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# Oralmucoadhesive paste of Triamcinolone Acetonide and Zinc Sulfate: Preparation and *in vitro* physicochemical characterization

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**A B S T R A C T**

Aphthous stomatitis and oral lichen planus may be found on mucosal surfaces including the gingival, tongue and lips. These conditions frequently require topical corticosteroid medication such as TriamcinoloneAcetonide (TA).Recently, studies showed that divalent inorganic salts such as Zinc Sulphate ($ZnSO_4$) are recommended for treatment of aphthouse, herpes ulcers and other ulcers in the body. In this study we developed orabase formulation of $ZnSO_4$ 0.25% and TA 0.1% that is suggested tohavesynergistic effect on ulcer treatment.To achieve this goal, different ratio of bioadhesive polymers such as pectin, gelatin, NaCMC and plastibase were used and the effects of these factors were evaluated on physicochemical properties of the pastes.The *in vitro*bioadhesive strength, spreadability test and occlusivity strength properties of the Orabase were investigated using new designed device, while swelling behavior was studied in different media, namely, distilled water and simulated salvia solution. TA and $ZnSO_4$ concentration were determined using HPLC and voltammetry system, respectively. The *in vitro* drug release was investigated in phosphate buffer (pH=7) at 37°C by Franz diffusion cell.The optimum formulation showed that the increase in NaCMC content and decrease in water content were found to elevate the bioadhesive and occlusivity strength. Also decrease in NaCMC content was found to elevate the drug release rate. Optimum formulation had adhesion strength equal to 131.948 mN/cm$^2$, spreadability equal to 0.067 cm, percent of occlusivity strength equal to 53.3% and a swelling index very similar to brand sample (Adcortyl0.1%) in both the distilled water and phosphate buffer.We canclaim that optimum formulation is comparable to brand sample and we suggest that it is a promising and suitable carrier for transmucosal drug delivery system.

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## Introduction

A bioadhesive has been defined as a synthetic or biological material, which is capable of adhering to a biological substrate or tissue for administration of the drug of choice [1]. When the biological substrate is mucus, the term "mucoadhesive" has been employed [2]. One method of optimizing drug delivery is achieved throughthe use of adhesive dosage forms.

Mucoadhesion can be defined as a state in which two components, of which one is of biological origin, are held together for extended periods of time by the help of interfacial forces. As stated, mucoadhesion is the attachment of the drug as well as a suitable carrier to the mucous membrane. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Mucoadhesion has the following mechanism:[2]

1. Intimate contact between a bioadhesive and a membrane (wetting or swelling phenomenon)
2. Penetration of the bioadhesive into the tissue or into the surface of the mucous membrane (interpenetration) [3, 4].

Residence time for most mucosal routes is less than an hour and typically in minutes. This time can be increased by the addition of an adhesive agent in the delivery system which is useful to localize the delivery system and increases the contact time at the site of absorption [5].

The mucosal lining is richly vascularized and more accessible for the administration and removal of a dosage form. Additionally, buccal drug delivery has a high patient acceptability compared to other non-oral routes of drug administration. Moreover, rapid cellular recovery and achievement of a localized site on the smooth surface of the buccal mucosa are among the other advantages of this route of drug delivery. The disadvantages associated with this route of drug delivery are the low permeability of the buccal membrane [3], specifically when compared to the sublingual membrane [4,5], a smaller available surface area for drug absorption about 170 $cm^2$[6,7], and continuous secretion of saliva (0.5–2 l/day) which leads to subsequent dilution of the drug [5]. Swallowing of saliva can also potentially lead to the loss of dissolved or suspended drug and, ultimately, the involuntary removal of the dosage form. Nevertheless, the advantages and recent progress in delivering a variety of compounds, specifically peptides and proteins, render the disadvantages of this route less significant. Fortunately, the enzyme activity in the buccal mucosa is relatively low compared to other mucosal routes [8].

Oral lichen planus (OLP) is a common disease, which may be found on mucosal surfaces including the esophagus, larynx, gingiva and lips [9].

Canker sores are small ulcer craters in the lining of the mouth that are often painful and sensitive. Canker sores are also medically known as aphthous ulcers or aphthous stomatitis. These conditions frequently require topical corticosteroid medication such as 0.1% TA (Adcortyl) or 0.5% hydrocortisone (Orabase HCA®) [10].

Conventional formulation for local delivery to the oral mucosa includes mouthwashes, oral suspensions and lozenges.

These systems provide high drug levels in the oral cavity as a whole, but only for a short time [4]. Due to these problems, mucoadhesive dosage forms with long contact time are an alternative and more effective formulation [11]. Mucoadhesive polymers such as hydroxyl propylcellulose, carbopol®934, sodium carboxymethylcellulose, gelatin and pectin have been employed in TA formulations used for the oral cavity [12].

The objective of the present study was to evaluate the effects of vehicle composition on the in vitro characteristics of TA and $ZnSo_4$orabase.

## Material and Methods

### *Materials*

TriamcinoloneAcetonide, Zinc Sulfate and Sodium CMC from Merck company (Germany), pectin and gelatin from Scharlav Chemic S.A company (Spain), liquid paraffin and low-density polyethylene from Ghatran company (Iran), propyl paraben and methyl paraben where obtained from Merck company (Germany).

 

### *Preparation of plastibase and mucoadhesive*
### *Plastibase*

The first step in preparing mucoadhesive base is to prepare plasti-base. The polyethylene was put in the lab dish and liquid paraffin (80°C) was added, which was twice the weight of polyethylene [13]. The mixture was stirred in 130°C well to make a viscose gel. The remaining liquid paraffin was added gradually and the stirring was continued until all the paraffin wasadded to the dish. The mix was poured in a glass jar wrapped with aluminum foil, as it had already been cooled down fast by ice and salt. The product was plastibase gel.

### *Orabase preparation*

The formula introduced for making this base includes 16.6 percent gelatin, 16.6 percent pectin, 16.6 percent sodium carboxymethyl cellulose, and up to 100 percent plasti-base [14]. The best method for making mucoadhesive paste is gradual addition of sodium carboxymethyl, cellulose, pectin and ultimately, adding gelatin to the plastibase and constant stirring to obtain a homogeneous base. In order to study the effects of different substances on the adhesive power of mucoadhesive paste, formulations in various percentages of raw materials were made (table 1).

**Table 1.** Percent of polymers in mucoadhesive pastes and results of initial assessment of mucoadhesive formulations.

| Formulation | NaCMC | Pectin | Gelatin | Plastibase | Thumb test* | Uniformity* | Existence of separate particles |
|---|---|---|---|---|---|---|---|
| F1 | 16.6 | 25 | 8.3 | 50 | ++++ | +++ | - |
| F2 | 16.6 | 8.3 | 16.6 | 58.3 | +++ | ++++ | - |
| F3 | 25 | 10 | 15 | 50 | ++++ | ++++ | - |
| F4 | 16.6 | 16.6 | 8.3 | 58.3 | +++ | ++++ | - |
| F5 | 8.3 | 16.6 | 16.6 | 58.3 | +++ | ++++ | - |
| F6 | 16.7 | 16.6 | 16.6 | 50 | ++ | +++ | - |
| F7 | 16.7 | 8.3 | 24.9 | 50 | + | ++ | + |
| F8 | 25 | 16.6 | 8.3 | 50 | ++ | ++ | - |
| F9 | 8.3 | 25 | 16.6 | 50 | + | + | + |
| F10 | 16.6 | 8.3 | 25 | 50 | ++ | + | ++ |

(++++ high +++ medium +++ low +very)

### *Physicochemical characterization of mucoadhesive*

### *Physical appearance*

The formulas were evaluated in terms of homogenicity and existence of separate particles. The unsuitable formulations were omitted.

### *Thumb test*

This is simple test used for the qualitative determination of peel adhesive strength of the bioadhesive delivery systems. The adhesiveness is measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time. Although the thumb test may not be conclusive, it provides useful information on peel strength of the polymer [15].

### *Determination of adhesive power of mucoadhesive pastes*

One of the common methods in studying the mucoadhesive power is using a Stable Micro Systems texture analyzer. This machine puts forces on the bonds between the mucoadhesive system and its ground to determine maximum mucoadhesive power [16, 17, 18] In the experiment, we designed a new device similar to a texture analyzer and the bioadhesive strength of the pastes was measured [19] This system looks like a two-floor scales, and on one of its arm, the rubber cap of the vial is hanged by a string. The rabbit tongue is placed on the rubber cap. A balloon for weighing water is fixed on the other arm. In measuring the adhesive power, one gram of mucoadhesive base wasweighed and flattened on the lower platform of the machine. A drop of phosphate buffer solution (pH=7.4) was poured on it. The rubber cap with rabbit tongue

 

(mucosa part) cover was placed on the lower platform gently. After 3 minutes of exposure, water waspoured on the opposite arm by a syringe until the moment when the water weight stretches the string. Then, the rubber cap covered by rabbit tongue was separated from the mucoadhesive base.The weight of water showed maximum adhesive power of mucoadhesive paste.

### *Determination of occlusivity test*

To evaluate the occlusivity strength, a device was designed according to previously published method [20]. Since one of the most important advantages of mucoadhesive in treating aphthousulcer is its occlusivity power, measuring this parameter is very importantin this test a plastic cylinder was used that one side of it was closed.The diameter of the cylinder was 3 cm. The hot gelatin solution (10%) was prepared and was spread on a dish in 1 centimeter height. A few cylinders with no caps were put inside it and left to cool.

After the development of a gelatin layer with 1 cm thickness in this end of cylinders, the cylinders were removed. 2 ml distilled water was poured in the opposite side of the cylinders with screw heads and cap fixing shape. The cap was fixed and the cell was weighed. The cylinders were put in dissector in room temperature and changes in weight of the dish were studied in lapse of time. The test was performed once in blank form (with no bases) and then, 300 mg/cm$^2$ of each one of the bases was flattened on the gelatin layer, including the side of cap containing cylinder water. The water evaporation speed was re-measured through studying changes in weight of cell.

In this test, the gelatin layer made a situation similar to skin and by comparing the water evaporation kinetic in the two states mentioned above, the occulisivity power of the bases was calculated from following equation and were dually compared.

Occlusivity power = (aB- aP)/ aB

In which, aB and aP are water evaporation line slope in lapse of time for control situation (without product) and sample subject of test.

### *Spreadability test*

To evaluate the Spreadability parameter, a device was designed according to previously published method [21]. This device includedtwo upper and lower round transparent plates. The internal surface of a rubber ring wassoaked in glycerin and then was put on the lower plate. The cavity made of the ring wasfilled with the concerned base and its surface wasleveled by spatula. Then the rubber ring wasremoved. After making sure the round plate wasbalanced, it wasreleased on the upper plate from a certain height and the expanded diameter wasmeasured in the two vertical axis 30 seconds and 3 minutes after being released.

### *Determination of swelling test*

The paste swelling studies were conducted using two media of distilled water and simulated saliva solution which consisted of phosphate buffer saline solution (2.38 g $Na_2HPO_4$, 0.19 g $KH_2PO_4$ and 8.00 g NaCl per liter of distilled water adjusted with phosphoric acid to pH=7). Each paste sample was weighed and placed in a preweighed stainless steel wire mesh with sieve opening of approximately 800 µm. The mesh containing the film sample was then submerged into a 15 ml medium contained in a plastic container (diameter 5.00 cm, height 1.54 cm). Increase in weight of the paste was determined at time intervals until a constant weight was observed (Figure 1.). Each measurement was repeated three times [21]the degree of swelling was calculated using this equation:

Swelling index = $(Wt - W_0)/W_0$

Where Wt is the weight of paste at time t, and $W_0$ is the weight of paste at time zero [22].

**Fig. 1.** The designed device for swelling study.

 

### *Viscosity test*

To perform this test, the viscosity of optimized formulation was studied by Brook Field (spindle 52). The shear rate and shear stress were repeated three times and by drawing the diagram of shear stress vs. shear rate, the formulation flow was determined.

### *Examination of the in-vitro release of TA and $ZnSO_4$*

The in-vitro drug release was investigated by Franz diffusion cell. The receiver side of the diffusion cell was filled with 50 ml of isotonic phosphate buffer saline (pH=7.4) and diffusion cell was kept in an incubator with 37°C temperature.

The medium was stirred at a constant rate and at predetermined time intervals; samples of dissolution fluid (2 ml) were removed and replaced by fresh medium.

TA concentration was determined using an HPLC system (LC-10AS Liquid Chromatography, SCL-10A System Controller, SPD-10AV Detector, Shimadzu, Japan)[10].The analytical conditions were as follows: HPLC Pack C18 column (5 µm, 4.6×250 mm); UV detection 240 nm; mobile phase (methanol: water 50:50 v/v); flow rate at 1 ml/min and 25 µl of injection volume.

Zinc Sulfate concentration was determined using stripping voltammetry. The voltammetry was performed by Metrohom VA 797 computrace (Metrohm, Zofingen, Switzerland) with a three-electrode system: a hanging mercury drop electrode (HMDE) as working electrode, silver-silver chloride (Ag/AgCl) as reference electrode and a platinum wire as counter-electrode. For all type of voltammetric measurements, the supporting electrolyte (phosphate buffer solution, pH 7.4) was placed in polarographic cell which degassed by bubbling of pure $N_2$ gas for 3 min. The striping voltammetric measurement was carried out by keeping constant both concentration of the $ZnSO_4$ and the total volume of solution, while the drug concentration varied.

## Result

### *Preparation and characterization of mucoadhesive formulation*

After preparing plastibase, 10 mucoadhesive formulations were prepared that is described in Table 1.

The prepared formulations were studied in terms of homogenicity, existence of separate particles, and adhesion by using thumb test method. In this method, the adhesion of mucoadhesive paste to the finger is used as a quality test for initial evaluation of the samples (Table 2).

**Table 2.** Evaluation of the maximum adhesion strength of formulated mucoadhesive ($mN/cm^2$):Comparison of results of occlusivity power and spreadability strength of pastes after 30 seconds (cm) and after 30 min (cm).

| **Formulation*** | **F1** | **F2** | **F3** | **F4** | **F5** | **Adcortyl** |
|---|---|---|---|---|---|---|
| **Maximum of adhesion (mN/cm2)** | **115.31±4.18** | **93.16±4.35** | **131.95±2.78** | **99.57±1.85** | **88.02±4.48** | **136.06±3.42** |
| % Occlusivity | 40% | 30% | 53/3% | 10% | 33/3% | 46/6% |
| Spreadability after 30 sec. | 2.30±0.20 | 2.40±0.11 | 2.50±0.30 | 2.57±0.35 | 2.50±00 | 2.43±0.23 |
| Spreadability after 30 min. | 2.43±0.21 | 2.57±0.15 | 2.57±0.21 | 2.83±0.21 | 2.63±0.15 | 2.44±0.23 |

* The tests were replicated three times (mean±SD)

By comparing these results, the formulation of F3 hasshown the adhesion strength equal to 131.95 $mN/cm^2$, comparable to adcortyl (136.06 $mN/cm^2$) ($P_{value}$>0.05).

By calculating the difference in water evaporation line slope in two samples (study and control), the percentage of occulisivity was determined. Maximum power of occlusivity is observed in formulation F3.

As shown in Fig. 2 and 3, formulation of F2 has a high swelling index in distilled water and simulated saliva solution. As more swelling is accompanied by decreased adhesion strength, formulation of F3 and Adcortyl with minimum swelling was chosen as optimum formulations.

 

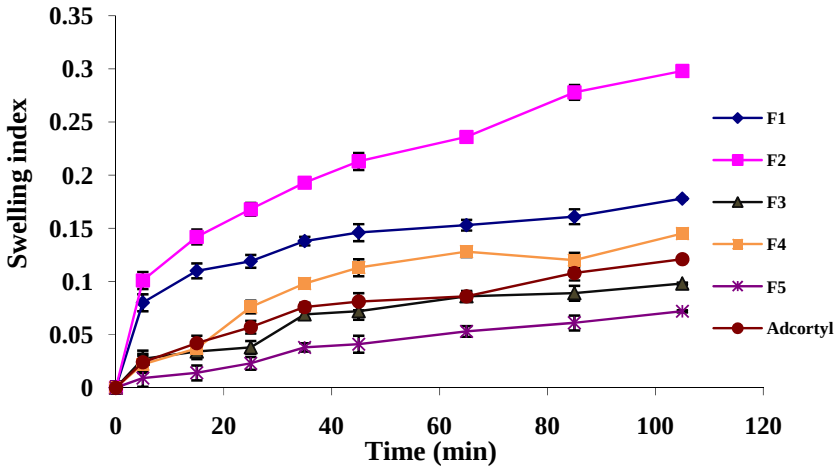


**Fig. 2.** Swelling versus time profile of pastes in distilled water; mean ± SD. (n =3).

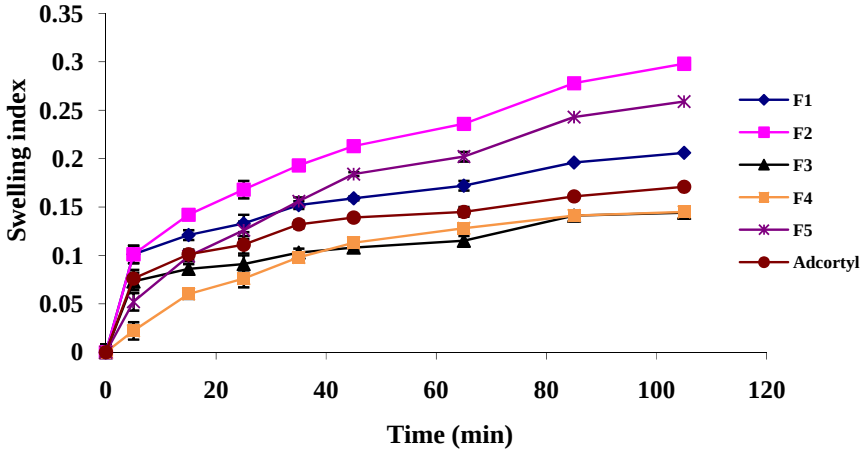


**Fig. 3.** Swelling versus time profile of pastes in simulated salvia solution; mean ± SD. (n =3).

In the pastes, at the time of initial stress, flow started and continues to slow. Incidence of this phenomenon represents broadcast quality properties of suitable base. The results are respectively presented in Table 2. The statistical comparison showed that there are no significant differences in spreadability of formulation and it is comparable to adcortyl ($P_{value}$>0.05).

The diagram in figure 4 shows that when stress is low or absent, the viscosity is indefinite and there is no flow. However, after yielding stress to the matrix, the current starts and the structure of the substance is disintegrated. With respect to the characteristics mentioned, the mucoadhesive shows simple plastic current in respond to the force entering to it and the appearance of this phenomenon, with respect to the heterogeneity and matrix nature of the mucoadhesive paste, is predictable.

 

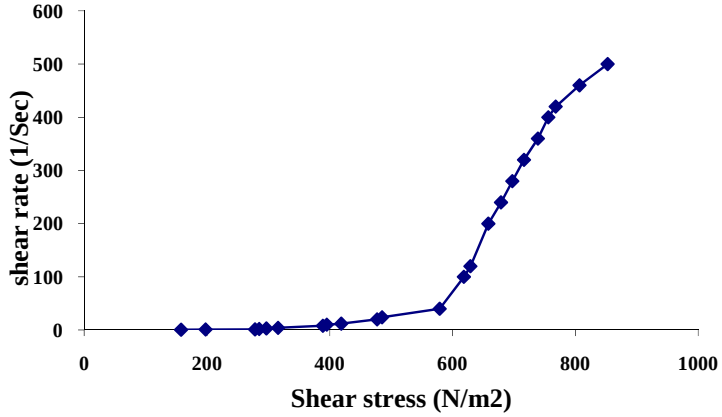


**Fig. 4.** Rheogeram of optimized formulation (F3)

The analysis method adopted for TA quantization is new developed and valid HPLC method. In this method the maximum wavelength of absorbing 240 nm was used and the relevant standard curve was drawn. The adopted analysis method for zinc sulfate is voltametric method. Existence of high amount of correlation coefficient of average line and low percent of criteria deviation are our evidences.

For finding the release kinetic, we fitted data in zero and first order kinetics, first law fick,higuchi and peppas models[22]

**First law fick: Q = Kt**

**Higuchi law = $kt^{1/2}$**

**Zero order kinetics: $C = C_o - K_o t$**

**First order kinetics: $\log C_1 = \log C - K_1$**

**Peppas law: $Q = Kt^{1/2}$**

**Q:** Cumulative amount of drug released per surface

**C:** The remaining percentage of drug for release

**$C_o$:** Initial amount of drug, T: time and k: constant drug release.

It was concluded that TA and $ZnSO_4$ follows Higuchi law and first order kinetic with $R^2$was more than 0.99 (Fig 5,6). Appearance of this phenomenon with respect to the heterogeneity of mucoadhesive matrix could be predicted. By comparison of formulations, it could be seen that as quantity of sodium carboxymethyl cellulose in formula increases, the release rate was increased.Perhaps this isdue to its capability of more water absorption, swelling and ultimately, establishing astronger polymer network.The speed of drugs release from mucoadhesive base decreases, although its adhesive power increases.

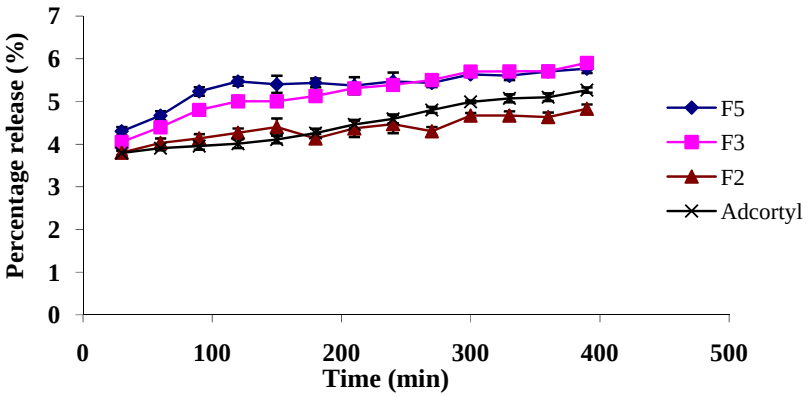


**Fig. 5.** Release profile of TA from mucoadhesive formulation in PBS; mean ± SD. (n = 3).

 

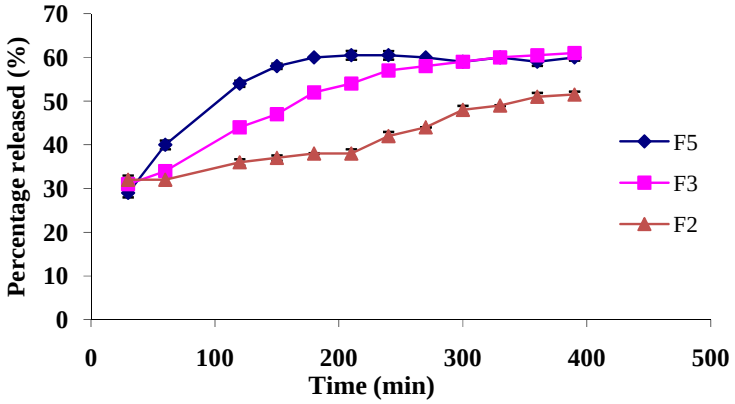


**Fig. 6.** Release profile of $ZnSO_4$ from mucoadhesive formulation in PBS; mean ± SD. (n = 3).

## Discussion

Inflammatory injuries are one of the painful problems in oral cavity that appear in different age groups. Several medical treatments have been suggested to control the aphthous pain, such as Diphenhydramine, tetracycline in form of gargle solution. In addition to other drugs which are used in aphthous treatment, triamecinolone under Adcortyl© has been used as an effective medicine in treating oral inflammatory injuries. With respect to the effectiveness of oral zinc in accelerating healing process of body scars, we formulated triamcinolone acetonide in presence of zinc sulfate in an Orabasemucoadhesive base.

By preparing such formulation, two major goals would be achieved:

- Applying a mucoadhesive layer on an injury to prevent any exposure fromforeign factors that might prevent progress of recovery.
- The duration of medicine contact with injury increases and the effectiveness of the medicineimprove.

The optimization of method to prepare plastibase with the best characteristics is one of the most important procedures of the work. The mixing time, mixing heat, speed and method of cooling affect the structure of plastibase. The plastibase should be clear, transparent and have no bi-phase structure.

Having studied published reports, no specific method had been suggested to add polymers and other exipients to plasti-base and thus, one of the achievements of this paper is that it presents a suitable method to add elements for preparing mucoadhesive paste.

Obviously, the most important characteristics are homogeneity, absence of separate particles, and suitable adhesion. The substances of mucoadhesive are usually hydrophilic macromolecules which in their structure, there are chains containing groups with capability of establishing hydrogen bonds. These substances are able to absorb water in contact with mucus, become inflamed, hydrated; and stick to the place [22, 23]. Different mechanisms have been considered for adhesion of substances of mucoadhesive including:the electrical double layers, electrostatic reactions, hydrogen bonding, Van der waal،s forces, wetting, physical entanglements and surface free energy [24-26].

Amount of NaCMC swelling in distilled water is much higher than buffer and this shows that the ion power and pH play important roles in polymer swelling [24].NaCMC absorbs water instantly during 4-5 minutes, becomes hydrated and reaches its highest swelling in buffer [27].Then the full hydration is reached, and the adhesion power between the tissue and polymer is suddenly lost and polymer is destroyed [28]. This polymer is an

 

anionic polymer with large number of carboxylic groups which establish hydrogen bonds with the tissue surfaces [21].

As shown in table. 2, it could be observed as the percentage of NaCMC increases, the adhesive characteristic improves [17, 27].It seems that if the percent of low soluble elements such as gelatin or pectin is increased in the formula, the opportunity of hydration and suitable inflammation of NaCMC is reduced, but becomes effective in continuity of adhesion and maintaining the adhesion in the place [17].

Ivanova and colleagues developed a model composed of mucoadhesive pastes based on Carbopol 971P NF and Carbopol 974P NF. The best formulation provides better kinetics of drug release, up to 120 minutes to 80%. They found that the inclusion of 2% magnesium stearate in the composition of mucoadhesive pastes provides very high stability of the system, with regards to separation of oil [29].

In study of Khazaeli et al., oral mucoadhesive paste containing myrtle essential oil was prepared by compounding of sodium carboxy methyl cellulose, pectin and gelatin in plastibase and the best formulations were selected for the clinical trial. They showed that mocuadhesive paste is a suitable formulation for treatment of recurrent aphthous stomatitis, with regard to its adhesive properties, the reduced time of burning sensation and the reduced size of lesion, significantly [30].

Fini *et al.* describe the *in vitro/ex vivo* buccal release of chlorhexidine (CHX) from mucoadhesive aqueous gels (1% w/v).

The mucoadhesive/gel forming materials were carboxymethyl-(CMC), hydroxypro-pylmethyl-(HPMC) and hydroxypropyl-(HPC) cellulose. The combination of HPMC or HPC with CMC showed slower drug release when compared to each of the individual polymers. Gels were compared for the release of previously studied tablets that contained Carbopol and HPMC, alone or in mixture. CMC in gels allows a more rapid CHX release than Carbopol in tablets, which could be useful in acute situations; CHX tablets can be suggested for therapies that require prolonged treatment or prevention of buccal infections [31].

The optimum formulation shows the suitable spreading characteristics of base with minimum stress performed. Therefore, the product could be used in moucal surfaces easily. In addition, the occulisivity characteristic of bases shows that as the percentage of sodium carboxymethyl cellulose increases, the occulisivity power of pastes decreases and as the percentage of plastibase decreases, the occulisivity power of pastes increases. Therefore, formula 3 has the highest occulisivity power.

## Conclusion

In this study we prepared a new mucoadhesive paste for delivering TA and $ZnSO_4$ in oral aphtous treatment. Previous studies showed that the polymer chains of mucoadhesive substances could penetrate inside glycoprotein chains in mucus and form a strong layer with high resistance against destruction. Therefore, a polymer that could easily penetrate inside mucus network and make several hydrogen binds could have more desirable mucoadhesive power; however, increase in density of this network would decrease the release power.

Ultimately, by considering all parameters (adhesion, occulisivity, viscosity, swelling, drug releasing, etc.), it seems that mucoadhesive paste containing16.6% NaCMC, 25% Pectin, 8.3% Gelatin and 50% Plastibaseis the most desirable base.

Based on the results of the presented study, mucoadhesive composition was optimized to be investigated further in vivo studies.

## Conflict of interest

Authors certify that no actual or potential conflict of interest in relation to this article exists.

 

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