African Journal of Pharmaceutical Research and Development

Original Article

In vitro Evaluation of the Bioadhesive Properties of Sodium Carboxymethyl Cellulose, Acacia, Veegum® and Their Admixtures

IBEZIM, E. C* AND OFOEFULE, S. I.
Faculty of Pharmaceutical Sciences,University of Nigeria, Nsukka

* Correspondence

Accepted (Revised) July, 2005

A study was carried out to determine the suitability of the hydrocolloids, sodium carboxymethyl cellulose (SCMC), Veegum® (VG), acacia (AC) and their admixtures as bioadhesive matrices for metronidazole. Aqueous dispersions containing 8 % w/v of the hydrocolloids and their admixtures were prepared. The bioadhesive properties were evaluated using detachments of coated glass beads and tablet compacts from isolated biological tissue, as well as the adhesive force between aqueous dispersion and I-mucin measured with a tensiometer adapted to measure adhesive force. The viscosity of the aqueous dispersion of the polymers/polymer admixtures and swelling capacity of the metronidazole tablet compacts were also determined. The dissolution profiles of metronidazole from the various tablet compacts were assessed in simulated intestinal fluid (SIF) without enzyme. The hydrocolloids and their admixtures were found to possess bioadhesive properties. On the basis of bead detachment, sodium carboxymethylcellulose used alone, exhibited the highest bioadhesive strength while acacia exhibited the least. On the basis of tensiometry, dispersions containing SCMC alone exhibited the highest bioadhesion followed by the dispersion containing admixtures of VG, SCMC and AC (3:3:2), while the least bioadhesion was obtained with the dispersion containing VG, SCMC and AC (2:3:3). Results of detachment of the coated glass beads, indicated highest bioadhesion for VG/SCMC/AC (1:4:3 and 3:4:1). The slight differences between the result of the tensiometry and detachment of coated glass beads are attributed to difference in hydration of the two systems.

Keywords: bioadhesion, sodium carboxymethylcellulose, acacia, Veegum, admixtures, *in vitro*.

INTRODUCTION

Bioadhesion of certain water-soluble polymers, which become adhesive on hydration, can be used for targeting a drug at a particular region of the body for extended periods of time. Bioadhesion is simply the state in which two materials, at least one of which is of a biological nature, are held together for extended periods of time by interfacial forces (1). For drug delivery purposes, the term implies attachment of a drug carrier system to a specific biological surface, which can be an epithelial tissue or the mucous coat on the surface of some tissues.

Treatment of chronic inflammatory lesions of the oral mucosa such as aphthous stomatitis, has often been hampered by the difficulty in maintaining contact between the treatment composition and the mucosa for a prolonged time (2). The setbacks associated with the various means of drug administration have led to the increasing interest in the development of bioadhesive, controlled release dosage forms for the treatment of both topical and systemic diseases. Adhesion is believed to be an interfacial phenomenon, which is influenced by surface energies (3). This implies that interaction between the two surfaces involved must occur for adhesion to be established. In the course of this interaction, an adhesive junction, interface or bond is formed.

Several factors affect bioadhesion and include nature of medium, molecular weight and concentration of polymer, flexibility of polymer chains and spatial conformation of the polymer molecule, pH of polymer-substrate interface, pressure initially applied to mucoadhesive tissue, contact site and contact time.

Bioadhesive polymers are used for many hard and soft tissue applications in dentistry and orthopaedics (4). These dosage forms can bind to mucous or epithelial surface and be retained in that position for a long time, thus increasing overall drug absorption. Adhesive polymers are classified according to their physical form, nature of connected materials, type of

setting and chemical structure (5). Three major categories of polymers have been utilized successfully as bioadhesives and include the carboxyl-containing, the hydroxyl-containing and the polymers with charged species (6).

In this present study, the bioadhesive properties of three hydrocolloids - SCMC, acacia, Veegum and their admixtures were studied and the release of the antiprotozoal drug, metronidazole from bioadhesvie compacts of the matrices evaluated.

MATERIALS AND METHODS

Materials

The following materials were employed in the study as procured from their manufacturers: SCMC (Merck, Darmstadt), Veegum® (RT Vanderbilt, USA), acacia (FMC Corp., USA) and mucin.

Methods

Preparation of mucin

A freshly isolated guinea pig ileum was excised open, rinsed with chilled saline to remove the waste and mucin was scrapped from the mucus surface with a glass slide. The mucin was mixed with five-fold its volume of distilled water, homogenised by stirring for 2 h and equilibrated by storage at 4 °C for 48 h. It was later centrifuged at 2,600 rpm for 30 min and the supernatant (S-mucin) together with the precipitate (I-mucin) recovered.

Preparation of polymer dispersion

Aqueous dispersions containing 8 % w/v of the single polymers and their admixtures were formulated according to the formula in Table 1, and allowed to hydrate for 24 h.

Surface tension measurement

The aqueous dispersions prepared above were individually coated on glass plates to a thickness of 2 mm and allowed to dry for 5 min. A 2 ml volume of the I-mucin was poured into glass plates, allowed for 7 min for polymer-mucous interaction, and placed on the platform of the tensiometer. The force required to remove the glass plate from the surface of the mucin was obtained with the aid of a tensiometer (Lecomte du Nouy Tensiometer, Model Nr. 3124, Kruss, Germany) (7).

Viscosity measurement

The viscosities of 50 ml volumes of the 8 % w/v aqueous dispersions of the polymers and their combinations were determined using a Universal Torsion viscometer (Pascall Eng., England).

Bioadhesion of coated beads on isolated intestinal mucus surface

The apparatus designed and used in this study was made of a separatory funnel clamped on a retort stand, with a rubber tube attached at the end of the funnel, and a metal support used to position a plastic support at an angle of 30° (8). Freshly isolated and excised hog ileum (1.7 x 15 cm) was pinned on the plastic support. A beaker was placed directly under the plastic support to collect the detached beads. Glass beads of average diameter and mass of 2.5 cm and 5.6 mg respectively, were thoroughly cleaned with distilled water and then with acetone to maximise the roughness factor (9). The beads were immersed in aqueous dispersions of 8 % w/v of the polymers to ensure uniform coating. The coated beads were air-dried and stored in a desiccator containing calcium chloride for 48 h. Ten coated beads were placed on the exposed mucus surface of the tissue. The mucus-polymer interaction and hydration of the polymer coat was allowed to take place over a 15 min period. Simulated intestinal fluid (SIF) with no enzyme (250 ml) was then allowed to flow over the beads at a rate of 30 ml min^{-1}. The number of detached beads was noted and used as a measure of bioadhesion. The experiment was repeated three times and the average value noted.

Swelling studies of polymer compacts

Appropriate quantities of the different polymers or their admixtures as shown in Table 1 were weighed and mixed thoroughly in a specimen bottle. The compacts of each of them weighing 450 mg were compressed at a constant load of 50 KN in an F-3 single punch electric tabletting machine (Manesty, UK) fitted with 12.5 mm flat faced punches. The diameter and thickness of each compact were measured with a Vernier caliper. The compacts were placed in a Petri dish containing 100 ml quantity of SIF. The diameter and thickness of the compacts were carefully measured at hourly intervals for eight hours. The swelling studies were performed in triplicate and the average volume increase plotted against swelling time to yield characteristic swelling isotherms.

Measurement of bioadhesive strength of metronidazole tablets

Bioadhesive metronidazole tablets were formulated to contain 200 mg of metronidazole each with 8 % w/w of either the polymers or polymer admixture, and enough direct compression excipient (Avicel) to yield a 450-mg tablet. The bioadhesive strengths of the tablets were determined exactly as with the tablet compacts except that in this case, the tablets were attached to the glass plate by means of glue.

Table 3: Bioadhesive strength of tablet compacts prepared with dispersions of the polymers and their combinations

Batch	Compositions (g) of the polymers			Tension (Bioadhesive strength, NM^{-1}) X 10^1
	Veegum	SCMC	Acacia	
1	4	1	3	1.22 ± 0.01
2	1	3	4	1.07 ± 0.00
3	3	3	2	1.23 ± 0.01
4	3	4	1	1.25 ± 0.01
5	0	8	0	1.28 ± 0.00
6	0	0	8	1.01 ± 0.01
7	8	0	0	1.18 ± 0.02

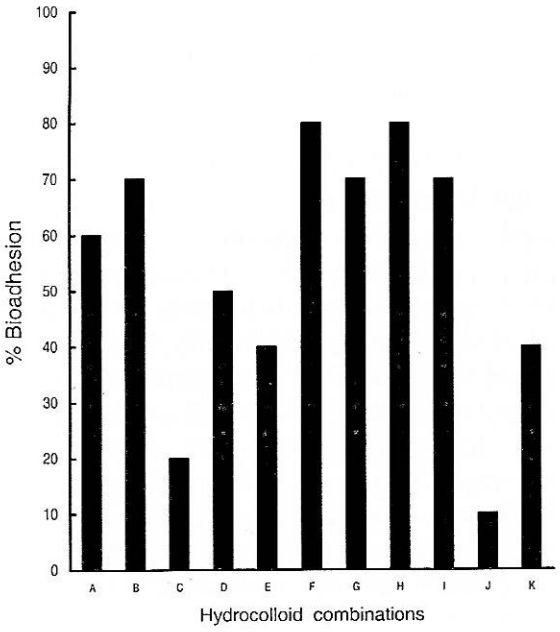

Fig. 1 Chart showing the % bioadhesion of the various hydrocolloids and their admixtures using coated beads

Table 3 shows that the tablet compacts formulated with SCMC equally exhibited the highest bioadhesive strength. It is also of interest that the compacts produced from polymer combinations had higher tensions than those produced with either acacia or Veegum used alone. Formation of complexes may also account for this. These effects are in agreement with some earlier studies (17-19).

From Fig.1, the coated beads containing SCMC alone, as well as those containing high amounts of SCMC in the combinations, exhibited very high bioadhesive strengths. The formulations containing acacia and Veegum used alone produced very low bioadhesive strengths of 10 % and 30 % respectively. None of the formulations, however, had a 100 % bioadhesion. The results of the swelling studies are presented in Fig 2 while Fig. 3 shows the release profiles of the tablet compacts. All the polymers and their admixtures absorbed the SIF to varying degrees as shown in the increase in volume expressed in the graphs. Batch B containing blends of the polymers showed hysteresis mechanism of swelling indicating that diffusion of SIF into tablet compact may have taken place at some time intervals. The swelling results indicate that the tablet compacts produced with the polymers and their combinations can swell and release the metronidazole.

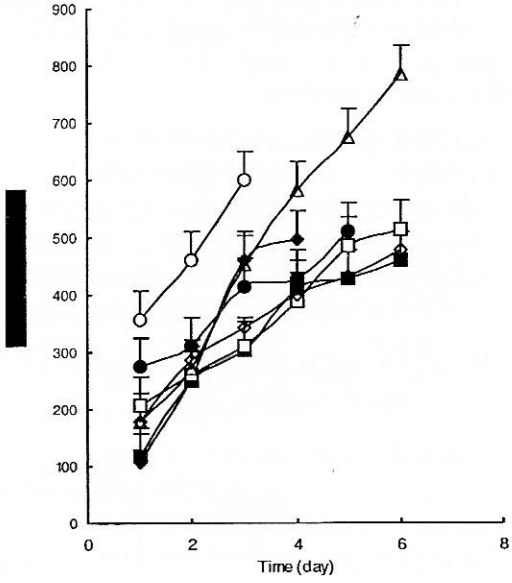

Fig. 2 - Swelling volumes of the polymer combinations upon storage

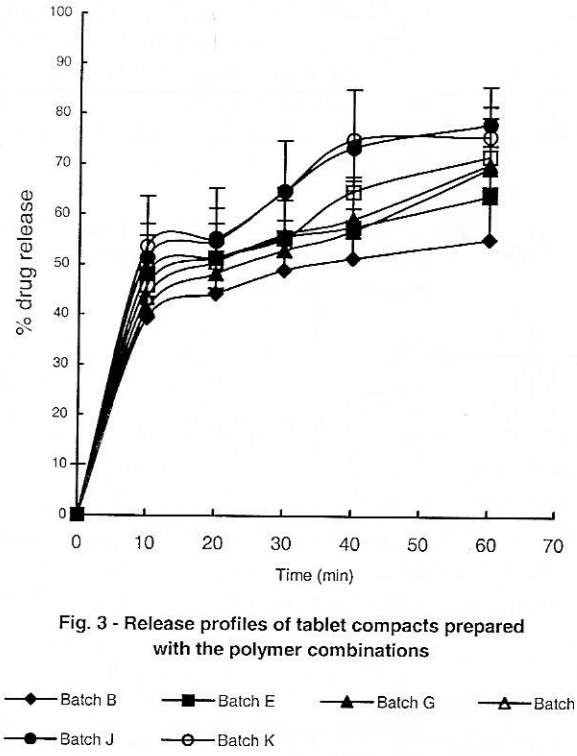

Fig. 3 - Release profiles of tablet compacts prepared with the polymer combinations

This is further evident in the release studies (Fig. 3). The objective of bioadhesive drug delivery is to target a certain portion of the gastrointestinal tract or other area within which the bioadhesive formulation will stick and release its contents. It should undergo appreciable degree of swelling to enable all the incorporated drug to be released, and at the same time, allow other activities specific to the site to go on, without losing its bioadhesive strength. It is therefore necessary for bioadhesive formulations of gastrointestinal tract to swell only to a degree that would enable the release of its content without blocking the intestine. The hydrocolloids and their admixture in this case, released the incorporated drug without excessively swelling. The bioadhesive strength of hydrocolloids is expected to increase initially with swelling due to initial hydration that leads to bioadhesion. It is also known to increase with time (20). However, at maximum swelling, excess absorbed fluid may weaken the adhesion bond due to over-hydration thus lowering bioadhesion (21). In this study, the time interval between the initial swelling and equilibrium swelling was however long enough (6 h) for all the incorporated drug to be released.

From Fig. 3 Batches I, J and K exhibited very high release rates with Batch I (containing SCMC) showing the most extensive release, while Batch B showed the least release, followed by Batch E. Porosity of tablet compacts affects the release rates of drugs. All the formulations however gave relatively high maximum releases.

CONCLUSION

SCMC yielded tablets with highest bioadhesive characteristics of all the polymers and their admixtures studied. Acacia, yielded tablets of poor bioadhesive strength. Blending the polymers improved the bioadhesive strengths of some of the polymers. Drug release from the polymers (used singly) and co-polymers, was prolonged, indicating their suitability for the delivery of bioadhesive controlled-release metronidazole tablets.

REFERENCES

1. Jimenez-Castellanos, M. R., Zia, H. and Rhodes, C. T. (1993), Mechanisms of bioadhesion, *Drug Dev. Ind. Pharm.*,19:143-150.

2. Mikos, A. G. and Peppas, N. A. (1993) Bioadhesive phenomena in controlled release systems, *Pharmakeftiki*, 6: 1-6.

3. Mortazavi, S. A., Carpenter, B. G. and Smart, J. D. (1993) Comparative study on the role played by mucus glycoproteins in the rheological behaviour of the mucoadhesive/mucosal interface, *Int. J. Pharmaceut.*, 94: 195-201.

4. Wright, P. S. (1981) Bioadhesives in Medicine, *J. Dent.* 9: 210 – 218.

5. Park, K. and Robinson, J. R. (1984) Bioadhesive polymers as platforms for oral-controlled drug delivery, *Int. J. Pharm.*, 128: 107-128.

6. Smart, S. D., Kellaway, I. W. and Worthington, H. E. C. (1983) An *in vitro* investigation of mucosa adhesive material for use in controlled Drug Delivery, *J. Pharm. Pharmacol.*, 36: 295 – 299.

7. Harkins, W. D. and Jordan, H. F. (1930) A method for the determination of surface and interfacial tensions from the maximum pull on a ring, *J. Amer. Chem. Soc.*, 52: 1751-1783.

8. Ibezim, E. C., Attama, A. A., Dimgba, C. I. and Ofoefule, S. I. (2000) Use of Carbopols-SCMC admixtures in the formulation of bioadhesive metronidazole tablets, *Acta Pharm.*, 50: 121 – 130.

9. Bickermann, J. J. (1958) Surface Chemistry, Theory and Applications, 2nd ed., Academic Press, New York, pp. 195-199.

10. Tur, K. M. and Ching, H. S. (1998) Evaluation of possible mechanism of bioadhesion, *Int. J. Pharm.*, 160: 61-74.

11. Miyazaki, S. and Nadai, T. (1980) Use of fibrin film as a carrier for drug delivery: *in vitro* drug permeabilities of fibrin film, *Chem. Pharm. Bull.*, 28: 2261-2264.

12. Miyazaki, S., Ishii, K. and Nadai, T. (1981) The use of chitin and chitosan as drug carriers, *Chem. Pharm. Bull.* 29: 3067-3069

13. Takayama, K. and Nagai, T. (1987) Application of interpolymer complexation of polyvinyl pyrrolidone/carboxyvinyl polymer to control drug release, *Chem. Pharm. Bull.*, 35: 4921-4928.

14. Ishida, M., Bambu, N. and Nagai, T. (1982) Mucosal dosage form of lidocaine for toothache using hydroxypropyl cellulose and Carbopol, *Chem. Pharm. Bull., 30: 980-984.*

15. Ozeki, H., Yuasa, H. and Kanaya, Y. (1998) Mechanism of medicine release from solid dispersion composed of poly(ethylene oxide) – carboxyvinyl polymer interpolymer complex and pH effect on medicine release, *Int. J. Pharm.*, 171: 123 – 132.

16. Vazquez, M. J., Casalderry, M., Duro, R., Amoza, J. L., Martinez-Pacheco, R., Souto, C. and Consheiro, A. (1996) Atenolol release from hydrophilic matrix tablets with hydroxy propyl methylcellulose mixtures as gelling agent: Effects of the viscosity of the HPMC mixture, *Eur. J. Pharm. Sci.*, 4: 39-47.

17. Smart, J. D. and Kellaway, W. I. (1982) *In vitro* techniques for measuring mucoadhesion, *J. Pharm. Pharmacol.*, 34: 70-78.

18. Khanna, R., Agarwal, S. P. and Ahuja, A. (1996) Preparation and evaluation bioerodible buccal tablets containing clotrimazole, *Int. J. Pharm.*, 138: 67 – 73.

19. Lehr, C. M., Bouwstra, J. A., Schacht, E. H. and Junginger, H. E. (1992) *In vitro* evaluation of muco-adhesive properties of chitosan and some other natural polymers, *Int. J. Pharm.*, 78: 43-48.

20. Taylor, D. C. (1986) Sites and mechanism of intestinal drug absorption, *Pharm. Int.*, 179: 10 – 16

21. Chen, J. L. and Cyr, G. N. (1970) Adhesion in biological systems, Academic Press, London, pp. 163-181.