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# IN VITRO EVALUATION OF SPRAY-DRIED MUCOADHESIVE MICROSPHERES FOR NASAL ADMINISTRATION

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## ABSTRACT

Microspheres of disodium cromoglycate (DSCG) were prepared with either polyacrylic acid (Carbopol 934) or sodium carboxymethylcellulose (NaCMC) by the spray-drying technique. The arithmetic mean diameter of the spray-dried particles ranged from 3.2 to 5.7 microns. The plain DSCG particles and the microspheres containing NaCMC were spherical and had a smooth surface, whereas the microspheres containing Carbopol 934 were more irregular

and partly shrunken. The dissolution rate of the plain DSCG was prolonged when the drug was incorporated with the polymers. The more polymer the microspheres contained the slower the drug release rate. The in vitro mucoadhesion test showed that the plain DSCG was nearly as mucoadhesive as the the plain polymers. The microspheres of DSCG with either of the polymers were, however, clearly more mucoadhesive than the plain starting materials. The adsorption isotherms showed the hygroscopic nature of the polymers and DSCG. The hydration of the microspheres increased as a function of the drug content.

## INTRODUCTION

Intranasally administered drug substances are normally transported towards the pharynx at an average speed of 6-10 mm/min because of mucociliary clearance (1). The rapid clearance of drug particles can be considered the major factor for inefficient nasal absorption of both local and systemic medication (2). Mucoadhesive polymers which absorb water and stick to the mucin layer of the mucosal tissue may be used to increase contact time between a dosage form and a mucosal layer. Thus use of polymers may enhance drug adsorption. Adsorption of water is an important step in the mucoadhesion process, because only hydrated polymer chains are free to move and stretch, and thus become both mechanically and chemically interlocked with the glycoproteins of mucus.

According to Gu and coworkers (2) drugs may be incorporated with mucoadhesive matrixes by either synthesizing the polymer with the drug in the reaction mixture, or loading the mucoadhesive by swelling the polymer in a saturated drug solution. Stability of the drug may be a concern in the former case and low loading yield in the latter. The spray-drying technique may also be used in formulating mucoadhesive microspheres: a solution or suspension of an active ingredient and a mucoadhesive polymer is dispersed into a hot air stream as small droplets. The liquid is evaporated and solid microspheres containing both the drug substance and the mucoadhesive polymer are obtained. Spray drying technique can be used for sensitive materials; thus stable microspheres with relatively high loading capacities may be formulated.

Modified surface tension testers are commonly used when in vitro mucoadhesive strength is determined (3). Animal tissues such as rat jejunum or stomach (4), rabbit stomach (5), or mucous membranes from the eosophagus of various animals (6) have been used. Because animal tissue experiments are quite complicated, more simplified methods based on artificial membranes have been developed (7). When a mucoadhesive bond strength of different polymers is determined, different in vitro techniques and testing equipment generally give comparative values rather than the absolute strength of mucoadhesion (8). In the present study mucoadhesive disodium cromoglycate microspheres were formulated by the spray-drying technique. The physical properties as well as the in vitro nasal mucoadhesion of the plain starting materials and the microspheres were determined.

## MATERIALS AND METHODS

The plain disodium cromoglycate (DSCG) (BP 1988, Fermion, Finland) was spray-dried (Buchi Mini Spray Dryer, type 190, FRG) from a 6 % w/w water solution using the slightly modified method by Vidgren et al. (9). The microspheres were spray dried from aqueous solutions containing either polyacrylic acid (Carbopol 934) or sodium carboxymethylcellulose (NaCMC) as the mucoadhesive component. Each polymer was separately dissolved in water to give 1 % w/w solution. DSCG was added to the polymer solution to give either 3:1 or 1:1 drug-polymer ratio. The plain DSCG and the microspheres were spray-dried with a 0.7 mm nozzle at a feed rate of 380 and 250 ml/h respectively. The nozzle air pressure was 350 Nl. The inlet and output temperatures were about 220 °C and 149°C, respectively.

Particle size distributions were determined from scanning electron micrographs (Jeol Scanning Electron Microscope, type 35, Japan). Feret's diameter of 200 particles was measured. Electron micrographs were also used for studying particle shape.

The DSCG content of the microspheres was analyzed spectrophotometrically at 238 nm (Hitachi 220, Japan). The mucus secreted from a healthy mucosal layer has been reported to be slightly acidic and have weak ionic strength (10-12). The dissolution medium of our study simulated to some extent physical properties of mucus of nasal cavities. The dissolution profiles were determined with a through flow cell method using potassium phosphate buffer as a dissolution medium. The pH of the buffer was adjusted to 6.0 by dipotassium hydrogen phosphate and potassium dihydrogen phosphate buffers, whose ionic strength had been adjusted to 0.0935 by sodium chloride. The buffer solution, 900 ml in volume and 37 °C in temperature, was mixed with a blade stirrer at the rotation speed of 50 rpm. The powder samples were added into the dissolution medium to form a suspension. The pH of the dissolution medium was monitored during the dissolution test. The drug concentrations in the dissolution media were analyzed spectrophotometrically at 238 nm at different time intervals. Each test was repeated five times.

A modified surface tension tester (GWB Kruss 13271, Germany) was used to evaluate the mucoadhesive properties of the samples (5). The plain polymers as well as the spray-dried DSCG and the microspheres consisting of DSCG and either of the polymer were evaluated by measuring the force required to separate two filter paper disks (Macherey-Nagel 617) between which the examined sample was placed. The lower filter paper disk was secured on a steel stand. The upper filter paper disk, connected to the force measurement system, was placed over a cork stopper and secured with an aluminium cap with a hole (surface area of 50.2 $mm^2$). The disks of filter paper were saturated with 2.5 % w/w mucin gel (Type I-S, from bovine submaxillary glands, Sigma Chemicals, USA). The examined sample was spread over the exposed surface of the upper filter paper, and the excess of the sample was carefully blown away by pressurized air. The two surfaces of the filter paper disks were adjusted into contact with each other. After a 30-second contact time, realized with the weight of the upper section (960 mg), the lower filter paper section was lowered, and the force required to detach the surfaces was measured. A lipophilic steroid, beclomethasone dipropionate (BDP), was used as practically non-mucoadhesive reference material. Each test was repeated five times.

The adsorption isotherms of the plain DSCG, BDP, NaCMC and Carbopol as well as the microspheres were determined by the gravimetric method. During the 30-minute test the examined sample was stored under high relative humidity (RH 97 %) created with saturated potassium sulphate solution. The increase of mass was recorded with a microbalance connected to the computer system.

## RESULTS AND DISCUSSION

Low drug content is often a problem when mucoadhesive microspheres are prepared (2). However, with the spray-drying technique it was possible widely and reliably to change the amount of the drug incorporated with the microspheres. The initial drug loading of the feed solution remained constant in the spray-drying process resulting at drug contents of on average either 50.0 +/- 4.7 % or 75.0 +/-2.1 %.

According to Rabbe and coworkers (13) 4 microns is a sufficient particle size for nasal administration. The arithmetic mean diameter with the standard deviation of the plain DSCG particles was 5.4 +/- 3.2 microns. The size of the microspheres ranged from 3.2 +/- 2.8 microns (DSCG:NaCMC 50:50) to 5.7 +/-3.9 microns (DSCG:Carbopol 75:25). In all the samples about 50 % of the particles had, however, the diameter of 4 microns or more. The NaCMC samples contained fewer large particles than the Carbopol samples did. Thus the spray-dried microspheres were suitable for nasal administration being, however, close to the lower proposed size limit.

The plain spray-dried DSCG particles and the microspheres containing NaCMC were nearly spherical, whereas the particles containing Carbopol as the mucoadhesive ingredient were irregular and partly shrunken (Fig. 1). The differences in the particle shape and in the surface structure of the intranasally administered particles may affect aerodynamic properties as well as sticking, wetting and swelling behaviour of the microspheres. Therefore also differencies in mucoadhesion, dissolution and absorption properties may partly be due to the particle shape and the surface structure of the microspheres.

In the in vitro dissolution test the plain DSCG dissolved totally in 6 minutes (Fig. 2). The dissolution of DSCG was prolonged when the drug was incorporated with the

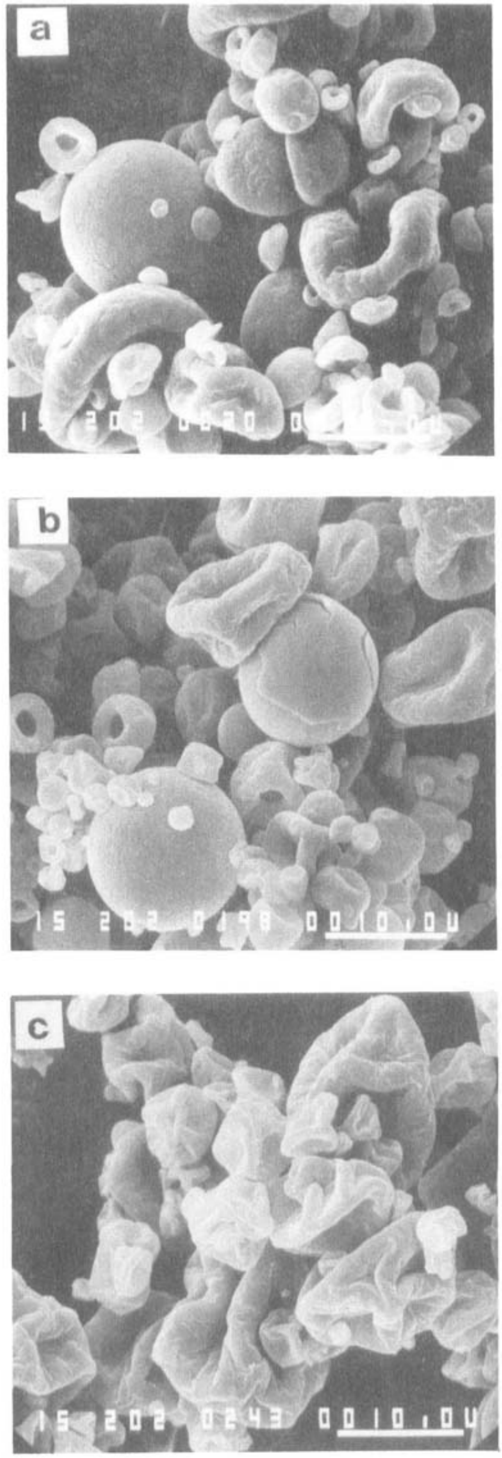


FIGURE 1
Typical scanning electron micrograps of the spray-dried disodium cromoglycate (a) and the microspheres containing either sodium carboxymethylcellulose (b) or Carbopol (c). The lenght of the bar is 10 microns.

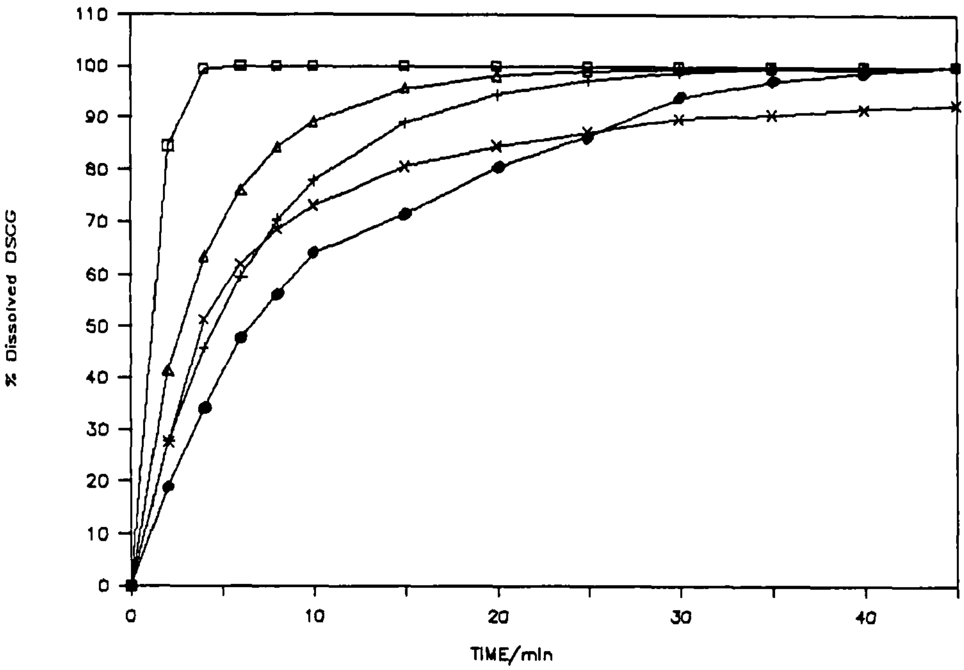


FIGURE 2

Dissolution profiles of the plain disodium cromoglycate (DSCG) particles and the microspheres containing either sodium carboxymethylcellulose (NaCMC) or Carbopol. [ DSCG:NaCMC (75:25); DSCG:NaCMC (50:50); DSCG:Carbopol (75:25); DSCG:Carbopol (50:50)and DSCG]

polymers. The increase in the polymer content resulted in the decrease in the drug release rate from the microspheres. At the beginning of the dissolution process NaCMC prolonged the release of DSCG more than Carbopol did. The total amount of DSCG was released from the microspheres in 45 minutes. Besides the proportion of the polymer in the microspheres the properties of the polymer network inside the microspheres and the differencies in the surface properties of the microspheres as well as the drug polymer interactions may have contributed to the release of DSCG. The pH of the dissolution media decreased from 6.0 to 5.9 and 5.6 when Carbopol microspheres of 25 % and 50 % polymer content, respectively, had dissolved. The dissolution of the NaCMC microspheres and the plain DSCG did not change pH of the dissolution media. Carbopol is a polyacrylic acid, which donoted hydrogen ions to the buffer solution, thus increasing acidity of the solution. NaCMC and DSCG both acted as weak alcalines, and the acidity of the dissolution solution remained unchanged. The possible unphysiological changes due to Carbopol in nasal cavities may theoretically be harmful. To decrease these effects a sodium salt of polyacrylic acid could be used (14).

Carbopol and NaCMC have been classified as excellent mucoadhesives (15). In the present study Carbopol seemed to be more mucoadhesive in vitro than NaCMC was.

Hygroscopic DSCG turned out to be surprisingly mucoadhesive: a larger force was required to detach the mucin coated surfaces when the examined sample was DSCG than when it was NaCMC. A lipophilic steroid, BDP possessed hardly any mucoadhesion compared to the polymers and DSCG.

Table 1. The mean mucoadhesive strenght (dyne/$cm^2$) with the standard deviation of the plain starting materials and the spray dried particles (n=6).

| | | |
|---|---|---|
| Starting materials | | |
| DSCG | | 859 +/- 160 |
| NaCMC | | 615 +/- 137 |
| Carbopol | | 1014 +/- 292 |
| BDP | | 219 +/- 48 |
| Spray dried microspheres | | |
| DSCG:NaCMC | (75:25) | 1032 +/- 158 |
| DSCG:NaCMC | (50:50) | 1202 +/- 51 |
| DSCG:Carbopol | (75:25) | 930 +/- 61 |
| DSCG:Carbopol | (50:25) | 1532 +/- 137 |

DSCG = Disodium cromoglycate, NaCMC = sodium carboxymethylcellulose, Carbopol = polyacrylic acid and BDP = beclomethasone dipropionate.

When DSCG was incorporated with the polymers, mucoadhesion of the microspheres increased (Table 1). The more polymer the particles contained, the stronger the mucoadhesion. When the polymer content of the microspheres was 25 %, both polymers resulted in almost similar in vitro mucoadhesion. The strongest mucoadhesion was achieved with the microspheres, whose Carbopol content was 50 %. DSCG increased the mucoadhesion of the microspheres probably by contributing to the wetting of the particles and thus to the loosening of the polymer chains. This is also supported by Peppas and Buri, who reported that at high polymer concentrations, such as the

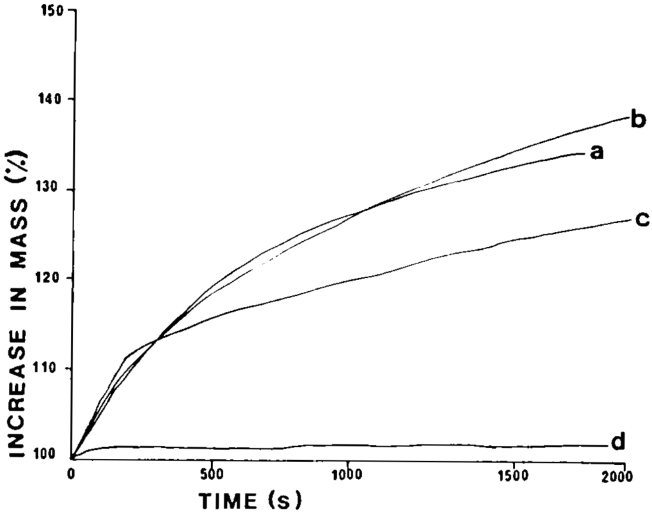


FIGURE 3 A

Adsorption isotherms of the plain disodium cromoglycate particles (a); sodium carboxymethylcellulose (b); Carbopol (c) and beclomethasone dipropionate (d).

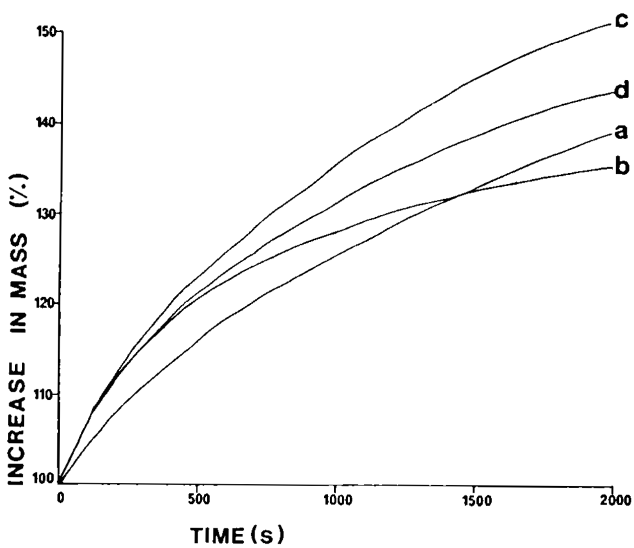


FIGURE 3 B

Adsorption isotherms of the microspheres containing disodium cromoglycate (DSCG) and either sodium carboxymethylcellulose (NaCMC) or Carbopol.
[a = DSCG:NaCMC (50:50); b = DSCG:Carbopol (50:50);
c = DSCG:NaCMC (75:25); d = DSCG:Carbopol (75:25)]

plain polymer, mucoadhesive formulations exhibit less adhesion with the mucus than at lower polymer concentrations (16). At lower concentrations the polymer structure is more loose and the polymer chains have more space to extend within the mucus. As the number of polymer chains penetrating per unit volume of mucus is increased a strong bond, either chemical, mechanical or the both, is formed between the mucus and the polymer (9). The adsorption isotherms showed clearly the hygroscopic nature of DSCG and the polymers (Fig. 3 A). The increase of mass was clearly the smallest for Carbopol, whereas DSCG and NaCMC adsorbed water equally effectively.

The mass of the microspheres increased more than the mass of the plain starting materials did. DSCG is a hygroscopic drug substance that binds up to eight molecules of water within its crystal structure (17). This property contributed to a better wetting and thus increased mucoadhesion of the microspheres. The largest increase in mass was obtained for the microspheres of NaCMC, whose drug content was 75 % (Fig 3 B).

Adsorption of water was fastest during the first 4 minutes. Thus the hydration of polymers occured relatively fast. The total increase of mass ranged from 27 % (pure Carbopol) to 52 % (DSCG:NaCMC 75:25). BDP adsorbed no water at all. Because the wetting of the microspheres correlated only partly with the results of the in vitro mucoadhesion, the mucoadhesion can only partly be explained by the adsorption properties of the microspheres.

## CONCLUSIONS

It is possible to prepare mucoadhesive microspheres by the spray-drying technique. The amount and the type of the polymer can be changed, and the microspheres can be incorporated with relatively large amounts of DSCG. Both the dissolution and the mucoadhesion properties of the microspheres can be altered by varying the proportion and the type of the polymer incorporated with DSCG.

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