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Research Article

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Influence of Compression Force on The Behavior of Mucoadhesive Buccal Tablets

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Abstract. The purpose of this research was to study the compression force influence on polymers, tablet behavior and drug release rate. Several tablet batches were produced by varying the compression force and by using hydroxyethyl cellulose (HEC) and Carbopol 940 in the 1:1 ratio as matrix forming polymers. All batches were characterized by DSC and X-ray analyses and in terms of swelling, *ex vivo* and *in vivo* mucoadhesive time, *ex vivo* mucoadhesion force, and *in vitro* and *in vivo* release. No significant excipient–excipient or excipient–drug interactions were observed in any of the batches. All the tablets hydrated quickly and their high hydration percentage showed that the compression forces used did not remarkably affect the water penetration and the polymeric chain stretching. Mucoadhesion performances and drug release were mainly influenced by compression force; its increase produced higher *ex vivo* and *in vivo* mucoadhesion and the *in vitro* and *in vivo* drug releases were seen to decrease with the increase of the compression force. However tablets fabricated by using the lowest compression force showed the best *in vivo* mucoadhesive time and hydrated faster when compared to the others. Tablets 4 and 5, prepared with the highest forces, caused pain during *in vivo* application and gave rise to irritation needing to be detached by the volunteers while tablet 1, prepared with the lowest force, gave the best results because it was able to produce the highest drug salivary concentration and no pain. All tablets exhibited an anomalous release mechanism.

KEY WORDS: buccal delivery; compression force; *in vitro* release; mucoadhesive tablets; physico-chemical interaction studies.

INTRODUCTION

Acute necrotizing ulcerative gingivitis (ANUG) is an acute infection due to invasion of soft tissue by ubiquitous organisms namely *Prevotella intermedia*, alphahemolytic streptococci, *Actinomyces* species or oral spirochetes. ANUG is also caused by inadequate oral hygiene and plaque removal, blood dyscrasias and situations of host defense lowering. The most common problems are bleeding gums in response to minimal local trauma, local pain, alterations in taste and foul breath. Additionally fever, halitosis, marked gingival edema and ulceration, especially in the interdental papillae, have been reported as well. ANUG may result in accelerated destruction of affected tissue, as well as local or systemic spread of infection (1). The clinical treatment of this pathology involves oral hygiene and mechanical and chemical oral plaque removal. This gum disease usually requires a thorough cleaning of teeth and tooth roots, namely "root planing," that is the removal of plaque and tartar from exposed root surfaces, and "sub gingival curettage," that is the removal of the surface of the inflamed layer of gum tissue. Both of these procedures are performed by a dentist and are usually accompanied by the use of oral antimicrobials, such as metronidazole (MET) and amoxycillin. MET, a nitroimidazole anti-infective drug, is today mainly employed because it is particularly effective in the treatment of infections caused by anaerobic bacteria. MET activity is linked to the nitro group that, in anaerobic conditions, is chemically reduced and the derivatives (free radicals) are responsible for disrupting the DNA helical structure, thus inhibiting nucleic acid synthesis (1). In this regard, the use of tablets containing 250 mg of MET are the best approach currently available and the therapeutic regimen consists of one every 8 h (750 mg/day) administered over a 5 day treatment period (1). The oral therapy produces systemic exposure and may lead to hypersensitivity, gastrointestinal intolerance and development of bacterial resistance (2,3).

However it has been reported that this kind of administration is not completely effective in maintaining therapeutic concentrations at the site of action (4). A solution to this problem could be the design of mucoadhesive sustained release products capable of retaining the device in the oral cavity so it keeps the drug concentration within the therapeutic range, in order to require less frequent administrations.

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Therefore, mucoadhesive systems may represent valid alternatives in light of their easiness to use because they can be applied and removed directly by patients (5–8).

The strategy for designing mucoadhesive tablets is based on the use of polymers with suitable physical and chemical properties, such as polyacrylic acid and cellulose derivatives. Recently new mucoadhesive systems, suitable to treat buccal affections, were developed (9,10) and mucoadhesive tablets, containing MET, were described. These tablets were prepared by using different mixtures of cellulose and polyacrylic derivatives. The best results were achieved when hydroxyethylcellulose (HEC) and Carbopol 940 in a 1:1 ratio, as mucoadhesive polymers, and 20 mg MET were used (10). This kind of tablet formulation, although promising, needs further investigation. For this reason the aim of the present work was to evaluate the influence of compression forces on polymer, tablet behavior, and drug release rate. For this purpose, non-medicated tablets and 20 mg medicated tablets, at five different compression forces (1×10^3, 3×10^3, 5×10^3, 7×10^3, and 9×10^3 kg), were prepared and characterized by differential scanning calorimetry, X-ray diffraction, and in terms of swelling properties, *ex vivo* and *in vivo* mucoadhesive times, *ex vivo* mucoadhesion force, and *in vitro* and *in vivo* release.

MATERIALS AND METHODS

Materials

HEC (Natrosol-250HHX) was obtained by Aqualon (Hercules incorporated, USA), Carbomer 940 was purchased by Galeno (Italy). Metronidazole was obtained by Farchemia (Italy). Pig buccal mucosa (obtained from Large White pigs weighing ~165 to 175 kg) was furnished by the veterinary service of USL N 1 of Umbria (Italy) from a slaughterhouse and used within 12 h of pig euthanasia. Simulated saliva solution (pH 6.75) was prepared with 2.38 g of Na_2HPO_4, 0.19 g KH_2PO_4 and 8.00 g NaCl in 1,000 ml of distilled water (11).

Manufacturing of Non-medicated Tablets

A physical blend of 200 mg of HEC and Carbopol 940 was homogeneously mixed with mortar and pestle and then the mixture was compressed for 30 s using a 13 mm diameter die on an infra-red hydraulic press (Perkin Elmer, England) using five different compression forces (1×10^3, 3×10^3, 5×10^3, 7×10^3 and 9×10^3 kg) (12). Tablets were divided into five groups according to the compression force. All the prepared disks had 13 mm diameter and their thickness was measured by a micrometer (Borletti, Italy; Table I).

Physical Characterization

Crushing Strength

The crushing strength was analyzed, according to the Italian Farmacopea Ufficiale XI Ed. (F.U.XI) using a hardness tester (instrumented uniaxial press ERWEKA TBH 220). Data were reported as an average of ten measurements and the error expressed as S.D.

Friability

Tablet friability was determined according to FU XI by submitting 20 previously weighed tablets to falling shocks for 4 min in an Erweka friabilator (TA 200), set at 25 rev/min After 4 min, the tablets were reweighed and the percentage friability was calculated.

Physico-chemical Interaction Studies

Differential Scanning Calorimetry (DSC) studies

DSC thermograms were performed using an automatic thermal analyzer (Mettler Toledo DSC821e). Temperature calibrations were performed with indium as a standard. Sealed and holed aluminum pans were used in the experiments for all samples and an empty pan, prepared in the same way was used as a reference. Samples of 3–6 mg were weighted directly into the aluminum pans and the thermal analyses were carried out using two different methods:

1. Two consecutive heating ramps from 15 to 160 °C at 10 °C/min scale up rate; cooling in between the two ramps was performed at 5 °C/min rate
2. one heating ramp from 15°C to 500°C at 10°C/min rate.

Before the analysis, all samples were vacuum dried for 24 h.

X-ray Diffraction

X-ray powder diffraction pattern (XRPD) was performed with a PW 1710 Philips diffractometer (Lelyweg, The Netherland), using Ni-filtered, Cu Kα radiation, step scanning method (step size 0.03°) and elaborated with PC-APD program.

Swelling Studies

The swelling properties and the erosion characteristics of tablets were evaluated by determining % of hydration and

Table I. Physical Characteristics of the Tablets

Tablet	Compression Force (kg)	Thickness (mm)±SD (n=5)	Crushing Strength Force (N)±SD (n=10)	Friability (%)±SD (n=20)
1	1×10^3	1.26±0.007	103.9±5.1	0.0247±0.0113
2	3×10^3	1.25±0.007	107.1±7.9	0.0484±0.0221
3	5×10^3	1.24±0.006	124.8±13.9	0.0974±0.0155
4	7×10^3	1.22±0.008	97.1±9.7	0.1221±0.0316
5	9×10^3	1.20±0.005	108.8±2.5	0.0740±0.0204

matrix erosion, or dissolution (DS), as previously reported (10) using simulated saliva fluid (11) at pH 6.75. The experiments were performed in triplicate and the data were calculated using the following Eqs. 1 and 2:

$$\% \text{ of Hydration } = \frac{(W2 - W1)}{W2} \times 100 \quad (1)$$

$$DS = \frac{W1 - W3}{W1} \times 100 \quad (2)$$

where W1 is the dry tablet weight, W2 is the weight after immersion in the saliva fluid for predetermined time intervals (0.5, 1, 2, 3, 6, 9, 12 h), and W3 is the swollen tablet weight after drying at 60 °C for 24 h in an oven and desiccation ($CaCl_2$ desiccator) for 48 h (in triplicate).

Ex Vivo Mucoadhesion Time

The *ex vivo* mucoadhesion time was performed (in triplicate) after application of tablets on fresh cut porcine buccal mucosa (13). The porcine buccal tissues, used within 12 h of pig euthanasia, were pasted to the internal side of the beaker with cyanoacrylate glue. Each tablet side was wetted with 50 µl of simulated saliva fluid and attached to the porcine buccal tissues by applying a light force with a finger tip for 20 s. The beaker was filled with 800 ml of simulated saliva fluid, kept at 37 °C and, after 2 min, a stirring rate of 150 rpm was applied to simulate the bsuccal cavity. Tablet behavior was monitored until complete detachment.

In Vivo Mucoadhesive Performance of Non Medicated Tablets

In vivo studies were performed (in triplicate) on five healthy volunteers who applied the buccal tablets themselves on the left or right upper gums in order to assess: (1) residence time, (2) organoleptic characteristics, (3) fragment loss, (4) possible irritation, (5) swelling and saliva level variations. Each tablet was placed on the internal gum by pressing lightly with a fingertip for 20 s.

Ex Vivo Mucoadhesion Force

The *ex vivo* adhesion strength was measured in terms of the force needed to pull out a tablet from porcine buccal

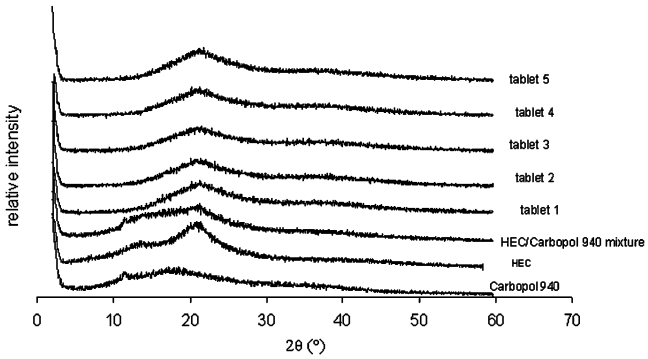

Fig. 1. X-ray diffraction pattern of polymers and not medicated tablets

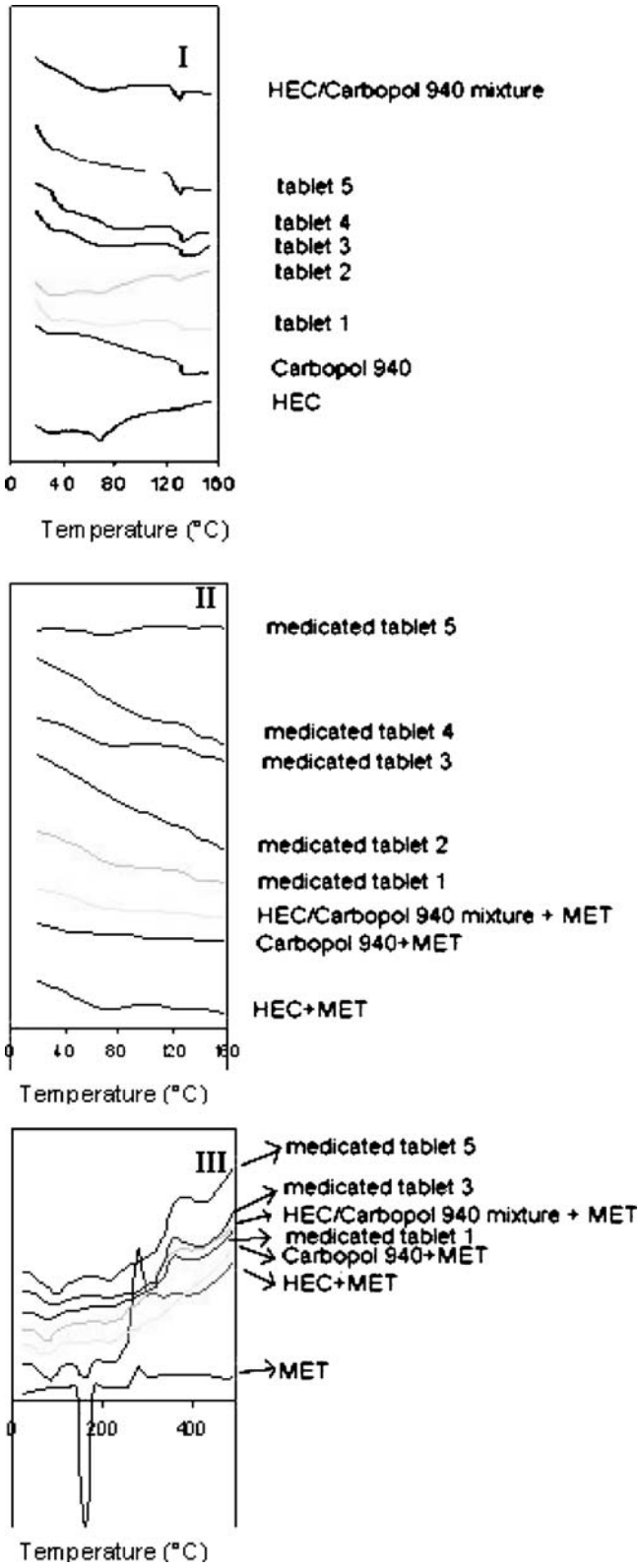

Fig. 2. DSC thermograms (second heating scan) of: polymers and empty tablets (*I*), polymers and MET and drug loaded tablets with method A (*II*) and polymers and MET and some drug loaded tablets with method B (*III*)

mucosa. It was assessed, as previously reported (10), by a dynamometer (Lehrmittelbau, Bonn, Germany) using the above cited porcine mucosa. Data were expressed as an average of three measurements (n=3) and the confidence interval was also determined at 0.05 significance level.

In Vitro Release Study

Tablets were tested, as previously reported (10), using a modified basket apparatus (F.U.XI) properly modified and simulated saliva as dissolution medium. MET concentration in each sample was determined by using an UV spectrophotometer (JASCO Ltd, UK V-520) at λ_{max}=320.0 nm, according to previously determined calibration curve (y=9312.2x−0.0071, r=0.9998) and using simulated saliva medium as blank. The percentage released at each time point was expressed as a fraction of the total amount of MET in the tablet. The MET concentration was reported as an average of three determinations and the error expressed as S.D.

In Vivo Release Study

In vivo release studies were performed by applying tablets, after the approval of the Ethic Committee of the Aziende Sanitarie dell'Umbria (CEAS), in accordance with the Declarations of Helsinki and Tokyo, to five healthy volunteers with their written consent. The volunteers were instructed to press the tablets against their gums, without moistening them before application, for 20 s. No food or water were allowed half an hour prior to the beginning of the study. Fasting was strictly observed during the experiment. Drinking was allowed *ad libitum* 30 min after tablet application and swallowing saliva was allowed; no drinking was allowed 10 min before the collection of salivary samples (14). Care was taken to avoid the tongue to come in contact with the tablets 10 min before sampling in order to avoid abnormally high drug levels (15). The tablet behavior was monitored in order to evaluate: tablet residence time, possible local irritation, fragment loss, bad taste and dry mouth or excessive salivation. Each volunteer tested each tablet formulation in triplicate. Saliva samples were collected prior to tablet application. At predetermined times (5, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 420, 480, 540, 600, 660 and 720 min) saliva samples (ca. 2 ml) were collected and each sample was filtered through a Millipore cellulose acetate membrane filter (0.45 μm) and then the filtrate (1 ml) was diluted with 1 ml of simulated saliva fluid. MET concentration in each sample was determined by means of UV spectrophotometry at λ_{max}=320.0 nm according to previously determined calibration curve and using saliva (filtered and diluted 1:2 with simulated saliva fluid) as blank.

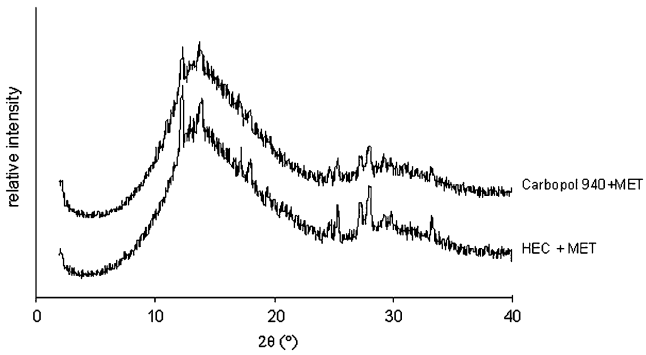

Fig. 3. X-Ray diffraction pattern of MET and polymers physical mixture

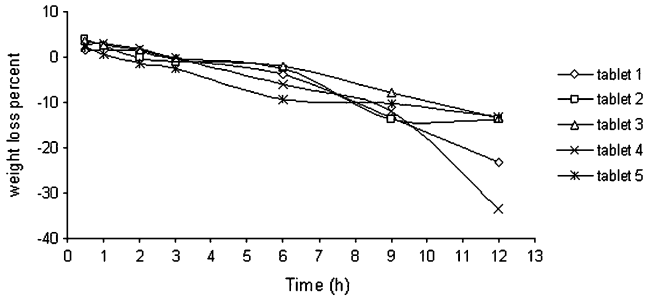

Fig. 4. DS or matrix erosion of the tablets

Drug Release Mechanism

The in vitro release profiles were fitted (regression analysis) according to the Eq. 3 (16).

$$M_t/M_\infty = kt^n \tag{3}$$

where M_t/M_∞ is the fractional release of drug at time t, k is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the diffusional coefficient, indicative of the drug release mechanism.

RESULT AND DISCUSSION

Physical Characterization

Tablet characteristics (thickness, friability and crushing strength) related to compression force are reported in Table I. For all the compression forces used, the thickness variation was minimal, and it decreased when compression force increased. In regarded to the hardness test, all the tablets showed similar crushing strength (ca. 100 N), but clear correlations could not be inferred by the compression force.

The tablet friability behaved unexpectedly. In fact, the increase of the compression force caused higher friability in all cases, except for the tablet at the maximum compression force (tablet 5). However, friability data were always very low and often <1%, that in this case represents a desirable value. The friability and hardness data show that tablet formulations were resistant and stable and all the compression forces used were suitable for their fabrication.

Chemical Interaction Studies

This is an important step during the development of a new formulation because excipient–excipient or excipient–drug interactions in the solid state can cause chemical and physical changes that may produce a different therapeutic response.

In the present study X-rays and DSC were used as a tool to evaluate chemical and physical stability of this new solid dosage form. X-ray diffraction patterns of HEC and Carbopol

Table II. Mucoadhesive Characteristics of the Tablets

Tablet	*Ex vivo* Mucoadhesive Time (h)±SD (n=3)	*In vivo* Mucoadhesive Time (h)±SD (n=3)	*Ex vivo* Mucoadhesive Force (N)±SD (n=3)
1	40±0.15	24±0.35	0.57±0.07
2	40±0.20	24±0.15	0.90±0.07
3	48±0.75	24±0.25	1.17±0.08
4	48±0.15	12[a]±0.25	1.70±0.04
5	40±0.30	16[a]±0.35	1.75±0.08

[a] Removed by patient for irritation and pain

940 (Fig. 1) did not show any characteristic peaks and this indicates that the structure is amorphous; only a little crystalline structure lasted upon physical mixing and compression of the two polymers. Furthermore, the different compression forces did not cause any differences in the tablets.

DSC studies were performed in order to observe the glass transition (Tg) temperature of the two amorphous polymers. At this temperature the transition from glassy state to rubbery state was observed and this could change their chemico-physical properties. The DSC thermograms of the HEC, Carbopol 940, the physical blend (ratio 1:1), and of non medicated tablets are reported (method A) in Fig. 2 (I). During the first heating scan, water was eliminated (data not reported). In the second heating scan, the HEC Tg was observed around 70 °C (17) and the Carbopol Tg was recorded around 130 °C (18,19). These values were kept even in the physical blend and in the tablets without alterations in agreement with the results obtained from the X-ray analysis. Figure 2(II) shows the polymer second heating scans (Method A) in the presence of MET (HEC: Carbopol 940:MET proportion 1:1:0.2) and medicated tablets. MET did not cause any alteration of polymer Tg proving a lack of interaction between the polymer matrix and the drug. Medicated tablet thermal profiles were very similar to those of non medicated tablets, but for tablet 5 (fabricated using the highest compression force) the Tg was less visible. In Fig. 2 (III), thermal analyses of the same samples (only tablets 1, 3 and 5), performed using the B method, are shown. MET thermal profile shows an endothermic peak due to drug fusion at 161 °C (ΔH=−106 J/g) (20). The profile of HEC–MET physical blend had a broad endothermic peak between 60 and 100 °C, due to evaporation of water overlapping the HEC Tg transition, whereas the endothermic peak around 161 °C, due to MET melting (20) with ΔH=−37.5 J/g of drug, means that MET keeps only a little of its crystalline form. In the Carbopol 940–MET physical blend profile, the endothermic peak of the melting point is not visible because of the higher interactions between them and MET has almost lost its crystalline structure. The melting point is not visible in the other thermal profiles. X-ray of HEC–MET and Carbopol 940–MET physical mixtures confirmed the DSC data (Fig. 3).

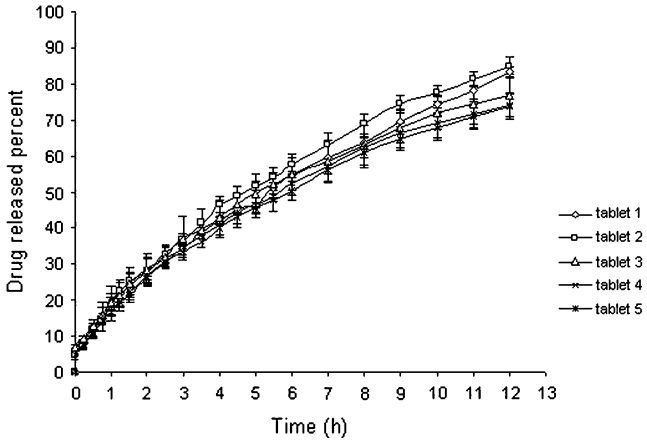

Fig. 5. *In vitro* drug release profile (n=3; α=0.05)

Swelling Studies

The hydration studies (data not shown) demonstrated that all tablets were characterized by very similar hydration profiles. They hydrated quickly and showed high hydration percentage (63.57–66.53%) in half an hour and every one reached 95% hydration after 12 h without significant differences. These results showed that the different compression forces did not remarkably influence the hydration (water penetration) rate.

Tablet hydration capacity is a very important parameter in the design of a new drug swellable dosage forms because of a strict relationship between water absorption and the drug release mechanism. Since tablet erosion is favored by swelling and gel formation, DS analyses were performed. DS data (Fig. 4) showed that all tablets had negative values. In fact, the final weight was higher than the initial because of the presence of water that balanced the weight loss during the erosion. This factor was evident for all tablets because the used mucoadhesive polymers are very hydrophilic and retain large amounts of water even after drying at 60°C and left in desiccation over $CaCl_2$.

All tablets showed a similar behavior: DS values stayed around 0% for the first 3 h and then started to decrease progressively. These data are in agreement with good tablet hydration and absence of erosion (error bars in Fig. 4 were not reported for graph clarity as these may be confusing since many profiles may overlap).

In order to verify the influence that the amount of water present in the polymer has on tablet hydration, tests were performed on tablets kept in desiccator for 24 h; no meaningful differences were observed (data not reported).

Mucoadhesive Studies

Ex Vivo Mucoadhesive Time

Ex vivo mucoadhesive times of tablets are reported (Table II). All tablets showed high mucoadhesive time (40–48 h) and good adaptability to the mucosa. Tablets 3 and 4 showed the highest mucoadhesion time.

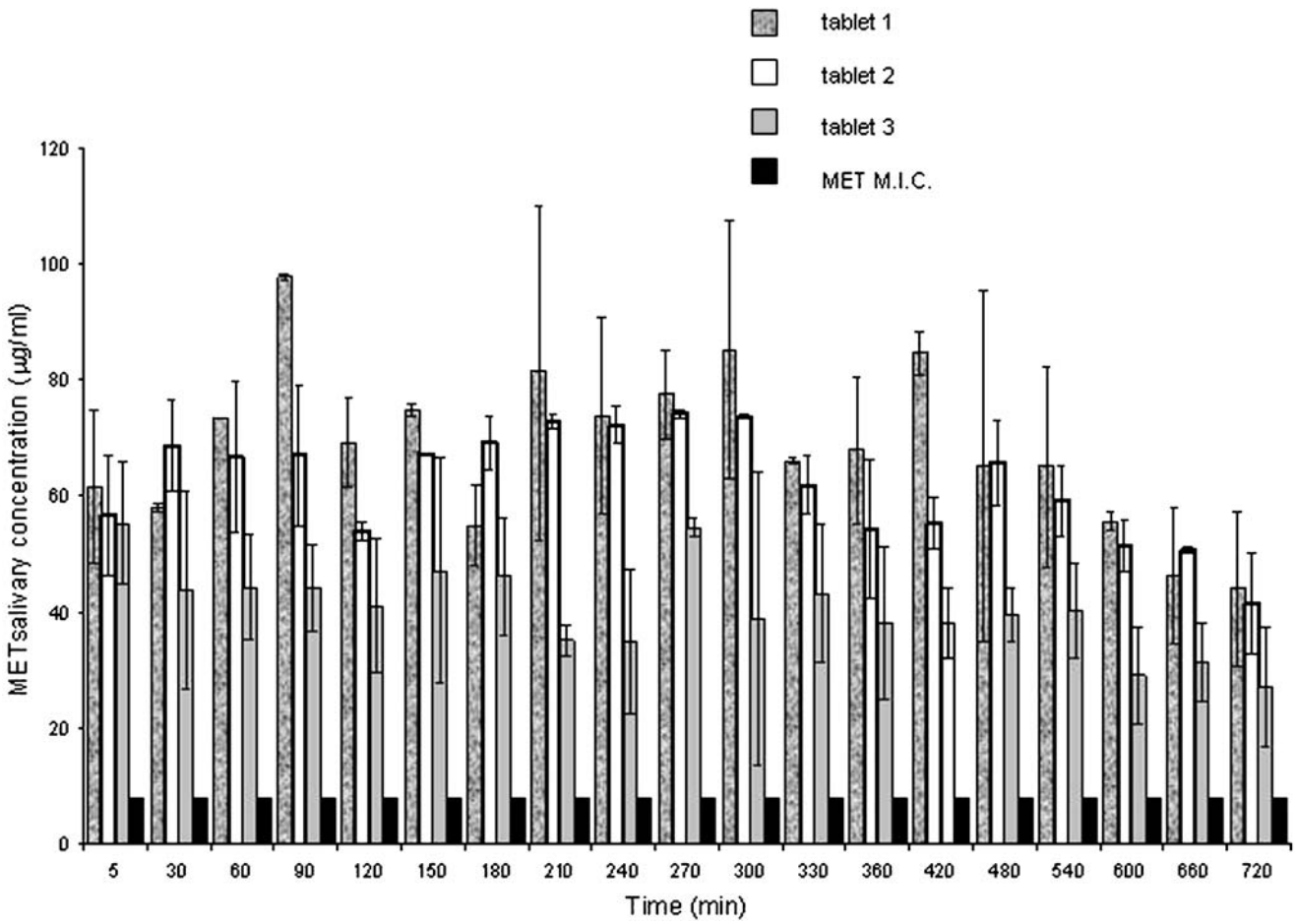

Fig. 6. *In vivo* drug release profile ($n=5$; $\alpha=0.05$)

During the test, tablet behaviors were also monitored. After 15 min all tablets showed a visible swelling; after 30 min tablets 1 and 2 were more hydrated than the others. Water penetration rate was very fast for tablet 1 that showed a limited portion of not hydrated polymers (central core); after 2 h, tablets 2, 3 and 4 showed a smaller core, while the same result was reached by tablet 5 only after 6 h. After 20 h all the tablets were completely hydrated and swelled. Tablet 1 was the most hydrated, while tablet 5 the least. During the test all tablets showed a solid and dense gel without erosion. Gelification is proportionally inverse to the compression force used. This observation is in agreement with the results obtained from DS studies.

In Vivo Mucoadhesive Time

In vivo mucoadhesion times of tablets are reported (Table II). All tablets showed high residence time (12–24 h). No tablet had fragment loss or bad taste. While tablets 1, 2 and 3 did not cause irritation or pain on the gums, application of tablets 4 and 5 were particularly painful requiring tablet detachment by volunteers (after 12 and 16 h, respectively).

Table III. Statistical Analysis of *In Vitro* Release Data ($Mt/M_\infty = Kt^n$)

Diffusional Coefficient n	Tablet 1	Tablet 2	Tablet 3	Tablet 4	Tablet 5
1	$y=0.0011x+0.13$ $r=0.9881$	$y=0.0011x+0.135$ $r=0.9626$	$y=0.001x+0.1493$ $r=0.9778$	$y=0.001x+0.1292$ $r=0.9812$	$y=0.001x+0.1271$ $r=0.9783$
0.9	$y=0.0021x+0.1069$ $r=0.9932$	$y=0.0022x+0.11$ $r=0.9879$	$y=0.0019x+0.127$ $r=0.9853$	$y=0.0019x+0.1078$ $r=0.9880$	$y=0.0019x+0.1049$ $r=0.9856$
0.8	$y=0{,}004x+0.0789$ $r=0.9970$	$y=0.0043x+0.0798$ $r=0.9934$	$y=0.0038x+0.1001$ $r=0.9915$	$y=0.0037x+0.0819$ $r=0.9936$	$y=0.0038x+0.0781$ $r=0.9917$
0.7	$y=0.008x+0.0442$ $r=0.9992$	$y=0.0085x+0.0424$ $r=0.9973$	$y=0.0075x+0.0667$ $r=0.9962$	$y=0.0073x+0.0497$ $r=0.9975$	$y=0.0075x+0.0448$ $r=0.9962$
0.6	$y=0.0159-0.0005$ *$r=0.9992$*	$y=0.0169x-0.0059$ *$r=0.9991$*	$y=0.0149x+0.0238$ *$r=0.9988$*	$y=0.0145x+0.0083$ *$r=0.9994$*	$y=0.0149x+0.002$ *$r=0.9986$*
0.5 Higuchi (0–60% release)	$y=0.0296x+0.0342$ $r=0.9965$	$y=0.0325x-0.0522$ $r=0.9968$	$y=0.0297x-0.0263$ $r=0.9974$	$y=0.0285x-0.0371$ $r=0.9969$	$y=0.0294x-0.0457$ $r=0.9968$

Probably, because of slower hydration rate of these tablets, the polymers showed higher possibility to link mucin chains. In fact polymer chains can make hydrogen bond either with water or mucin and when the water links happened slowly (slow hydration) the mucin links are preferred (21).

Ex Vivo Mucoadhesive Force Studies

All tablets showed good mucoadhesive forces with values ranging between 0.57 and 1.75 N (Table II). It is noteworthy to point out that the mucoadhesive force increased with the increase of the compression force. In fact tablets 4 and 5 showed the highest mucoadhesive forces (around 1.70 and 1.75 N, respectively). The higher and stronger compression force probably is responsible for the slower hydration rate and the consequent higher and stronger links with mucin chains; the last accountable for pain on volunteer gum. The same tests were repeated on tablets containing MET and no relevant differences were observed (±0.08 N) if compared with non medicated tablets (data not shown).

In Vitro Release Studies on Tablets

Twenty milligrams MET medicated tablets were submitted to the *in vitro* release studies (Fig. 5). During the first 6 h all tablets showed very similar behavior reaching the 50–60% of drug release. However after the sixth hour, some differences appeared. Tablets 1 and 2 showed the highest percentage of drug release after 12 h (about 85%) in agreement with the *ex-vivo* swelling data; tablets 4 and 5 released the lowest percentage of MET (75% after 12 h), while tablet 3 showed an intermediate behavior (80% drug release); drug release decreased proportionally with the increase of the compression force used.

In Vivo Release Studies on 20 mg MET tablets 1, 2 and 3

This study was performed only on tablets 1, 2 and 3, since tablets 4 and 5 caused pain during *in vivo* application and gave rise to irritation needing to be detached by volunteers. The other tablets did not show irritation, fragment loss, bad taste and did not provoke saliva level modification. The MET saliva concentrations found during 12 h ranged between 27.1 and 98.7 μg/ml (Fig. 6). All these values were greatly higher than MET minimum inhibitory concentration (MIC; 0.1–8 μg/ml) against anaerobic bacteria responsible for periodontal disease (22). Tablet 1 showed the highest MET salivary concentration and, considering the real use conditions (food and drink presence), it can assure buccal drug levels higher than the MET MIC.

Kinetic Studies

The *in vitro* release data were submitted to statistical investigation to study drug release kinetics (Table III). The drug release mechanism was evaluated from its diffusional exponent (n). The best fitting resulted for $n=0.6$ indicating an anomalous, or non-Fickian, release mechanism (Table III). This was thought to be indicative of a case II transport as reported for swellable systems.

It is known that the release kinetics from swellable system is controlled by the water penetration rate, responsible for drug diffusion, and polymeric chain relaxation rate. When $n=1$, the released drug from the system occurred as an apparent zero-order mechanism; when the drug release follows the square root of time ($n=0.5$), the release is governed by a pure Fickian diffusion mechanism and the liquid penetration rate is slower than the relaxation rate of the polymeric chains. When the relaxation process is slower than diffusion, a case II transport occurs. Therefore, the non-Fickian release behavior obtained may suggest that MET release was controlled both by drug diffusion process through the matrix and by polymeric chain relaxation time.

CONCLUSION

The investigated compression forces did not greatly affect tablet characteristics, as thickness friability crushing strength, and the polymers physico-chemical properties while hydration and mucoadhesive ability were influenced. In conclusion, the lowest compression force resulted proper to prepare a mucoadhesive tablet able to produce adequate drug salivary concentration and acceptable by patients.

ACKNOWLEDGEMENTS

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