Bucco-adhesive tablets containing metoprolol tartarate: formulation, *in vitro* and *in vivo* characterization

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The main goal of this work was to develop bilayered buccoadhesive tablets to provide delivery of metoprolol tartarate (MT) in a unidirectional fashion to the mucosa. The polymers used included Carbopol 934P, Hydroxy propyl methyl cellulose and Sodium alginate, individually at different concentrations and as a mixture of each two polymers at different ratios. The prepared tablets were characterized by evaluating their physical properties such as weight variation, content uniformity, swelling index, in vitro bioadhesion force and surface pH. The in vitro drug release was also studied. In addition, a comparison of the pharmacological effects of MT on blood pressure and heart rate of healthy rabbits after buccal administration compared to those of oral commercial tablets, Betaloc, was carried out. Moreover, pharmacokinetic parameters of MT were studied. The results revealed that the swelling values increased by increasing the polymer concentration. The adhesion strength was found to be a function of the type and concentration of the polymers used. It was found that tablets containing CP 934P showed the longest residence time and the shortest residence time was obtained with sodium alginate. The rate of drug release was found to be dependent on the type and concentration of polymer used. The reduction effect of MT buccoadhesive tablets on blood pressure and heart rate was found to be faster and greater than that administered orally. The bioavailability of MT after buccal administration was found to be significantly higher than that obtained from an equivalent oral dose.

Key words: Buccal muco-adhesion - Metoprolol tartarate (MT) - Bioavailability.

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient. However, peroral administration of drugs has disadvantages such as hepatic first-pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs, especially peptides and proteins. Drug buccal administration, on the other hand, is highly acceptable by patients and the oral mucosa (*Figure 1*) is relatively permeable with a rich blood supply [1]. Furthermore, oral transmucosal drug delivery avoids first-pass effect and provides for facile removal of the dosage form in case of need. Within the oral mucosal cavity, delivery of drugs is classified into three categories: 1) sublingual delivery, which is the systemic delivery of drugs through the mucosal membranes lining the floor of the mouth; 2) buccal delivery, which is drug administration through mucosal membranes lining the cheeks (buccal mucosa); and 3) local delivery, which is drug delivery into the oral cavity.

Two of the major limitations associated with buccal route of administration are the lack of dosage form retention at the site of absorption and the low flux, which results in low drug bioavailability. Consequently, bioadhesive polymers have extensively been employed in buccal drug delivery systems in the form of adhesive patches [2], adhesive films [3], adhesive tablets [4] and buccal gels [5]. For those drugs that penetrate the oral mucosal membranes slowly or incompletely, one strategy can be used: the co administration with a penetration enhancer [6]. Buccoadhesives have long been employed to improve the bioavailability of drugs undergoing significant hepatic first-pass metabolism [7, 8] and control the release of drugs from hydrophilic matrices [9].

Metoprolol tartarate (MT) is a synthetic, selective β1-adrenoreceptor blocking agent widely used in the management of essential hypertension and other cardiac disorders such as angina pectoris, arrhythmias and myocardial infarction (*Figure 2*). Oral metoprolol tartarate has low bioavailability, since from 50-60 % of the dose is subjected to extensive first-pass metabolism by the liver [10]. In addition, the drug has some unwanted gastrointestinal tract side effects such as diarrhea, nausea, gastric pain, constipation, flatulence, digestive tract disorders and heart burn [11].

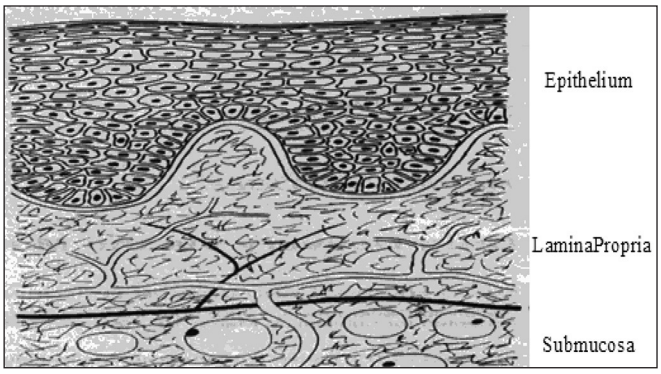

Figure 1 - Structure of the oral mucosa [1].

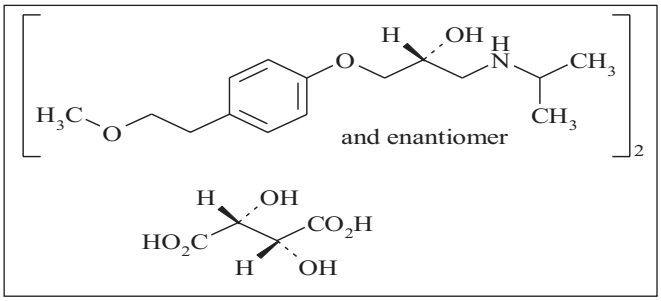

Figure 2 - Chemical structure of metoprolol tartarate [10].

The aim of this study was to develop bilayered buccoadhesive tablets of MT to avoid first-pass metabolism, to improve oral bioavailability and to control the release of the drug from the matrix

forming polymers, because the half life of the drug is low (3-4 h). The prepared buccoadhesive tablets were evaluated for the different physical properties and subjected to the following investigations: swelling index, bioadhesion force, surface pH, *in vitro* drug release studies and contact time to buccal mucosa. In addition, the pharmacological effects of MT on blood pressure and heart rate of healthy laboratory rabbits compared to commercial oral MT tablets, Betaloc, were carried out.

I. EXPERIMENTAL

1. Materials

Metoprolol tartarate was kindly donated by Sid. Co., for Pharmaceutical and Chemical Industry, Egypt. Carbopol 934P (CP 934P) and hydroxypropyl methylcellulose (HPMC) K4M were purchased from Morgan Chemical Co., Egypt. Sodium alginate (Na Alg.) was purchased from the General Chemical & Pharmaceutical Co., Ltd., United Kingdom. Ethylcellulose (EC) type N100 was bought from Hercules Inc., United States. Anhydrous lactose was bought from El Gomhouria Co., Cairo, Egypt. Porcine stomach mucin and Urethrane were purchased from Sigma Aldrich Chem., Germany. All other reagents and ingredients used were of analytical grade.

2. Methods

2.1. Preparation of bilayered buccal tablets (BBT) of MT

Bilayered buccal tablets of MT were prepared by direct compression techniques using different polymers of varying concentration (*Tables I and II*). The tablets were prepared using CP 934P, HPMC and sodium alginate as polymers. The drug-polymer combination was sieved through 120 μm sieve and was triturated for 15 min in a glass mortar to obtain homogeneous mixture. The tablets were compressed using a 13 mm flat circular punch on a single-station compression machine (Carver Inc., United States). Upper punch was raised and the backing layer of ethyl cellulose (EC) was placed on the above compact. Then 2 layers were compressed into a mucoadhesive belayed tablet with a total weight of 250 mg/tablet.

Table I - Formulation composition of BBT of MT containing single polymer.

Formula code	MT (mg)	CP 934P (mg)	HPMC (mg)	Na Alg (mg)	Lactose (mg)	EC (mg)	Total weight (mg)
F1	100	45	--	--	55	50	250
F2	100	60	--	--	40	50	250
F3	100	75	--	--	25	50	250
F4	100	90	--	--	10	50	250
F5	100	--	45	--	55	50	250
F6	100	--	60	--	40	50	250
F7	100	--	75	--	25	50	250
F8	100	--	90	--	10	50	250
F9	100	--	--	45	55	50	250
F10	100	--	--	60	40	50	250
F11	100	--	--	75	25	50	250
F12	100	--	--	90	10	50	250

Table II - Formulation composition of BBT of MT containing mixture of two polymers.

Formula code	MT (mg)	CP 934P (mg)	HPMC (mg)	Na Alg (mg)	Lactose (mg)	EC (mg)	Total weight (mg)	Polymer ratio
F13	100	45	45	--	10	50	250	1:1
F14	100	30	60	--	10	50	250	1:2
F15	100	60	30	--	10	50	250	2:1
F16	100	45	--	45	10	50	250	1:1
F17	100	30	--	60	10	50	250	1:2
F18	100	60	--	30	10	50	250	2:1
F19	100	--	45	45	10	50	250	1:1
F20	100	--	30	60	10	50	250	1:2
F21	100	--	60	30	10	50	250	2:1

2.2. Evaluation of BBT of metoprolol tartarate

The thickness, diameter, weight uniformity and drug-content uniformity were determined as per the procedure of British Pharmacopoeia [12].

2.3. Surface pH

BBT were allowed to swell for 5 h on the surface of an agar plate (1 % w/v) at room temperature in phosphate buffer pH 6.8 and surface pH of swollen BBT's was measured using pH paper [13].

2.4. Swelling index

Four buccal tablets were weighed individually (W1) and placed separately in 1 % (w/v) agar gel plates in phosphate buffer pH 6.8 with the core facing the gel surface and incubated at 37 ± 1 °C. After time intervals of 0.5, 1, 2, 3, 4 and 5 h, the tablet was removed from the Petri dish and excess surface water was removed carefully with blotting paper (*Figures 3 and 4*). The swollen tablet was then reweighed (W2) and the swelling index were calculated using the formula given in the following equation [14]:

$$\text{Swelling index} = [(W2 - W1) \div W1] \times 100 \qquad \textbf{Eq. 1}$$

where W1 is the initial weight of the tablet and W2 the final weight of the tablet.

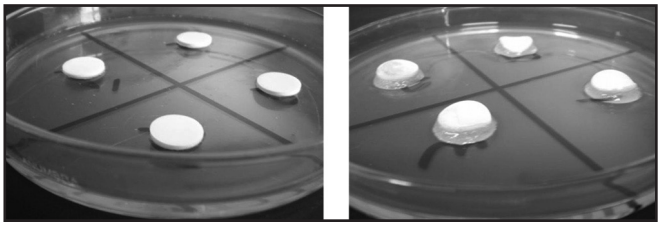

Figure 3 - Photographs of BBT during swelling studies using agar-gel plate method: left, at zero time and right, after 5 h.

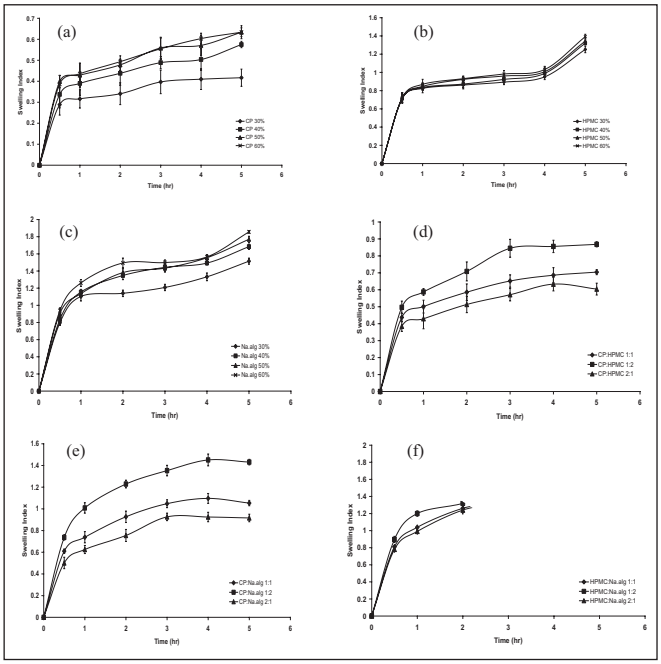

Figure 4 - Swelling index of metoprolol tartarate bucco-adhesive tablets containing different concentrations and different ratios of polymers using agar-gel plate method in phosphate buffer pH 6.8: (a) CP 934P, (b) HPMC,(c) Na Alg, (d) CP 934P and HPMC, (e) CP 934P and Na Alg, (f) HPMC and Na Alg.