ELSEVIER

International Journal of Pharmaceutics 142 (1996) 169–174

In-vitro bioadhesion of carbopol hydrogels

H. Blanco-Fuente, S. Anguiano-Igea, F.J. Otero-Espinar*, J. Blanco-Méndez

Departamento de Farmacología, Farmacia y Tecnología Farmacéutica, Laboratorio de Farmacia Galénica, Facultad de Farmacia, Campus Universitario, 15706 Santiago de Compostela, Spain

Received 24 May 1996; accepted 10 July 1996

Abstract

The main goal of this work was to study the adhesive capacity of hydrogels obtained from carbopol, this was achieved using a tensile tester in which adhesion work was the main parameter. The intended use of these hydrogels was the buccal administration of propanolol HCl. The adhesion assays were carried out under two hydration conditions, in order to evaluate the influence of water on adhesion. Results showed that adhesion capacity was considerably increased when water was limited in the system. The influence exerted on adhesion work by the polymer molecular weight and the crosslinking percentage were also studied and results showed that an increase in either of the mentioned parameters gave rise to a decrease in adhesion.

Finally, propranolol HCl was included into the hydrogels. It was observed that when water was limited in the system there was an increase in adhesion due to the increase in elasticity caused by the formation of a complex between the polymer and the drug. However, when there was no water limitation there was a slight decrease in adhesion caused by the precipitation of the complex carbopol-propranolol HCl.

Keywords: Carbopol-propranolol complex; System elasticity; Molecular weight; Crosslinking; Adhesion work; Hydration volume

1. Introduction

During the past few years there has been an increasing interest in the development of pharmaceutical forms which can control-release a drug through mucoses by using bioadhesive polymers. The main reason for this interest is that it offers the prospect of prolonging the residence time of controlled release formulations at the site of drug absorption and a close contact on the absorption surface (Duchêne et al., 1988; Gu et al., 1988; Gandhi and Robinson, 1994; Kopeckova et al., 1994).

The term bioadhesion is used to describe a phenomenon that is related with the capacity

* Corresponding author.

PII S0378-5173(96)04665-0

presented by some synthetic, biological or hydrocolloidal macromolecules to adhere to biological tissues, this process only takes place in the presence of water (Longer and Robinson, 1986; Boddé and Leiden, 1990).

There are numerous articles in the literature describing the characteristics a compound needs in order to have appropriate adhesive capacity: functional groups able to form hydrogen bridges (-OH, COOH), anionic charges, sufficient elasticity for the polymeric chains to interpenetrate the mucus layer and finally a high molecular weight (M_r) (Gurny et al., 1984; Smart et al., 1984; Park, 1986; Leung and Robinson, 1988; Lejoyeux et al., 1989; Duchêne and Ponchel, 1989).

Prior to selecting a bioadhesive compound to prepare a controlled release pharmaceutical formulation, it is necessary to determine its adhesive capacity, thus adhesion assays need to be carried out. Preliminary studies for in vitro screening are needed which in turn limit the amount of formulations and/or polymers that are going to be tested later in vivo, thus sparing an unnecessary high number of animal lives.

The tensile tester is one which is used widely to evaluate the adhesive capacity of different polymers and formulations and is well documented (Robert et al., 1985; Ponchel et al., 1987., Thermes et al., 1992; Jiménez-Castellanos et al., 1993; Ferrari et al., 1994; Mortazavi and Smart, 1995). This method determines the maximum work or force needed in order to separate two materials that exist in intimate contact.

In the present work the adhesive capacity of hydrogels—obtained from carbopol (CP) which were designed for the buccal administration of propranolol HCl—was evaluated using the tensile tester. The variables, such as polymer M_r and cross-linking, which influence adhesion values were studied. The assays were conducted in different hydration environments in order to evaluate their effect on adhesion. Further, an important factor which needs to be taken into account is that drug loading can modify all the adhesive characteristics of a formulation (Anlar et al., 1994).

2. Materials and methods

2.1. Materials

CP 941, CP 934 and CP 940 of nominal M_r 1 250 000, 3 000 000 and 4 000 000, respectively (Goodrich) were obtained from J. Escuder; propranolol chlorohydrate was supplied by Roig Farma (Spain).

Tanned leather was used as the adhesive substrate due to the good correlation obtained between the tanned leather and bovine sublingual mucose in a previous study (Otero-Espinar et al., 1994a).

2.2. Methods

2.2.1. Hydrogel preparation

Hydrogels were obtained by compressing at high pressure the polymer or the polymer and drug in a hydraulic press applying a force of 7500 kg for 2 min. The diameter used was 13 mm. Cross-linking was achieved by applying heat using the following temperatures: 90, 110 and 130°C for 4 h (Blanco-Fuente et al., 1996).

Adhesion studies were carried out on hydrogels obtained from non cross-linked CP 941, CP 934 and CP 940 and the same hydrogels subjected to cross-linking temperatures of 90, 110 and 130°C. Assays were performed on formulations obtained from 200 mg of polymer and afterwards on formulations containing propranolol hydrochloride (keeping the polymer amount constant and adding 50 mg of the drug).

2.2.2. Adhesion studies

The adhesion capacity was determined by applying the tensile-tester (Lloyd, Instruments LR 5K). The hydrogel was adhered to the upper support and the substrate to the lower support using a cyanoacrylate adhesive. Upon contact of hydrogel and substrate a defined force was applied during certain time. This was followed by an extension phase at a defined rate until total separation of the components was achieved. Adhesion studies were conducted as detailed in Otero-Espinar et al. (1994b). Previous results from this laboratory have demonstrated that in order to

obtain adequate adhesion work values using this type of polymers, the optimum conditions are: an applied force of 0.5 N and a contact time of 20 min. Furthermore, two hydration environments were tested as it has been described that this factor considerably influences adhesion:

(1) Assays where water was limited: studies were carried out using dry tanned leather as substrate. Water (25 μl) were homogeneously extended on the hydrogel situated on the upper support of the tension apparatus.

(2) Assays where there was no water limitation: this method was derived from the previous one. In these experiments the same assays and conditions as before were used, but the substrate and hydrogel were previously introduced into 25 ml of water at 37°C.

Six replicates were obtained from each formulation.

3. Results and discussion

Fig. 1 shows the adhesion results expressed per surface unit as a function of the polymer M_r in both environments. An increase in the polymer M_r gave rise to a decrease in adhesion in every formulation tested. This decrease was more noticeable when we changed from an almost linear polymer such as CP 941, to a branched polymer such as CP 934; as from this M_r value (3 000 000) adhesion remains practically constant. Similar results were obtained elsewhere (Saettone et al., 1989; Lejoyeux, 1991; Anlar et al., 1993). According to these authors, the optimum adhesion of carbopol is approximately 10^6 Da, where a compromise is reached between diffusion capacity of the polymeric chains which favours adhesion and a satisfactory cohesivity for the formation of a bond that possesses sufficient mechanical resistance. An increase in M_r gives rise to a decrease in chain diffusion. This is due to the polymer branched structure where the process is hampered, less coupling points created and the adhesion work decreased.

In experiments carried out without water, limitation adhesion values were lower, albeit maintaining the same pattern. Carbopol gets highly hydrated in the presence of water which causes a loss in mechanical resistance, and in the adhesive interface causes a decrease in density of the adhesion work promoter groups (Gurny et al., 1984).

On the other hand, an increase in cross-linking gave rise to a decrease in adhesion work (Fig. 2), this is due to the profound changes in density and mobility of the chains that occur when a polymer is subjected to cross-linking. Non cross-linked hydrogels display appropriate flexibility and elasticity properties, thus once in contact with the substrate the chains would rapidly diffuse, creating a strong bond, consequently their separation would require a higher force thus separation work considerably increases. Chain flexibility gave rise to a deeper penetration of the substrate thereby

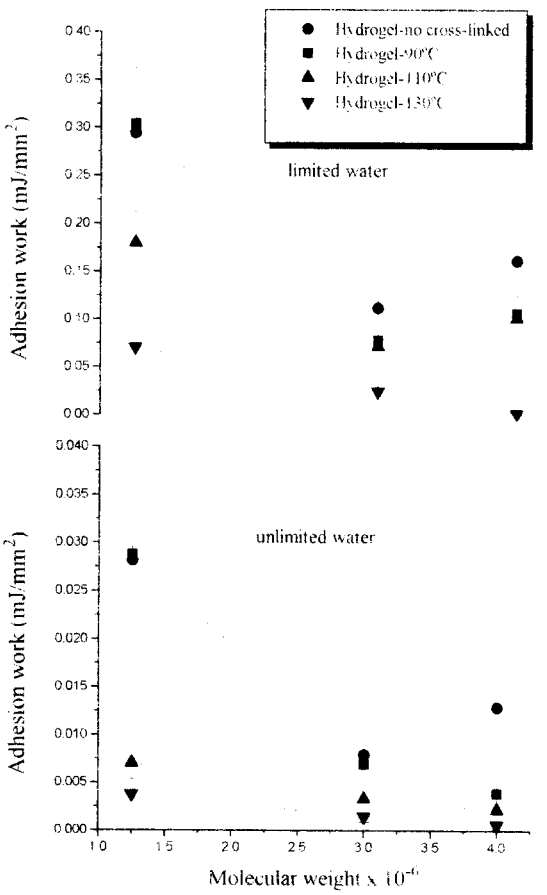

Fig. 1. Influence of carbopol molecular weight on adhesion work.

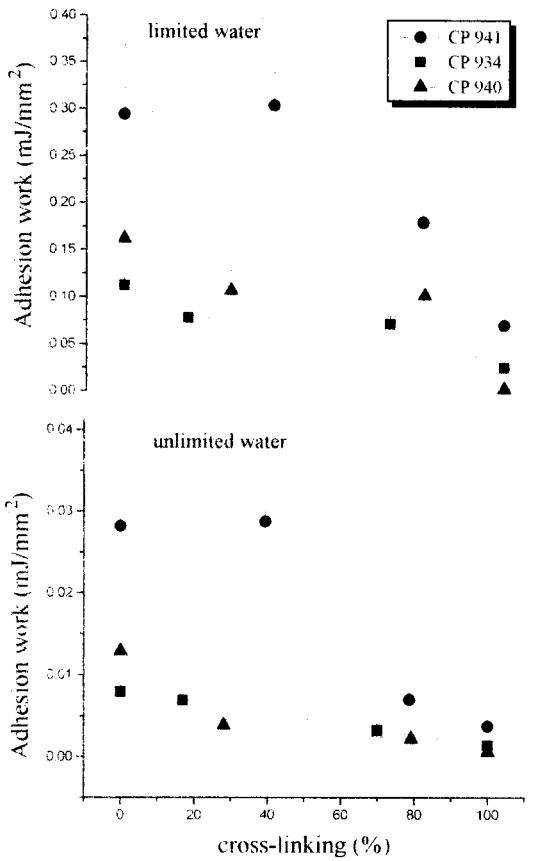

Fig. 2. Influence of cross-linking on adhesion work.

creating a stronger adhesion union. As the cross-linking percentage was increased, the chain elasticity and flexibility was decreased and consequently adhesion decreased. Therefore, the adhesive force is higher when the lower cross-linking percentage is used. Further, in crosslinked hydrogels there is a decrease of acid groups (which are responsible for the adhesive couplings) due to cross-linking taking place via the reaction between two acid groups to form the anhydride (Blanco-Fuente et al., 1996).

Although there exist many reports in the literature where no important modification in adhesion capacity has occurred upon inclusion of a drug in a formulation, there have been cases where the inclusion of certain drugs can alter the adhesive properties of a polymer (Anlar et al., 1994).

In this study different results were obtained depending on whether water was limited or not (Fig. 3). In assays where water was limited, there was an increase in adhesion. In order to explain this increase, the variations produced in the elasticity of the system when a drug is included should be taken into account. In Fig. 4, the modules of Young, of the systems comprising the substrate and the adhesive formulation in both environments studied, which were calculated from the initial rate of force-elongation graphs are plotted (Ponchel et al., 1987). From this graph, it can be observed that the inclusion of propranolol HCl gave rise to a decrease of the elasticity modules, thus an increase in the elasticity of the system was observed. Previous studies described the existence of a poorly soluble ionic complex between carbopol and propranolol (Pérez-Marcos et al., 1994) which under a low hydration environment improves the elasticity of the system thereby improving the adhesive characteristics.

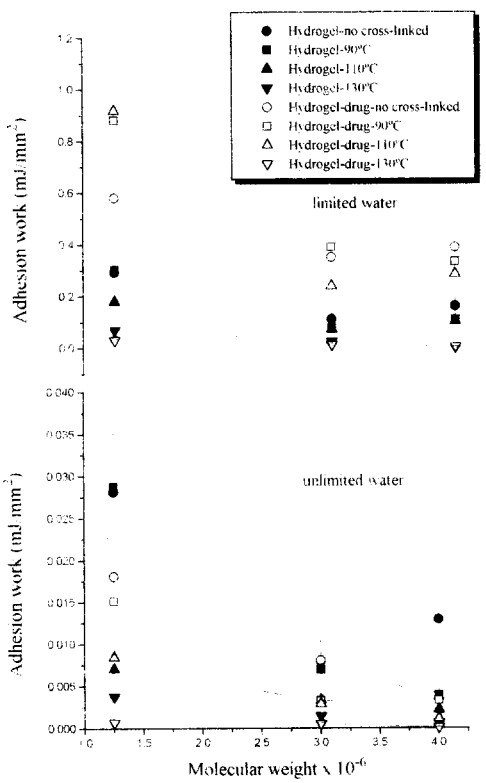

Fig. 3. Influence of propranolol HCl addition on adhesion.

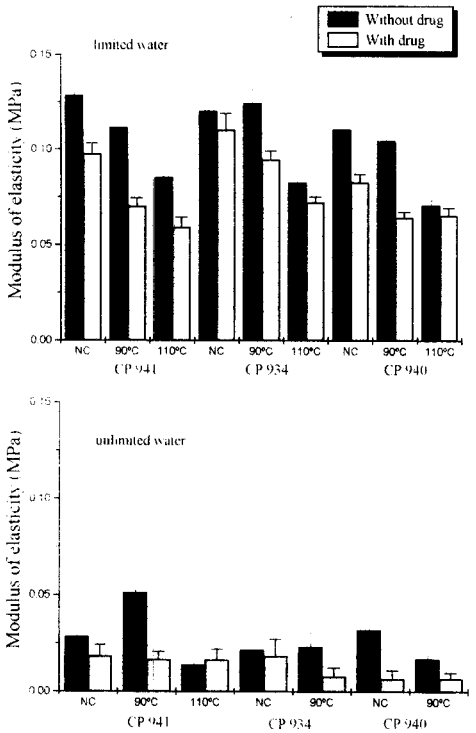

Fig. 4. Elasticity modules of hydrogels obtained from Carbopol (NC = no cross-linked).

The increase in elasticity is clearly obvious in the force-elongation curves obtained from hydrogels with and without the included drug (Fig. 5): the presence of propranolol increases the elongation of the system, which causes the increase in the adhesion work because in the majority of cases the maximum obtained force remains invariable. However, in the case of assays where there did not exist any aqueous limitation, propranolol addition caused a slight decrease in adhesion. This was probably due to the precipitation of the complex formed between the carbopol and propranolol, decreasing the mechanical resistance of the formulation and the concentration of CP responsible for adhesion.

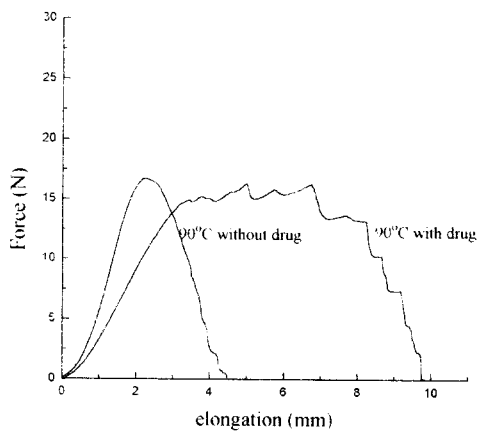

Fig. 5. Carbopol hydrogels force-elongation curves, obtained from adhesion studies.

Acknowledgements

This work was supported by a grant SAF92-0632 from the Comision Interministerial de Ciencia y Tecnología (CICYT). We acknowledge Boehringer Mannheim for LLoyd LR 5K.

References

Anlar, S., Çapan, Y. and Hincal, A.A., Physico-chemical and bioadhesive properties of plyacrylic acid polymers. *Pharmazie*, 48 (1993) 285–287.

Anlar, S., Çapan, Y., Güven, O., Gögüs, A., Dalkara, T. and Hincal, A.A., Formulation and in vitro-in vivo evaluation of buccoadhesive morphine sulfate tablets. *Pharm. Res.*, 11 (1994) 231–236.

Blanco-Fuente, H., Anguiano-Igea, S., Otero-Espinar, F.J. and Blanco-Méndez, J., Kinetics of anhydride formation in xerogels of poly(acrylic acid). *Biomaterials*, 17 (1996) 1667–1675.

Boddé, H.E. and Leiden, N.L., Principles of bioadhesion. In Gurny, R. and Junginger, H.E. (Eds.), *Bioadhesion Possibilities and Future Trends*. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 1990, pp. 44–64.

Duchêne, D. and Ponchel, G., Bioadhesion a new pharmacotechnical method for improving therapeutic efficiency. *S.T.P. Pharma.*, 5 (1989) 830–838.

Duchêne, D., Touchard, F. and Peppas, N.A., Pharmaceutical and medical aspects of bioadhesive systems for drug administration. *Drug Dev. Ind. Pharm.*, 14 (1988) 283–318.

Ferrari, F., Bertoni, M., Caramella, C. and La Manna, A., Description and validation of an apparatus for gel strength measurements. *Int. J. Pharm.*, 109 (1994) 115–124.

Gandhi, R.B. and Robinson, J.R., Oral cavity as a site for bioadhesive drug delivery. *Adv. Drug Del. Rev.*, 13 (1994) 43–74.

Gu, J.M., Robinson, J.R. and Leung, S.H.S., Binding of acrylic polymers to the mucin/epithelial surfaces:structure-property relationships. *CRC Crit. Rev. Ther. Drug Carrier Systems.*, 5 (1988) 21–67.

Gurny, R., Meyer J.M. and Peppas, N.A., Bioadhesive intraoral release systems: design, testing and analysis. *Biomaterials*, 5 (1984) 336–340.

Jiménez-Castellanos, M.R., Zia, H. and Rhodes, C.T., Assessment of an in vitro method for measuring the bioadhesiveness of tablets. *Int. J. Pharm.*, 89 (1993) 223–228.

Kopeckova, P., Rathi, R., Takada, S., Rihova, B., Kopecek, J. et al., Bioadhesive *N*-(2-hydroxypropyl)methacrylamide copolymers for colon specific drug delivery. *J. Controlled Release*, 28 (1994) 211–222.

Lejoyeux, F., Ponchel, G. and Duchêne, D., Influence of some technological parameters on the bioadhesive characteristics of polyacrylic acid matrices. *S.T.P. Pharma.*, 5 (1989) 893–898.

Lejoyeux, M.F., *Evaluation de la bioadhésion de systemes matriciels d' acide polyacrylique: influence de paramètres physicochimiques el pharmacotechniques*. Ph.D., University of Paris-Sud, 1991.

Leung, S.-H.S. and Robinson, J.R., The contribution of anionic polymer structural features to mucoadhesion. *J. Controlled Release*, 5 (1988) 3–231.

Longer, M.A. and Robinson, J.R., Fundamental aspects of bioadhesion. *Pharmacy Int.*, (1986) 114–117.

Mortazavi, S.A. and Smart, J.D., An investigation of some factors influencing the in vitro assessement of mucoadhesion. *Int. J. Pharm.*, 116 (1995) 223–230.

Otero-Espinar, F.J., Blanco-Fuente, H., Vila-Dorrío, B., Anguiano-Igea, S., Ganza-González, A. and Blanco-Méndez, J., *Influence of substrate on adhesion test*. 21st Int. Symp. Controlled Release of Bioactive Materials, Nice, France, 1994a, pp. 702–703.

Otero-Espinar, F.J., Blanco-Fuente, H., Vila-Dorrío, B., Anguiano-Igea, S., Ganza-González, A. and Blanco-Méndez, J., *Optimization of adhesion measurements by tensile tester*. 21st Int. Symp. Controlled Release of Bioactive Materials, Nice, France, 1994b, pp. 700–701.

Park, H., *On the mechanism of bioadhesion*. Ph.D. University of Wisconsin-Madinson, 1986.

Pérez-Marcos, B., Ford, J.L., Amstrong, D.J., Elliott, P.N.C., Rostron, C. and Hogan, J.E., Release of propranolol hydrochloride from matrix tablets containing hydroxypropylmethylcellulose K4M and Carbopol 974. *Int. J. Pharm.*, 111, (1994) 251–259.

Ponchel, G., Touchard, F., Duchêne, D. and Peppas, N.A., Bioadhesive analysis of controlled release systems. I. Fracture and interpenetration analysis in poly (acrylic acid) containing systems. *J. Controlled Release.*, 5 (1987) 129–141.

Robert, C., Buri, P. and Peppas, N.A., Experimental method for bioadhesive testing of various polymers. *Acta Pharm. Technol.*, 74 (1985) 399–405.

Saettone, M.F., Chetoni, S., Torracca, M.T., Burgalassi, S. and Giannaccini, B., Evaluation of muco-adhesive properties and in vivo activity of ophthalmic vehicles based on hyaluronic acid. *Int. J. Pharm.*, 51 (1989) 203–212.

Smart, J.D., Kellaway, I.W. and Worthington, H.E.C., An in vitro investigation of mucosa-adhesive materials for use in controlled drug delivery. *J. Pharm. Pharmacol.*, 36 (1984) 295–299.

Thermes, F., Grove, J., Rozier, A., Plazonnet, B., Constancis, A., Bunel, C. and Vairon, J.P., Mucoadhesion of copolymers and mixtures containing poly(acrylic acid). *Pharm. Res.*, 9 (1992) 1563–1567.