 200 ml of cold distilled water was added to 20 g of the seed powder and the slurry was prepared. Then the slurry was added to 800 ml of boiling water and boiled for another 20 min with continuous stirring. The solution was kept overnight to settle the solid matter. The clear solution was centrifuged for 20 min at 5000

rpm. The supernatant fluid was separated and twice the volume of acetone was added with continuous stirring. The formed precipitates were filtered and washed with petroleum ether and diethyl ether and then dried under vacuum at 50-60 °C. The dried materials were sieved through sieve No 80 and used for the formulation of tablets.

Formulation of mucoadhesive tablets

The mucoadhesive tablets of pentoxifylline (MATP) were prepared by using direct compression technique. Pentoxifylline, mucoadhesive polymer, microcrystalline cellulose, magnesium stearate were accurately weighed, mixed uniformly and this mixture was compressed into tablets by using Elite multi-station punching machine (Erweka) with 10 mm flat punches. The compression force was adjusted to give tablet hardness in the range of 7 to 11 kp. The constituent of the formulation is presented in table 1.

Table 1: Formulation of mucoadhesive tablets of pentoxifylline

Ingredients	F1	F2	F3
Pentoxifylline	400	400	400
Microcrystalline cellulose	152	122	92
MAPOB	30	60	90
Magnesium stearate	18	18	18
Total weight (mg)	600	600	600

All the quantities are in mg

Swelling study

The formulated MATP's were weighed (W1) individually and incubated at 37±0.5 °C separately in an agar gel (2%) plates. The tablets were removed from petri dish at regular time intervals of 1 h up to 6 h and the excess water on the surface was removed carefully with filter paper. The swollen tablet was reweighed (W2) and the swelling index was calculated by using the formula [23-25].

$$\text{Swelling index} = \frac{W2 - W1}{W1}$$

Mucoadhesive strength

The mucoadhesive strength (MS) of the formulated MATP's was measured by using a modified 2-arm balance (fig. 1) with rabbit buccal mucosa [26]. The apparatus consists of a modified double beam physical balance in which the right pan has been replaced by a

glass slide with copper wire and additional weight, to make the right side weight equal with left side pan. A Teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward protrusion of 2 cm height and 1.5 cm diameter on one side. This was kept in a beaker filled with phosphate buffer (PB) pH 6.8, which was then placed below the right side of the balance.

The rabbit buccal mucosa was used as the membrane and PB pH 6.8 as moisturizing liquid. The rabbit buccal mucosa was obtained from the local slaughterhouse and stored in Krebs buffer at 4 °C upon collection. The experiment was conducted within 3 h of the procurement of rabbit mucosa. The mucous layer was separated by using a surgical blade and washed with PB pH 6.8. It was then tied over the protrusion in the Teflon block using a thread. This set was kept in a glass beaker, which was filled with PB pH 6.8 up to the surface of the buccal mucosa to maintain buccal mucosa viability.

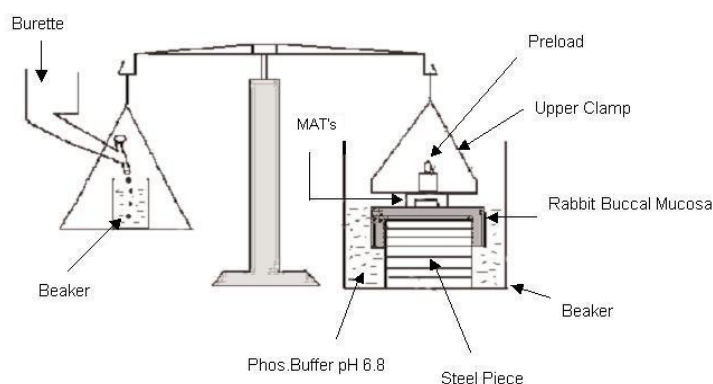


Fig. 1: Mucoadhesive strength measurement apparatus

The MATP was attached to the upper clamp of the apparatus and then the beaker was raised slowly until contact between rabbit buccal mucosa and MATP was established. A weight of 100 g was kept on the clamp for a pre-load time of 5 min to create a strong adhesion between rabbit buccal mucosa and the MATP. The pre-load and pre-load time were kept as constant for all the MATP's. After the pre-load time, the weight was removed from the clamp, and water was added at a rate of 60 drops/min into the beaker until the

separation of rabbit buccal mucosa and MATP. The weight of water required to detach the MATP from buccal mucosa was noted as MS and the same was repeated with fresh mucosa (n = 6). The MS was used to calculate the force of adhesion [25, 27-29] using formula.

$$\text{Force of adhesion (N)} = \frac{MS}{100} \times 9.81$$

In vitro drug release studies

The *in vitro* dissolution studies were carried out in Type-II USP dissolution test apparatus, using 900 ml of phosphate buffer saline (PBS) pH 6.8. The dissolution test was carried out at a speed of 50 rpm and the temperature was maintained at 37 °C±0.5 °C. 5 ml of the sample was withdrawn periodically at predetermined time intervals and assayed spectrophotometrically at 274 nm using Shimadzu UV spectrophotometer 1601. All the experiments were done thrice and the standard curve specification was $y=0.0392X$ ($r^2 = 0.9993$, $n = 10$).

Drug release kinetics

The data obtained from *in vitro* release of drug was plotted in various kinetic models such as zero-order (cumulative amount of drug released vs time), first-order (log cumulative percentage of drug remaining vs time), and Higuchi's model (cumulative percentage of drug released vs square root of time) to know the release kinetics [30–32].

Mechanism of drug release

The mechanism of drug release of the prepared MATP was calculated by using Korsmeyer equation (log cumulative percentage of drug released vs log time), and the exponent n was calculated through the slope of the straight line [33].

Statistical analysis

Each experiment was repeated at least three times. The results are expressed as mean±SD. One-way analysis of variance was used to

test the statistical significance of differences among groups. Statistical significance of the differences of the means was determined by Student's t-test.

RESULTS AND DISCUSSION

Polymers are most commonly used as an adjuvant in the manufacturing of different pharmaceutical dosage forms. They possess a variety of pharmaceutical properties, which include binding, disintegrating, suspending, emulsifying and sustaining properties at different proportion in different pharmaceutical dosage forms [34, 35]. But in the view of biodegradation and biocompatibility, the natural polymers are preferred. Even though many polymers are available, a search for new polymers still interesting to get more efficacious polymers with less toxic. The purpose of this research is to give scientific validation to the plant by isolating polysaccharides and then to screen them for the potential mucoadhesive property. The current research work is focused on the identification of a new mucoadhesive polymer and its application on the development of pentoxifylline mucoadhesive tablets

The plant OBL was selected for this study and the mucilage was isolated from the seeds by the method of Rao *et al.*, [22]. Three different concentrations of MAPOB was used to formulate mucoadhesive tablets of pentoxifylline. The formulated tablets showed a satisfactory evaluation report on hardness, friability, weight variation and drug content. The results were shown in table 2. The increase in concentration [25, 36] of the mucoadhesive polymer, increased the tablet hardness.

Table 2: Results of evaluation of thickness, hardness, friability weight variation and drug content for mucoadhesive formulations

Formulation code	Thickness (mm±SD)	Hardness (Neutons±SD)	Friability (%±SD)	Weight variation (mg±%)	Drug content (%±SD)
F1	6.259±0.022	68.649±4.004	0.2394±0.0895	0.6004±1.81	100.11±4.57
F2	6.266±0.024	73.553±4.623	0.2391±0.0194	0.5990±1.79	99.08±4.33
F3	6.249±0.029	79.4367±5.064	0.2053±0.1018	0.5992±2.16	100.78±2.48

(All values are mean±SD; n=6)

An appropriate swelling index is mandatory for the uniform and sustained release of the drug and effective mucoadhesion [25, 36]. The results of the swelling study showed that the rate of swelling was indirectly proportional to the concentration of MAPOB in tablets. The tablets formulated (F1) with a lower concentration of MAPOB showed a high swelling index (5.038±0.182), and the formulation (F3) with a higher concentration of MAPOB showed lower swelling index (3.334±0.087). Formulations F2 and F3 were showed no significant change in the shape and form of tablets for a period of up to 6 h, when

they kept in the agar gel (2%) plate, but the formulation F1 changed the shape and form completely. The results of the swelling index have been tabulated in table 3. The tablets, which had high swelling index described that the formation of a gel by the hydration of the polymer, did not have good adhesion, probably due to overhydration resulting less MS. The formulation F3 tablets adhered well to the agar gel plates and a layer of gel was seen adhering to the sides of the tablets. This suggests that the gel formed was firm and there was no overhydration, making the tablets adhere well to the plates.

Table 3: Results of swelling index, mucoadhesive strength and force of adhesion

S. No.	Formulation	Swelling index (±SD)	Mucoadhesive strength (g±SD)	Force of adhesion (Newton±SD)
1	F1	5.038±0.182	9.3566±0.0866	0.9179±0.0085
2	F2	4.471±0.120	19.7506±0.5695	1.9375±0.0599
3	F3	3.334±0.087	28.5532±0.4660	2.8011±0.0457

(All values are mean±SD; n=6)

MS of MATOB with rabbit buccal mucosa is shown in table 3. Wetting, interpenetration, and mechanical interlocking between mucus and polymer were the three different stages of occurrence of the mucoadhesion. The MS is affected by various factors such as polymer's swelling rate, molecular weight [37], contact time with mucus, and the biological membrane used for the study [38]. Tablets formulated with a high concentration of MAPOB showed good MS in a contact time of 5 min. This high MS of MAPOB may be due to the formation of secondary bioadhesion bonds with mucin and interpenetration of the polymer chains in the interfacial region. However, the formulations F1, F2 and F3 exhibited MS of

9.3566±0.0866, 19.7506±0.5695 and 28.5532±0.4660 g, respectively, with rabbit buccal mucosa.

The *in vitro* drug release studies (fig. 2) were carried out and the results showed that the release of the drug from the formulated tablets were based on the MAPOB concentration. The formulation F1, which has a high swelling index, becomes gel-like due to the over hydration of polymer, leads to more % of drug diffused from the polymer matrix [39]. The % of drug release (99.03±2.58) was more in formulation F1 but it was within a period of 4 h. The % of drug release was decreased gradually to 99.96±2.31 at 8 h for the formulation F2 and 99.84±1.86 at 10 h for the formulation F3. This

extend of time-release may be due to the increase in the concentration of MAPOB. It may be due to the in situ gelling property of mucoadhesive polymer, which slows the dissolution.

Tablets of batch F3 was remaining intact during the entire 10 h study period and the batch F1 and F2 were up to 4 h and 8 h respectively.

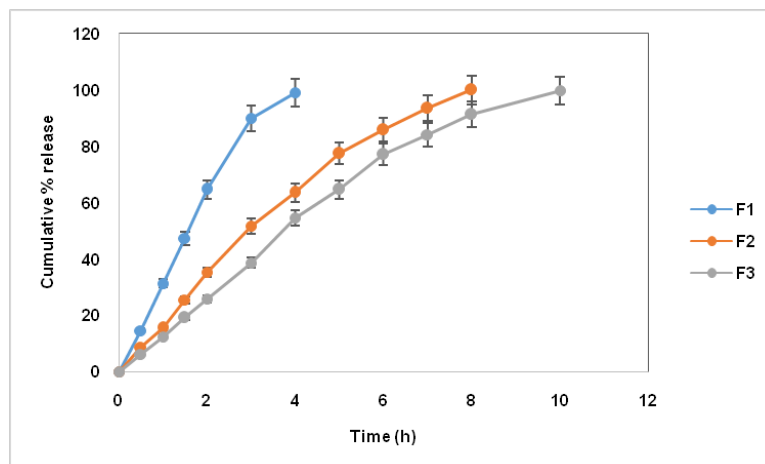


Fig. 2: The cumulative release profile of mucoadhesive tablets of pentoxifylline formulated with MAPOB. (mean±SD; n=3)

The zero-order release described that the release rate is dose-independent, which shows the cumulative amount of drug release vs time for zero-order kinetics. The first order release described the release rate is dose-dependent, which shows the log cumulative percent drug remaining vs time [40]. Higuchi's model described the release of drugs from an insoluble matrix as a square root of a time-dependent process based on Fickian diffusion. Higuchi square root kinetics, showing the cumulative percent drug release vs the square

root of time [41]. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined (table 3). It was found that the *in vitro* drug release of mucoadhesive tablets of pentoxifylline was following zero-order release, as the plot showed the highest linearity ($r^2=0.9693$, 0.9761 and 0.9731) for the formulations, F1, F2 and F3 respectively, and Higuchi's ($r^2=0.9887$, 0.9953 and 0.9896), which indicates the release rate was not depending upon the dose of the drug.

Table 3: Release kinetics of mucoadhesive tablets of pentoxifylline

Formulation	First order		Zero-order		Higuchi		Korsmeyer Peppas	
	Slope	r^2	Slope	r^2	Slope	r^2	Slope	r^2
F1	0.543	0.9197	25.999	0.9693	69.229	0.9887	0.8502	0.9772
F2	0.1675	0.9614	12.892	0.9761	45.795	0.9953	0.8807	0.9842
F3	0.1313	0.9626	10.805	0.9731	41.794	0.9896	0.9357	0.9892

The corresponding Korsmeyer-Peppas [39] plot (log cumulative percent drug release vs time) indicated good linearity ($r^2=0.9772$, 0.9842 and 0.9892) and showed the matrix release of the drug pentoxifylline.

CONCLUSION

The polymers are playing an important role in the field of controlled or sustained release drug delivery system. Since the seeds of the plant, OBL has rich mucilage content and that may prove to be an alternative to existing mucoadhesive polymers. Therefore, in the present study, an attempt was made to study the application of a novel mucoadhesive polymer isolated from the plant OBL for the development of pentoxifylline mucoadhesive tablets. The patient compliance may be increased, when the dosing frequency of the drug reduced. The tablets formulated with MAPOB showed the controlled release of pentoxifylline for a period of 10 h. The *in vitro* dissolution studies indicated that the drug pentoxifylline was released in zero-order pattern, as the plot showed the highest linearity. It also indicates that the increasing concentration of the polymer leads to a decrease in the release rate and increasing the mucoadhesive strength of the tablet.

AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICTS OF INTERESTS

All authors have none to declare

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