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Assessment of an in vitro method for measuring the bioadhesiveness of tablets

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Summary

A custom-designed apparatus has been constructed for the quantitative measurement of the bioadhesive properties of controlled release tablets, which measures both the adhesional and frictional forces required to separate two parallel surfaces (tablet/mucosa) from each other, while the tablet and mucus membrane are immersed in a testing medium. Preliminary results obtained for two batches of NaCMC tablets of various polymer contents indicated a good linear relation between maximum adhesion strength and the polymer content. The instrument so designed can be used to estimate the work of removing a bioadhesive tablet from a membrane by either sliding the tablet in a vertical direction or detaching the tablet from the surface.

Introduction

In recent years, hydrophilic polymers have become extremely popular in drug delivery. This is because these polymers help in prolonging the release of drug from a dosage form by sticking to a specific site of the body where mucus is present.

The performance of a bioadhesive can be evaluated in terms of various parameters, such as adhesion strength, adhesion number, and/or duration of adhesion. Measuring the mechanical properties of a bioadhesive is the most direct way to quantify the bioadhesive properties. The most commonly used types of stress to measure the force of adhesive joints are tensile, shear and peel stress. In tensile and shear loading, the stress is distributed uniformly over the entire joint. However, in peel loading, the stress is limited to a very fine line at the edge of the joint (Park and Park, 1990).

Several in vitro techniques have been reported to determine the bioadhesive potential of oral dosage forms (Jiménez-Castellanos et al., 1993). The majority of them measure the tension stress between the dosage form and membranes or tissues of various animals (Ishida et al., 1981; Al-Dujaili et al., 1986; Forget et al., 1988; Lejoyeux

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et al., 1989). However, tensile stress provides only a partial reflection of mucoadhesion, since the majority of mucus-covered surfaces (e.g., gastrointestinal and buccal area) have some elements of shear motion.

In the light of the above, we have developed an alternative technique with the intention of quantifying the bioadhesiveness of selected oral dosage forms by measuring the forces required to separate two parallel surfaces (membrane/tablet) with both adhesional and frictional forces being measured.

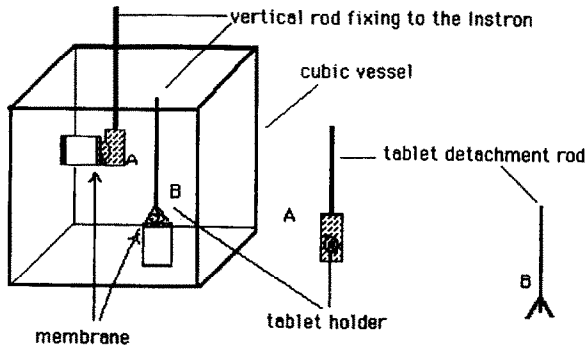

Fig. 1. Apparatus for determination of bioadhesiveness of tables: (A) sliding method; (B) direct detachment.

Materials and Methods

Materials

Microcrystalline cellulose (Avicel PH 101, FMC Corp., U.S.A., lot 14361), sodium carboxymethylcellulose (SCMC 7MF, cellulose gum, Aqualon Co., U.S.A., lot 67108), phenylpropanolamine HCl (Sigma, lot 100F-0393), dicalcium phosphate (Emcompress, Mendell, U.S.A., lot 9229) and magnesium stearate (Fisher Scientific, U.S.A., lot 742748) were used as received.

Preparation of the tablets

Tablets free of drug were prepared by mixing Avicel PH 101, and SCMC 7MF, at different percentages of polymer (12.5, 25, 50 and 75%) in a mixer (Turbula mixer) for 15 min. They were compressed in a Carver Press using a 12 mm diameter and circular normal concave punches. The final tablets had a weight of 600 mg. Two different batches of these formulations were prepared in order to validate the technique.

Tablets with drugs were prepared by mixing 24% phenylpropanolamine HCl (using only that model of drug), 35.4% SCMC and 40.6% Emcompress (as an excipient) for 10 min, then adding 5% of magnesium stearate (as a lubricant) and mixing for an additional 2 min. The tablets were compressed in a Carver Press using 9 mm diameter and circular normal concave punches. The final tablet had a weight of 500 mg and a hardness of 4.5 kg.

Measurement of adhesion by sliding

Fig. 1 shows a diagram of the custom-designed attachment for a tensile tester apparatus (Instron, model 1122) which consists of a small polyacrylic cylinder (3 cm diameter) fastened to the side wall of a polyacrylic vessel (13 cm) to hold the membrane by means of an O-ring. A rectangular aluminum piece with a hole in the middle was used as a support to hold the tablets. This hole had a diameter 2 mm greater than that of the tablets to allow for swelling of the tablets due to absorption of medium. After fixing the membrane to the cylinder with an O-ring, the vessel was put on the lower plate of the Instron while the aluminum support was connected with a vertical rod and fixed to the tensile tester.

Since the purpose of this study was only to develop and assess this technique, a microporeous membrane (Celgard®) was used as tissue. In this last case, an oxygenator can also be used.

In a typical adhesion test, after placing the tablet in the hole of the aluminum piece, the membrane and tablet were brought together until barely touching. The tablet and membrane surfaces were rigorously parallel. The vessel was filled with a constant volume of distilled water at 22°C. After 30 min (pre-swelling time),the force was recorded as a function of time until the tablet had crossed the membrane surface (for drug-free tablet: crosshead speed 20 mm/min, chart speed 50 mm/min, full-scale load 1 kg, for tablet with drugs crosshead speed 1 mm/min, chart speed 20 mm/min, full-scale load 1 kg).

Measurement of adhesion by direct detachment

The same apparatus as described above was used with minor modifications. In this case, the polyacrylic cylinder was fastened to the bottom of the polyacrylic vessel, and pincers were used to support the tablets. After the tablet was brought together with the membrane, the vessel was filled with a constant volume of distilled water at 22°C. After 30 min the force was recorded as a function of time until the break point (crosshead speed 0.2 mm/min, chart speed 20 mm/min, full-scale load 1 kg) was reached.

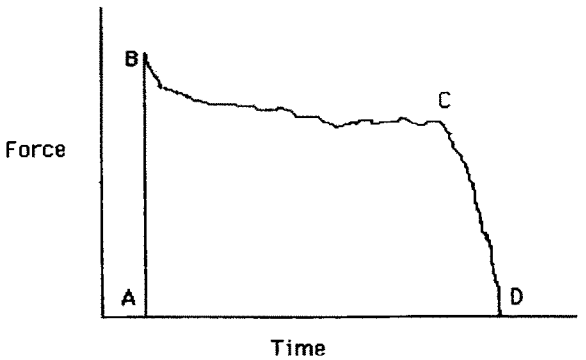

Fig. 2. A typical plot of variation of force necessary for sliding a NaCMC tablet over the surface of a membrane as a function of time.

Results and discussion

Fig. 2 shows a typical force versus time graph for one of the formulations studied. In general, the AB portion represents the maximum adhesion force after some time of contact with both surfaces. The second portion of this graph (BC) indicates a period where the adhesion force changes as a function of friction force. Finally, portion CD of the curve describes how the adhesion force changes as a function not only of friction force but also of the change in the area of contact between both surfaces.

As can be seen from this graph, two parameters can be obtained to analyze the adhesive characteristics of the tablets with the membrane: the maximum adhesion force, represented by point B, and the work of adhesion-shear, determined by the area under the curve. To this effect, Lejoyeux et al. (1988) reported that this last parameter gives more useful information concerning bioadhesion than does the maximum detachment force alone. Thus, they showed that a comparison of the adhesive powers of pure poly(acrylic acid) (PAA) tablets and pure HPMC tablets with bovine sublingual mucosa in liquid medium containing 100 g/l NaCl revealed no difference in detachment force (2.9 and 2.8 N). However, adhesion work was almost 3 times greater for (PAA) than for HPMC (2.59 and 0.88 mJ, respectively).

Maximum adhesion force and work of adhesion-shear values for the various formulations of two different batches are summarized in Table 1. No significant differences were found among the different formulations of the two batches in either parameter. However, from this table we can see a relation between the two parameters and the percentage of polymer in the tablets.

In fact, Figs 3 and 4 show that under the experimental conditions used, a linear correlation

TABLE 1

Adhesion forces and works of adhesion-shear for different percentages of polymer in two tablet batches

Percentage of polymer	Batch 1		Batch 2	
	Adhesion [a] force (kg)	Work [a] (kg mm)	Adhesion [a] force (kg)	Work [a] (kg mm)
12.5	0.181 (±0.012)	2.74 (±0.49)	0.183 (±0.012)	2.98 (±0.13)
25	0.255 (±0.008)	3.35 (±0.38)	0.250 (±0.036)	3.62 (±0.30)
50	0.555 (±0.057)	4.89 (±0.24)	0.593 (±0.037)	4.68 (±0.53)
75	0.828 (±0.070)	5.53 (±0.67)	0.806 (±0.050)	6.30 (±0.41)

[a] Average of three tablets (±S.D.).

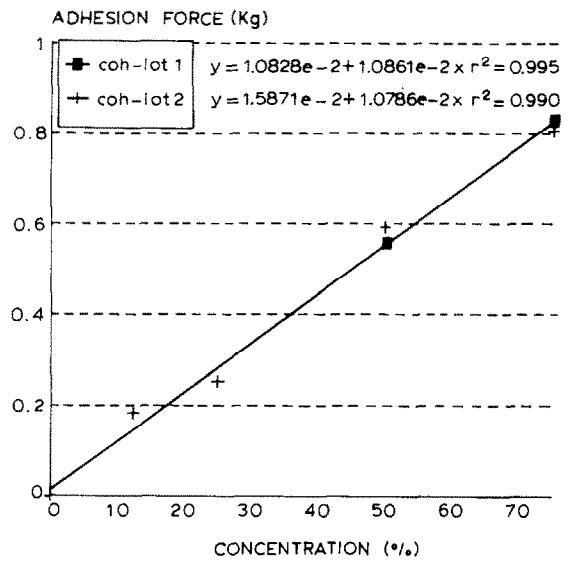

Fig. 3. Adhesion force between SCMC/Avicel® PH 101 for the two batches and membrane at 22°C as a function of the percentage of polymer, after water pre-swelling for 30 min.

exists between the adhesive strength and the work of adhesion-shear vs NaCMC content. Furthermore, as is evident from Fig. 5, there is good correlation between the adhesion force and work of adhesion-shear.

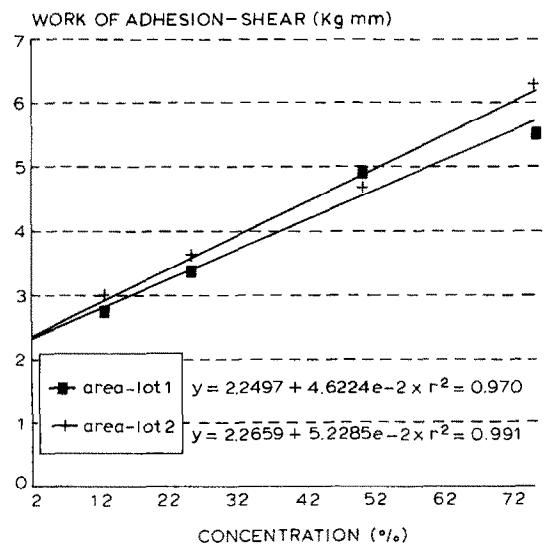

Fig. 4. Work of adhesion-shear between SCMC/Avicel® PH 101 tablets for the two batches and membrane at 22°C as a function of polymer percentage.

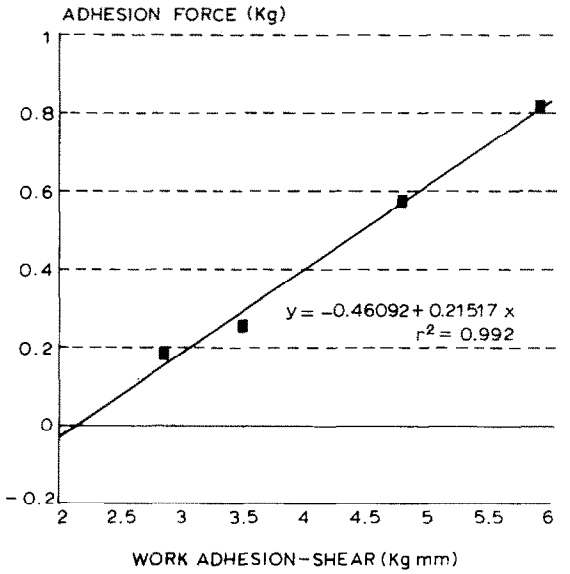

Fig. 5. Force of adhesion between SCMC/Avicel® PH 101 tablets (average of six tablets) and membrane as a function of the work of adhesion-shear.

Despite the difficulty in comparing these results with those of other authors, this was possible because of the different techniques used and also due to the compressive method of preparation of the tablets. We concur with these researchers, demonstrating a direct relation between adhesion properties and polymer content. Thus, Ishida et al. (1983) have shown that, within the range of 0–30% PAA, there is an almost linear increase in the adhesive characteristics of ointments composed of petrolatum, hydrophilic petrolatum or an absorptive ointment.

The above results agree with those of Hassan and Gallo (1989), showing an increase in N_b values (viscosity component due to bioadhesion) as the PAA concentration increases; with Leung and Robinson (1988), observing that the tensile stress of the PAA-mucin interaction decreased as the percentage of acrylic acid in the composition decreased; with Ponchel et al. (1987), reporting a direct correlation between the work of adhesion and the quantity of the bioadhesive agent PAA in tablets; and with Park (1989), showing that the mucoadhesive property of the copolymers acrylic and acrylamine increased sharply with increasing acrylic acid content until content reached 70%.

To prove that this method effectively measured the adhesion and friction forces at the same time, we used the same tablets and test as previously described, but in dry medium. Under these experimental conditions, Leung and Robinson (1988) observed that dry particles of the cross-linked copolymers (acrylic acid-methyl methacrylate) had no adhesiveness, whereas hydrated particles had significant adhesiveness. Therefore, if we measured any force, it must have been friction force.

In fact, one can see in Table 2 how the different tablets showed similar work for equal contact surfaces. Moreover, in every case the work in dry medium was less, than that in liquid medium, proving that our method measures the work of adhesion-shear at the same time.

However, it is possible to believe that this variation in the work for the different media used was a consequence of the different areas of surface contact of the tablets used in both media, resulting from the use of concave punches. If this were true, we would have found differences among work values for the different percentages of polymers in dry medium, as we did in liquid medium. Of course, under the experimental conditions used we cannot subtract both data, but this will be possible when flat punches are used.

To discover whether any relation existed between the mechanical parameters measured in the horizontal and vertical planes, tablets with phenylpropanolamine HCl, used only as a drug model, were made.

Table 3 lists the data for adhesion force and work of adhesion measured by sliding, and the work of adhesion measured by direct detachment for phenylpropanolamine HCl tablets. Under the experimental conditions used, we observe a relation between the adhesion force measured horizontally and the work of adhesion measured vertically. However, more experimental work is necessary to further prove that this relation exists between both parameters.

At present, we cannot state conclusively which in vitro procedure is best for measuring the real adhesion force of the tablets. However, the alternative method proposed was easier to manipulate under the experimental conditions used, because in the vertical method a negative initial force corresponding to tablet swelling made measuring difficult.

TABLE 2

Works of shear for different percentages of polymer using dry medium

Percentage of polymer	Work [a] (kg mm)
12.5	1.81 (±0.52)
25	1.97 (±0.38)
50	1.91 (±0.30)
75	1.98 (±0.06)

[a] Average of three tablets (±S.D.).

TABLE 3

Mechanical parameters of phenylpropanolamine HCl tablets measured by sliding or direct detachment

Adhesion force (kg)	Work of adhesion-shear [a] (kg mm)	Work of adhesion [b] (kg mm)
0.311 (±0.05)	2.695 (±0.19)	0.031 (±0.015)

[a,b] Average of three tablets (±S.D.).
[a] Sliding.
[b] Direct detachment.

Conclusions

The alternative method described for the determination of bioadhesion using a tensile apparatus allows both adhesional and frictional forces to come into play and can be used in either a dry or liquid medium. Moreover, the technique makes possible the calculation of mechanical parameters for a better understanding of the bioadhesion process. Furthermore, the technique does not require adhesive liquid to fix either the membrane or the tablet, avoiding any alteration of them. To this effect, a modification of the vertical technique was made using pincers as support for the tablets.

More studies using the vertical and horizontal methods are necessary in order to confirm the relation between the mechanical parameters measured.

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