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RESEARCH ARTICLE

Development of amitriptyline buccoadhesive tablets for management of pain in dental procedures

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Abstract

Administration of lidocaine and nonsteroidal anti-inflammatory drugs (NSAIDs) as a routine procedure for relief of dental pains by and large is restricted due to some side effects. Amitriptyline (AM) has long been known to exert analgesic activity as a result of blocking the Na^+ channels. The objective of the present investigation was to prepare suitable buccoadhesive tablets using cellulose derivatives in order to obtain new formulations containing AM to provide local analgesic action. The tablets were evaluated in terms of physical characteristics, mucoadhesion performance, drug release, and *in vivo* assessment of analgesic efficiency. Tablets containing higher amounts of high-viscosity hydroxypropylmethyl cellulose (HPMC-K4M) significantly demonstrated enhanced adhesive performances. On the other hand, presence of sodium carboxymethyl cellulose (NaCMC) in formulations including HPMC of lower-viscosity grade (HPMC-E5LV) provided further adhesiveness by increase in viscosity. Rate of drug release from HPMC-E5LV tablets was significantly higher than the HPMC-K4M tablets. Kinetically, patterns of AM release from the tablets fitted best to Higuchi model. Moreover, in a randomized double-blind trial, analgesic efficiency of the prepared bioadhesive tablets was revealed to be satisfactory. It is suggested that applying the topical AM mucoadhesive tablet containing the low amount of drug is a safe and promising alternative to relief the pain in the buccal region.

Keywords: Amitriptyline, mucoadhesive tablets, bioadhesive polymers, buccal analgesia, in vivo study

Introduction

The tricyclic antidepressant amitriptyline (AM) is commonly used in management of a variety of chronic and neuropathic pain syndromes as well as inflammatory illnesses like fibromyalgia, chronic fatigue syndrome, migraine, irritable bowel syndrome, and atypical facial pain for decades[1,2]. The analgesic effect of tricyclic antidepressant medicines seems unrelated to their antidepressant action as the doses used for analgesia are lower than those considered effective in the treatment of depression[1–7]. The analgesic effect of AM is almost certainly due to blocking of Na^+ channels[8]. Further experimentation has shown that AM is indeed a potent local anesthetic with longer effect compared with bupivacaine[9]. Gerner et al.[10] showed local anesthetic properties of AM *in vivo* and *in vitro*. Additionally, AM has administrated orally in order to relief atypical facial pain[11].

Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity to affect local or systemic pharmacological actions[12]. Among the various transmucosal routes, buccal mucosa has excellent accessibility that offers painless administration, easy drug withdrawal, fast onset of action, patient compliance, and attractive alternative for noninvasive delivery of some drugs[13–20]. The buccal region of the oral cavity is an attractive target for administration of the drug of choice[21]. Local delivery in the oral cavity has had particular applications in the treatment of toothache, periodontal diseases, and bacterial infections[22]. Many dosage forms

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such as toothpastes, mouthwashes, lozenges, gels, chewing gums, lollipops, films, patches, and tablets have developed for topical oral administration[19,23]. The conventional formulations often exhibit some drawbacks as they do not achieve a prolonged administration of actives components. Significant fraction of administrated dose may not be available for mucosal absorption due to wash-off process, constant flow of saliva, and the mobility of the involved tissues[16,24]. To optimize drug delivery via this route, the use of controlled release formulation with mucoadhesive properties is desirable. With the right dosage form, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation[25]. Suitable adhesion strength, adaptability to the mucosa, with no irritation and excessive salivation in buccal cavity are the majors to obtain successful buccal tablets formulation[25,26]. Formation of noncovalent bonds such as hydrogen bonds and ionic interactions or physical entanglements between the mucus gel layer and polymers provide mucoadhesiveness by mucoadhesive polymers[27,28].

HPMC and NaCMC are suitable polymers for use in buccoadhesive formulations in view of the fact that they could uptake the water, stick to the oral mucosa, and control the drug release. These bioadhesive polymers could also resist salivation, tongue movement, and swallowing for a significant period of time[29]. HPMC has been applied to formulate buccoadhesives of drugs like metronidazole, benzydamine, carvedilol, and so on[21,26]. The buccoadhesives of some drugs like metronidazole, benzydamine, prednisolone, and pindolol have been prepared by means of NaCMC as well[26,30,31]. Using both HPMC and NaCMC in the bioadhesive formulations could minimize the burst effect of HPMC-based systems due to the formation of a gel layer on the surface of the tablet[32]. These polymers have been applied together in the bioadhesive tablets of clotrimazole and pindolol[30,32].

The present study deals with preparing and developing of AM mucoadhesive tablets applying HPMC and NaCMC intended for the topical administration in the oral cavity. Providing local anesthetic effects of AM for short-term dental procedure, it possibly will relieve the pains associated with tooth, periodontal pockets, gingival, or other part of oral cavity. This can provide patients with noninvasive, easy to use, and non-intimidating option. Moreover, it has advantages over the use of lidocaine and nonsteroidal anti-inflammatory drugs (NSAIDs) due to minimizing the systemic side effects. To the best of our knowledge, AM has not administered topically in order to relief dental pains. We anticipated the dosage form would stick to the human gingival, affording an adequate rapid action. Several types of polymeric materials have been used in order to prepare such a system and most of them are hydrophilic macromolecules.

Materials and methods

Materials

AM hydrochloride (Dipharma, Italy), hydroxypropylmethyl cellulose (HPMC-K4M, E5LV; Colorcon Ltd., UK), sodium carboxymethyl cellulose (NaCMC, viscosity 2% aqueous solution 1200 cps; Colorcon Ltd.), lactose monohydrate, magnesium stearate, potassium hydrogen phosphate, and sodium hydroxide (Merck, Darmstadt, Germany) white wax B.P. (Thornton and Ross, Hudders Field, UK) were used in this study.

Preparation of buccoadhesive tablets

Tablets were prepared using different combinations of polymers as shown in Table 1. Various components with 10 mg of drug (AM) in each formula were mixed homogeneously and then were compressed by 8-mm diameter die using single punch machine (Erweka, Frankfurt, Germany). The compression pressure and dwell time were 19.6 kg/cm^2 and 30 sec, respectively. Lactose monohydrate used as filler in the formulations.

Physical test of mucoadhesive tablets

Tablets resistance to chipping and surface abrasion was determined by tumbling in a rotating cylinder. The percentage weight loss of 10 tablets after tumbling (25 rpm, 4 min) was measured as friability of the tablets. Hardness test for the tablets was performed using ERWEKA hardness tester (Gmbtt TAR 20) for each tablet ($n = 5$). Thickness of the tablets was determined using a digital micrometer (Mitutoyo, Tokyo, Japan). Disintegration test was carried out on the formulations with acceptable hardness, friability, and mucoadhesive strength values.

Table 1. Different formulations of buccal tablets with their respective compositions.

Formulation	AM[a] (mg)	HPMC-K4M (mg)	HPMC-E5LV (mg)	NaCMC (mg)	MgS[b] (mg)	Lactose (mg)
A	10	—	90	—	0.1	—
B	10	—	80	—	0.1	10
C	10	—	70	10	0.1	10
D	10	—	60	20	0.1	10
E	10	90	—	—	0.1	—
F	10	80	—	10	0.1	—
G	10	70	—	20	0.1	—
H	10	60	—	30	0.1	—

[a]AM: Amitriptyline.
[b]MgS: Magnesium stearate.

Ex vivo mucoadhesive strength

The mucoadhesive performance of the buccal tablets was evaluated using a modified balance method employing fresh rabbit's small intestine tissues[15]. Bioadhesive studies were carried out in triplicate and average bioadhesive strength was determined. Strength of the tablets to detach from the tissue was used to assess the mucoadhesive performance (Table 2). The fresh-cut rabbit's small intestine tissues were fixed in the internal area of a left side beaker of balance using cyanoacrylate glue. Tablet was attached to the tissue by applying light force with fingertip for 20 sec and then buffer was added into the beaker. The beaker was kept at 37°C and was filled with phosphate buffer (pH = 6). Water was added gradually to the right side beaker of the balance till the tablet detached. The amount of buffer used to separate the tablet from tissue is an indicator of the adhesion strength, which reveals mucoadhesive performance of the tablets.

In vitro drug-release study and release kinetics

The *in vitro* drug-release studies were conducted using the United State Pharmacopoeia (USP) paddle method (Erweka, DT 6R; Heusenstamm, Germany). The tablets were placed in 900 mL phosphate buffer and maintained at 37 ± 0.5°C for 3 h at pH 6. The stirring rate was 75 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper, the samples were subjected to spectrophotometric analysis (Spectrophotometer UV mini 1240; Schimadzu, Japan), and concentration of the AM was measured spectrophotometrically. Two model independent parameters (i.e. dissolution efficiency up to 2.5 h, $DE_{2.5}$%; and the amount of released drug after 60 min, $Q_{60\ min}$) were employed to compare the drug-release rate from different formulations (Table 3).

The dissolution efficiency (DE_t) of a pharmaceutical dosage form is defined as the area under the dissolution curve up to the time, *t*, expressed as the percentage of the area of the rectangle and is calculated using the following equation[33]:

$$DE_t = \frac{\int_0^t y dt}{y_{100} t} \times 100\%$$

where *y* is the percent of drug dissolved at time *t*.

To clarify the mechanism of release, the *in vitro* release profiles were fitted to five famous kinetic models: zero order, first order, Higuchi, Weibull, and power law (Pepas). The accuracy and prediction ability of the models were compared by calculation of squared correlation coefficients (RSQ) and absolute percent error (E) for each set.

Assessment of buccal analgesic efficacy of the tablets (in vivo)

Efficiency of the AM-loaded buccoadhesive tablets on pain relief was evaluated on 25 healthy volunteers (females, age range 20–45). Ethics Committee of Tehran University of Medical Sciences approved this study and informed consent was obtained from volunteers. AM or a placebo buccoadhesive tablet was administered to volunteers, as a single dose in a randomized double-blind trial. The tablet was inserted by applying a light force with finger tip for 20 sec, in buccal region at the upper lateral tooth gum. The tablet was removed after 15 min and the treated site was wiped clean to shot the region using a 27G sterile syringe. Severity of the shot-induced pain was evaluated by using the visual analog scale (VAS)[11,34]. Volunteers were asked to record their pain at 15, 20, 25, 30, 35, 45, 50, and 55 min after the syringe shot. They were instructed to record the associated pain on a 10-point scale (0 = no pain, up to 10 = intolerable pain). Additionally, any possible irritation or excessive sensitivity in the volunteers was assessed to study the safety of the formulations.

Statistical analysis

The statistical analyses were conducted via ANOVA and Tukey's multiple range tests to identify significant differences among mean values of variables. Data were represented as mean values ± SD (standard deviation). A *P*-value <0.05 was assumed for the statistically significant differences.

Results and discussion

Effects of formulation variables on hardness and friability of the tablets

The physical characteristics as well as the bioadhesive performance of the formulated tablets have been summarized in Table 2. Tablets were 8-mm flat-faced discs with

Table 2. Characteristics of different mucoadhesive tablets containing 10 mg of amitriptyline.

Formulation code	Thickness (mm)	Weight (g)	Hardness (kg)	Friability (%)	Mucoadhesive performance (g/mm²)
A	1.68 ± 0.13	0.095 ± 0.0015	8.64 ± 0.97	0.55 ± 0.17	1.60 ± 0.020
B	1.71 ± 0.23	0.103 ± 0.0012	8.36 ± 1.46	0.99 ± 0.18	1.60 ± 0.034
C	1.82 ± 0.10	0.104 ± 0.0015	6.66 ± 2.25	0.62 ± 0.10	1.70 ± 0.055
D	1.69 ± 0.07	0.098 ± 0.0013	7.26 ± 0.64	0.99 ± 0.18	1.93 ± 0.011
E	1.72 ± 0.043	0.096 ± 0.0012	10.52 ± 1.76	0.68 ± 0.18	1.60 ± 0.040
F	1.78 ± 0.074	0.096 ± 0.0014	9.48 ± 0.59	0.79 ± 0.20	1.60 ± 0.020
G	1.69 ± 0.061	0.097 ± 0.0012	8.38 ± 1.88	0.87 ± 0.13	1.40 ± 0.000
H	1.70 ± 0.230	0.097 ± 0.0010	6.80 ± 0.63	0.99 ± 0.14	1.40 ± 0.020

the mean thickness of 1.7 mm and their mean weight was 98 mg. More or less, all the formulations exhibited <1% friability. Formulations containing HPMC-K4M demonstrated relatively higher hardness and lower friability values compared with the ones containing HPMC-E5LV. Additionally, as it is apparent from Table 2, an increase in the amount of NaCMC decreased hardness and amplified friability of the tablets.

Effects of formulation variables on mucoadhesive performance of the tablets

Among several factors influencing mucoadhesive properties of a tablet, viscosity, hydrogen bonding capacity, and concentration of a polymer, as well as other environmental factors have a notable effect on adhesion forces[20,24,31]. Hence, it is possible to design tablets with suitable mucoadhesive properties via adjusting some of these parameters.

Previous studies in solid bioadhesive systems showed increase in amounts of polymers resulted in superior potency of mucoadhesion[24]. The data of mucoadhesive performance in Table 2 related to HPMC-K4M are somewhat in accordance with that finding. Incorporation of NaCMC to the HPMC-K4M containing formulations did not have noteworthy effect on the adhesion strengths, whereas formulations containing HPMC-E5LV and NaCMC slightly enhanced the mucoadhesive performance. It is evoked that further adhesiveness is caused by growth in viscosity in formulations with HPMC-E5LV followed by adding NaCMC.

Our findings revealed that variation in size, weight, and thickness of the tablets seemed to have no remarkable effect on their bioadhesive performance and physical properties.

In vitro drug release and kinetics

Dissolution test is a frequently used quality-control method to evaluate drug release from drug dosage forms. The drug-release profiles were presented by plotting the amount of AM released against time for the formulations with suitable performance of bioadhesiveness. According to the observations during the process, tablets did not go through disintegration in <60 min and they did preserve their external appearance until 150 min. Rate of drug release from HPMC-E5LV tablets was significantly higher than the HPMC-K4M tablets with $DE_{2.5}$% within 48–87% for the former and 36–43% for the latter (Figures 1 and 2, and Table 3). The $Q_{60\ min}$ values for the HPMC-E5LV and HPMC-K4M tablets were in the range of 42–99% and 24–44%, respectively (Table 3). Slower rate of drug release from HPMC-K4M tablets could be due to the higher viscosity of the HPMC-K4M[35,36].

Table 3. Release model independent parameters for different formulations.

Formulation code	A	B	C	D	E	F	G	H
$DE_{2.5}$%	48.2	63.7	60.8	87.2	36.8	43.3	42.9	26.8
$Q_{60\ min}$	42	67	53	99	32	39	44	24

$DE_{2.5}$% and $Q_{60\ min}$ exhibit dissolution efficiency up to 2.5 h and the amount of released drug after 60 min, respectively.

Considering RSQ and *E* values, the drug-release data nearly in all formulations fitted best to Higuchi model. The corresponding values of RSQ and *E* were above 0.95% and <10%, respectively. The model describes drug-release process dependent on square root of time based on the Fick's first law of diffusion[18]. In brief, different properties of the tablets resulted from the varieties in polymers, and concentration of the materials applied in the formulations might have contributed to the mentioned differences in patterns of drug release.

In order to provide an effective analgesic action from the AM-loaded tablets, ideally it would be desirable to rapid drug release in the initial stages to give an adequate and prompt onset of analgesic action. After taking into consideration the drug release, bioadhesive performance, and other physical properties of the

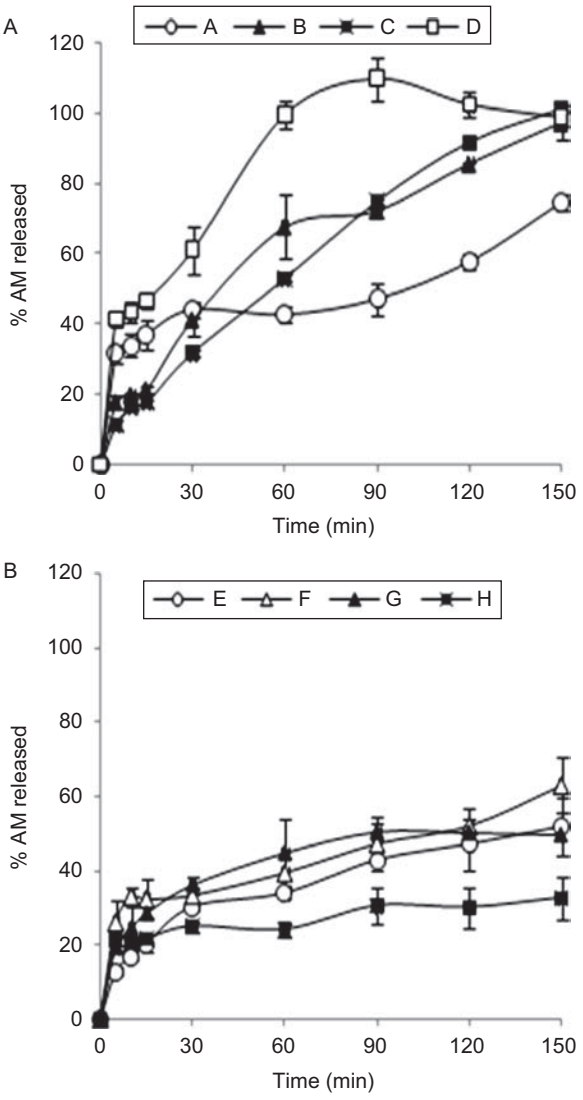

Figure 1. Release patterns of amitriptyline (AM) from different formulations: (A) HPMC-E5LV tablets and (B) HPMC-K4M tablets.

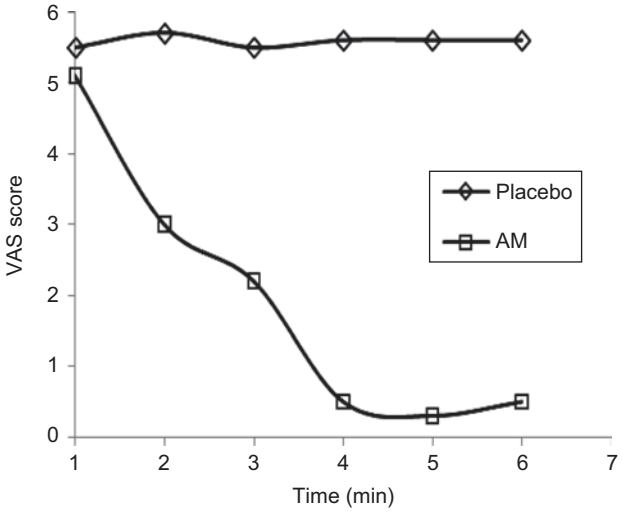

Figure 2. Effect of placebo- and amitriptyline (AM)-loaded tablets in management of shot-induced pain in volunteers.

tablets, Formulation D (Table 1) appeared to be the most suitable one to be used in the next part of *in vivo* study.

Buccal analgesic efficiency

Administration of lidocaine and NSAIDs as a routine procedure for relief of dental pains may be restricted because of some side effects. Alternatively, AM is a potent local anesthetic with longer effect compared with bupivacaine[9]. The analgesic effect of AM is most likely caused by blocking of Na^+ channels[8]. So therefore, we aimed to evaluate the analgesic effect of AM mucoadhesive tablet as a topical dosage form.

Figure 2 exhibits the distribution of pain scores in both placebo- and AM-treated volunteers. Analysis of variance on the results showed a notable difference between placebo and active formulations. The VAS scores for placebo- and AM-loaded buccoadhesive tablet-treated groups were about 5–6 and 1–5, respectively. In the AM-treated group, the mean onset of drug action was 25 ± 9.5 min after application of the tablet and duration of the analgesia was about 20 ± 6.8 min, whereas among the placebo-treated volunteers no analgesic effect was detected (data not shown). In a word, all of the volunteers exhibited a satisfactory buccal analgesia, indicating the noteworthy efficiency of the prepared AM-loaded bioadhesive tablets.

Conclusion

The study elucidates that the type and amount of agents used to prepare the bioadhesive tablets had a profound effect on characterization of the tablets. Rapid rate of drug release and a good mucoadhesive performance of AM-loaded tablets would be of value in achieving local pain relief. Likewise, the results obtained from clinical responses in volunteers were in accordance with the findings of *in vitro* evaluations. Overall, the present study suggests that AM-loaded buccoadhesive tablets are remarkably appealing candidates in alleviation of pain in dental cases, since they provide an excellent mucoadhesive performance and an adequate rate of drug release to establish desired local analgesia in buccal area.

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Declaration of interest

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