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Development and *In Vitro* Investigation of Mucoadhesive Paste with Methylprednisolone Hydrogen Succinate

Vladimira Ivanova, Bistra Kostova and Dimitar Rachev

ABSTRACT

Mucoadhesive pastes with Methylprednisolone hydrogen succinate are characterized with pronounced therapeutic activity in treating Pemfigus vulgaris. Two types of Carbomer as drug release carriers were used: Carbopol® 971P NF and Carbopol® 974P NF in concentrations between 27 to 32%. Mucoadhesive pastes were based on paraffin liquid with the use of Magnesium stearate to improve the structural characteristics of the systems. Tests for adhesion, stability and in vitro drug release of developed models of mucoadhesive pastes were carried out. The results obtained show the influence of the type and concentration of polymer used on the adhesion and the rate and degree of drug release. The stability of the developed mucoadhesive pastes was provided by inclusion of 2 wt % magnesium stearate.

Keywords: Methylprednisolone hydrogen succinate; drug delivery systems, mucoadhesive paste, carbomers.

Vladimira Ivanova, Bistra Kostova and Dimitar Rachev
Faculty of Pharmacy, Medical University, 2 Dunav Str., Sofia-1000, Bulgaria.

INTRODUCTION

Recent focus of pharmaceutical technological science has been directed towards the development of a mucoadhesive drug delivery system, which is able to target drugs to various mucosa such as buccal, nasal, ocular, pulmonary, rectal, vaginal etc (Ahuja *et al.*, 1997; Kharenko *et al.* 2009; Lee *et al.* 2000). As a result of adhesion, the controlled drug delivery localizes for long period at the delivery site, improving drug bioavailability in a site-specific manner using lower drug concentrations for disease treatment (Leung and Robinson, 1988). Mucoadhesion may be affected by a number of factors, including hydrophilicity, molecular weight, cross-linking, swelling, pH, and the concentration of the active polymer (Yang and Robinson, 1998; Andrews *et al.*, 2009). Mucoadhesive polymers have numerous hydrophilic groups, such as hydroxyl, carboxyl, amide, and sulfate, which (i) attach to mucus or the cell membrane by various interactions such as hydrogen bonding and hydrophobic or electrostatic interactions; (ii) cause polymers to swell in water and thus expose the maximum number of adhesive sites (Rahamatullah *et al.*, 2011; Mizrahi and Domb, 2008). Anionic polymers are the most widely employed mucoadhesive polymers within pharmaceutical formulation due to their high mucoadhesive functionality and low toxicity (Singla *et al.*, 2000; Park and Robinson, 1987). Such polymers are characterised by the presence of carboxyl and sulphate functional groups that give rise to a net overall negative charge at pH values exceeding the pKa of the polymer.

For Correspondence
Bistra Kostova
Faculty of Pharmacy,
Medical University,
2 Dunav Str., Sofia-1000, Bulgaria
Tel: +3592 9236 528

Typical examples include poly(acrylic acid) (PAA) and its weakly cross-linked derivatives. PAA polymers are available in a wide range of molecular weights. The buccal cavity offers many advantages for drug delivery application and is often associated with high patient compliance, low levels of irritation and significant ease of administration (Jones *et al.*, 2000; Sudhakar and Kuotsu, 2006). The oral cavity is used as a site for local and systemic drug delivery. Local drug therapy is used to treat disease states like aphthous ulceration gingivitis, periodontal disease, and pemphigus vulgaris. Different dosage forms are used to administer adhesive ointments, gels, pastes, tablets, films, and patches (Medlicott, 1994; Harman, 2003). The aim of this study was to develop and optimize a mucoadhesive hydrophobic paste with Methylprednisolone hydrogen succinate for treatment of pemphigus vulgaris and determine the influence of polymer type and concentration on: (i) the adhesion ability of the system; (ii) the stability and (iii) drug release kinetics.

MATERIALS AND METHODS

Materials

Polymers: Carbopol® 971P NF and Carbopol® 974P NF (BF Goodrich, USA). All other ingredients are in analytical grade.

Methods

Preparation of model compositions of mucoadhesive pastes containing Methylprednisolone hydrogen succinate

Hydrophobic formulations based on paraffin liquid were designed with 0.5% Methylprednisolone hydrogen succinate. Preliminary sieved magnesium stearate and methylprednisolone was sequentially suspended in the hydrophobic carrier of the paste paraffin liquid. To the reconstituted suspension, preliminary sieved adhesive polymer Carbopol® 971P NF or Carbopol® 974P NF was added by constant stirring.

Study of adhesion ability of model formulations

Their bioadhesive behavior was studied in a modified tensile tester in contact with artificial membrane and the force-elongation behavior was measured up at breakpoint. An artificial membrane was placed on an electronic balance. On the artificial membrane was applied uniformly researched adhesive and above it the aluminum cap covered with a membrane was placed by pressing. The strength of adhesion was equivalent to the mass indicated from the balance, by the time of rupture of the withdrawing adhesive (expressed in grams).

Stability studies

Weight method for determining the separate amounts of hydrophobic liquid under stress storage conditions (60 °C) was

used. On top of the wall of the glass 1.2800 ± 0.002 g of the model formulations were applied.

The glass with the sample was weighed on an analytical balance. After 48 hours equilibration at 60 °C in heating and drying oven (Heraeus T6) and after equilibration in desiccator, the separated oil was carefully absorbed with filter paper and the glass with the sample was weighed again on an analytical balance. The separated oil was calculated in milligrams.

In vitro drug release

Drug release profiles were evaluated using a dissolution test apparatus (Erweka DT 600, Hensenstmm, Germany). Dissolution of Methylprednisolone hydrogen succinate was carried out by USP 5 paddle over disk. At the bottom of the apparatus the artificial membrane was placed on the network disk. On the artificial membrane 1.21 g of adhesive paste was affixed uniformly. The test was carried out at a paddle rotation speed of 50 rpm, maintained at 37 ± 0.5 °C, in 250 ml dissolution medium at pH 6.8 – PBS. Withdrawing 5 ml filtered (0.45µm) samples at preselected intervals (5, 10, 15, 20, 30, 45, 60, 75, 90 and 120 minutes), the dissolution progress was monitored.

The quantity of Methylprednisolone in sample solutions was analyzed by UV absorbance at 246 ± 2 nm using a Hewlett-Packard 8452 A Diode Array spectrophotometer (New Jersey, USA). The cumulative percentage of drug release was calculated and the average of six determinations was used in the data analysis. The statistical analysis of the dissolution data showed a statistical difference ($p < 0.05$) using t-test by Origin Plot software.

RESULTS AND DISCUSSION

Preparation of model compositions of mucoadhesive pastes containing Methylprednisolone hydrogen succinate

Hydrophobic mucoadhesive paste was chosen because of (i) instability of Methylprednisolone hydrogen succinate in water solutions (Görög S, 1983); (ii) hydrophobicity of the paste does not allow for a rapid uptake of water in it (providing a gradual swelling of the hydrophilic polymer) and ensures prolonged contact with oral mucosa. Two types of carbomers: Carbopol® 974P NF and Carbopol® 971P NF were used as mucoadhesive polymers.

Our preliminary studies have shown that use of sunflower oil as a vehicle not provide sufficient adherence of the paste which is probably due to the steric effect of triglycerides on the adhesion of polymer. Moreover, developed preliminary models showed low stability during storage, resulting in separation of the oil. Therefore in this study liquid paraffin is used as a hydrophobic suspending medium. To improve the structural characteristics of the system magnesium stearate was included. The developed model compositions are presented in Table 1.

Table 1: Model compositions

Model (wt%)	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10
Methylprednisolone hydrogen succinate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Carbopol® 971P NF	32		32		32		29	29	27	27
Carbopol® 974P NF		32		32		32				
Paraffin liquid	67.5	67.5	65.5	65.5	63.5	63.5	68.5	66.5	70.5	68.5
Magnesium stearate			2	2	4	4	2	4	2	4

Study of adhesion ability of model formulations

Adhesion ability of the model compositions was tested using the developed methods.

The summarized data obtained from the study is presented in Fig. 1 and 2

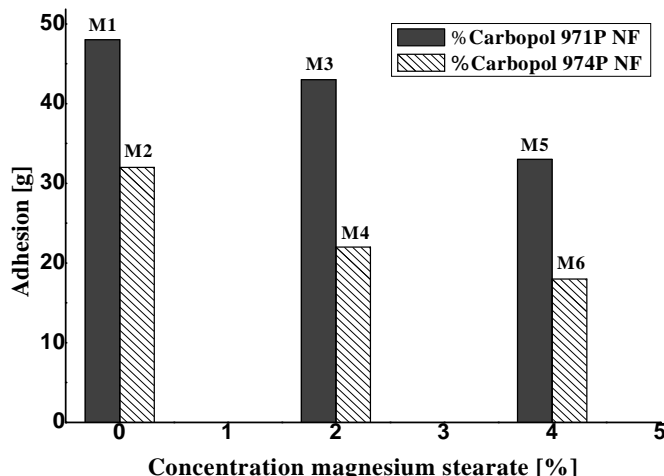


Fig.1: Influence of polymer type and concentration of magnesium stearate on the adhesion ability of the different model compositions (Models M1-M6, respectively).

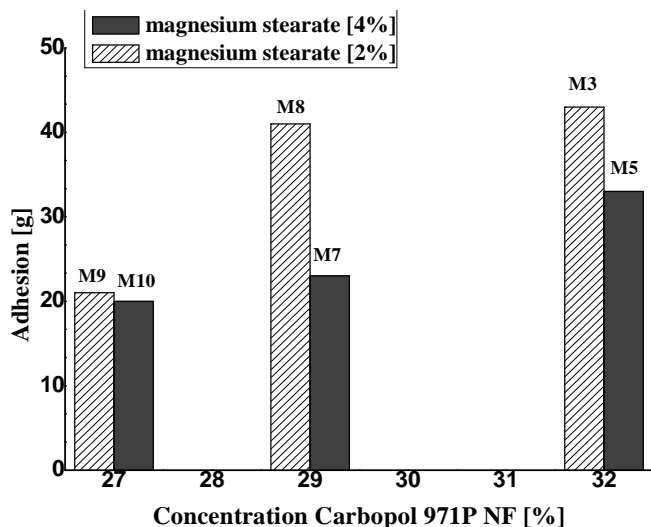


Fig. 2: Influence of the concentration of Carbopol[®] 971P NF and concentration of magnesium stearate on the adhesion ability of the different model compositions (Models M3, M5, and M7-M10, respectively).

From the data presented in Fig. 1 and 2 it can be clearly seen, that the type and concentration of polymer carrier as well as the inclusion and concentration of magnesium stearate affect the adhesion ability of the paste. Of particular importance is the type of mucoadhesive polymer carrier. Models based on Carbopol[®] 971P NF demonstrate higher adhesion ability compared to models based on Carbopol[®] 974P NF. That is due to the fact that Carbopol[®] 974P NF has a higher degree of crosslinking.

Thus, Carbopol[®] 971P NF polymer tends to be more efficient in controlling drug release than Carbopol[®] 974P NF polymer because it has smaller degree of crosslinking and provides three dimensional gel structure, which is more resistant to diffusion and erosion. With the inclusion of magnesium stearate as structural

forming additive, the adhesion ability decreases. The reduction of the adhesion ability is more pronounced in model compositions based on Carbopol[®] 974P NF. The adhesion ability of M4 and M6 decreased with 35% and 40%, respectively. The data obtained shows that adhesion ability of M3 based on Carbopol[®] 971P NF and 2% magnesium stearate decreases only with 5%, while with increasing the quantity of magnesium stearate to 4% in M5 reduces this parameter more than 30%. This is reasonable due to the significant hydrofobicity and hampered ability to wetting of the polymer.

The results presented in Fig. 2 clearly indicate the significant influence of the concentration of Carbopol[®] 971P NF on the adhesion ability of the samples. The relative adherence for M3 and M9 decreased from 43 to 21g, respectively with decreasing the concentration of polymer from 32% to 27%. The differences in relative adherence between 32% and 29% concentration of the polymer are not so insignificant (M3 and M7).

Based on the performed comparative studies, it could be concluded that model compositions based on Carbopol[®] 971P NF in concentrations higher than 29% have considerably better adhesion ability in the presence of not more than 2% of magnesium stearate.

Stability studies

Initially, test for estimating the stability of the developed model compositions under stress storage conditions (60 °C) for 48 hours was conducted. The results from the investigation are shown in Fig. 3. Data shows that amount of separated oil phase in model compositions M3, M7 and M9 is significantly reduced with inclusion of 2% of magnesium stearate. Increasing the concentration of magnesium stearate to 4% leads to deterioration of the structure of the paste, resulting in sliding (separated oil is greater than 10 mg). The change in concentration of the polymer carrier does not influence significantly on its stability.

It can be concluded that the introduction of 2% magnesium stearate in the investigated model compositions is effective in improving the physical stability of the systems.

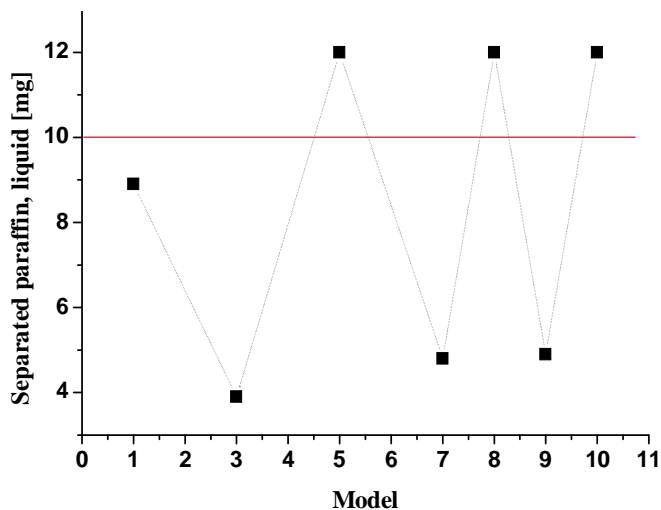


Fig. 3: Stability studies for model compositions based on Carbopol 971P NF under stress storage conditions (60 °C) for 48 hours.

Composition of M7 was conducted in preliminary stability study at room temperature for a period of 6 months. The results showed the absence of separation of oil and a similar release profile to that of freshly prepared model M7 (Fig. 4).

In vitro drug release

Based on the results obtained above, a study for the in vitro drug release was carried out for model compositions M3, M7 and M9. The drug release data are presented in Fig.4.

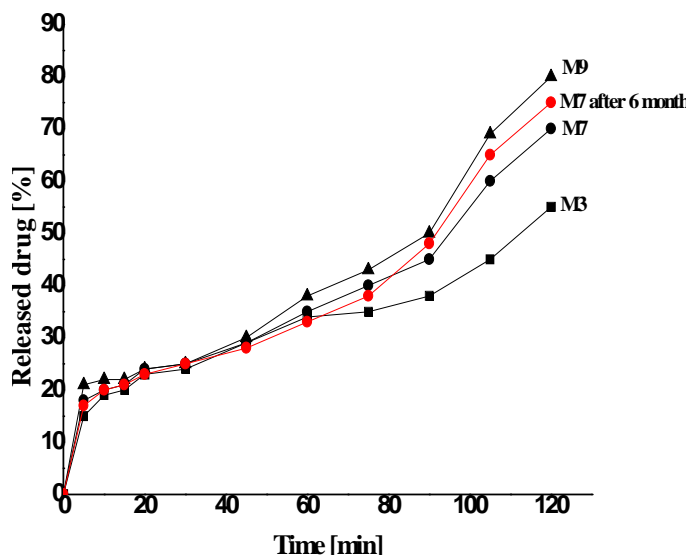


Fig. 4: In vitro release of Methylprednisolone hydrogen succinate from M3, M7, M9, and M7 after 6 months storage.

It is noteworthy that at all tested models in the process of Methylprednisolone hydrogen succinate release begins with a pronounced burst effect - 15-22% of the substance is released for 5 minutes. After that period kinetics of release is characterized by relatively constant and low release rate to approximately 80 minutes, then an increase in the rate of release of the included drug is observed. The rate increase of release of Methylprednisolone hydrogen succinate is due to the start of the process of erosion of the swollen gel structure. Most significant is sustaining the drug release from model composition M3 (containing 32% Carbopol® 971P NF), where at the 120 minute only 55% of the included drug is released. With decrease of the polymer concentration, the rate of drug release increases and at 120 minute reaches 71% and 80% for M7 and M9, respectively. This is a positive result according to a local action of Methylprednisolone hydrogen succinate in mucoadhesive pastes.

CONCLUSION

Model compositions of mucoadhesive pastes based on Carbopol® 971P NF and Carbopol® 974P NF have been

developed. The influence of the type and concentration of the polymer to the adhesion ability and drug release properties was established. The use of carbomer type Carbopol® 971P NF provides better adhesion ability than using carbomer type Carbopol® 974P NF, due to the higher degree of crosslinking of Carbopol® 974P NF. Concentrations of Carbopol® 971P NF over 27% provide better kinetics of drug release, up to 120 minutes to 80%. It was established 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. The results after 6 months storage of the model M7 showed absence of separation of oil and a similar release profile to that of freshly prepared model M7. Based on the results of the studies, mucoadhesive composition was optimized to be investigated further in vivo studies.

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