

## IN VITRO EVALUATION OF THE BIOADHESIVE PROPERTIES OF TACCA STARCH-CARBOPOL 940 ADMIXTURES AND THEIR APPLICATION AS BIOADHESIVE SYSTEMS FOR METRONIDAZOLE TABLETS

S.I. Ofoefule (PhD)

Department of Pharmaceutical Technology and Industrial Pharmacy, University of Nigeria, Nsukka, Enugu State, Nigeria.

### ABSTRACT

*Bioadhesive properties of Tacca starch-Carbopol 940 (TS - CP) admixtures were evaluated. Detachment of polymer coated beads and tensiometric measurement were employed as indices of bioadhesion. The admixtures were subsequently employed as mini-matrix in the formulation of metronidazole bioadhesive tablets. The release profiles of tablets were assessed in simulated interstitial fluid (SIF) without pancreatin. At all TS-CP admixture combination ratios [1:0, 1:1, 3:7, 7:3, 3:2, 2:3 and 0:1] good bioadhesive strengths were obtained on isolated pig intestine and on intestinal I-mucin. The metronidazole bioadhesive tablets exhibited higher tension than the polymer dispersions as a result of variation in the hydration of the polymer coat in I-mucin and in actual mucus surface. Tensiometric measurements and detachment of polymer-coated beads demonstrated significant influence of Tacca starch in the bioadhesion of the admixtures. Release of metronidazole from the bioadhesive tablets pointed to sustained release model.*

**Keywords:** Bioadhesion, Admixtures, Tensiometric Measurement, Coated Beads, Metronidazole, I-mucin.

### INTRODUCTION

Bioadhesion is the attachment of a material or object to the surface of a biological membrane. When the biological membrane involved is a mucosal epithelium it is referred to as muco-adhesion. Bioadhesive drug delivery systems offer a new approach to the treatment of certain local and systemic diseases [1, 2]. This approach, in

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addition, could be utilized to prolong duration of drug action and in optimization of drug delivery to specific organs, tissues and regions of the body such as rectal, gastrointestinal, nasal, ocular, and buccal regions. Drugs to be delivered are tableted with the required tooling by direct compression. Many polymers ranging from cellulose derivatives to polyacrylic acid polymers (e.g.) Carbopols) have been utilized as bioadhesive polymers [4, 5].

Cassava hydrogel was recently evaluated as a bioadhesive system for mucosal drug delivery [6]. Tacca starch is a starch extracted from the tubers of Tacca involunrata plant. The starch forms thick gel in the temperature range of 65-70°C and it has been employed as a tablet binder and disintegrant [7, 8] and as an adsorbent for ciprofloxacin [9]. The present study evaluated Tacca Starch and its admixtures with Carbopol 940 as bioadhesive materials and their possible application as bioadhesive polymers for drugs intended for delivery in the small intestine. Metronidazole was chosen as a test drug because it is employed therapeutically in the treatment of intestinal and extra intestinal amoebiasis. Evaluations of some polymer-admixtures as bioadhesive materials for this drug have been reported [10, 11]. For instance the drug has been used as a model drug in the in vitro study of bioadhesive controlled tablets in which Carbopol 934 and hypromellose mixtures were used as bioadhesive material [10]. We have recently employed Carbopol 940 and 941 - sodium carboxymethylcellulose admixtures in the formulation of adsorbent metronidazole tablets [11].

### EXPERIMENTAL

#### Materials

The following materials were used as procured from their manufacturers: Carbopol 940 (B. F Goodrich, USA), metronidazole (May and Baker, England). Other reagents are of analytical grade. Tacca starch was extracted from the tubers of Tacca involunrata plant by a process

previously reported [7]. Simulated intestinal fluid without pancreatin was freshly prepared according to B. P 1980 specification.

**Apparatus**

The apparatus adapted for bioadhesive test is shown diagrammatically in Figure 1. It is made up of a separating funnel. A metal support was used to position a polythene support at an angle of 50°. A freshly excised pig ileum was pinned on this polythene support. A beaker was placed under the polythene support to collect detached beads and the wash solution-simulated intestinal fluid without pancreatin. The pig ileum was chosen because the pig has physiological function similar to that of human [12].

**Coating of Glass Beads**

Glass beads of average weight (0.106g) and diameter (2.5mm) were washed with distilled water and acetone to maximize the roughness factor [13]. Different gels made of combination of Tacca starch and Carbopol 940 or single polymer was prepared according to the formula in Table 1. Tacca starch gels containing the different proportions of Tacca starch were prepared with the aid of heat. The polymer gels were used in coating the beads to uniform thickness as much as possible. Coated beads were air dried and stored in a desiccator.

**Table 1: Composition of polymer Admixtures**  
Composition (g)

Batch	Tacca starch	Carbopol	Total	Ratio
1	5.0	-	5	5.0
2	2.5	2.5	5	1:1
3	1.5	3.5	5	3:7
4	3.5	1.5	5	7:3
5	-	5.0	5	0.5
6	3.0	2.0	5	3:2
7	2.0	3.0	5	2:3

**Preparation of Mucin**

The ileum of a freshly killed pig was excised open and the waste materials therein were rinsed with cold normal saline. The mucus surface was scrapped with a glass slide. Equal volume of distilled water was added to the mucus. This was homogenized for two hours and stored at 4°C

for 48 hours. It was centrifuged at 2,500 pm for 30 minutes. The supernatant (S-mucin) and the precipitate (I-mucin) were recovered [14].

**Bioadhesion of Coated Beads on Isolated Intestinal Mucus**

A freshly excised pig's ileum of length 15cm and internal diameter 1.7cm was washed free of internal waste with normal saline. The tissue was pinned unto the polythene support of the bioadhesive instrument inclined at 50° to a metal support (Figure 1). Ten coated beads from each polymer dispersion were placed on the exposed mucus surface of the pinned tissue. The mucus-polymer interaction was allowed for 15 minutes. A 250 ml volume of SIF was allowed to flow over the beads at the rate of 30 drops per minute. The number of beads undetached at the end of the fluid flow was a measure of bioadhesion [11].

**Bioadhesion of Polymers using Tensiometric Method**

A 5%w/v aqueous gel of the various polymer admixtures was each coated on the glass plate of a tensiometer (A Kruss, Germany, model No. Nr. 3124) of weight 0.6 g to a thickness of 2 mm and allowed a contact time of 15

minutes. A 2 ml volume of the I-mucin was placed into the glass vial on the platform of the equipment. The glass plate on which the gel was coated was hung on the lever arm of the equipment. The coated plate was brought in contact with the I-mucin and a 7-minute contact time was allowed for polymer-mucin interaction. The coated glass plate was raised by means of a screw until it just detached from the surface of the mucin. The force required to detach the coated glass plate from the surface of the mucin was read off from the microform balance in degrees. Adequate conversion of the force to tension was obtained by calculation using the formula below [15].

$$T = \frac{mgf}{2l} \quad (1)$$

T = tension equivalent to bioadhesive strength  
m = weight required to return the lever point to its original position.

l = perimeter of the glass plate

g = acceleration due to gravity

Triplicate determinations were made in each case

**Preparation of Metronidazole Tablets and measurement of Bioadhesion**

Four batches of metronidazole tablet containing TS-CP in the ratios of 5:0, 3:7, 2:3 and 0:5 respectively were prepared. Each tablet contained metronidazole 100 mg, and enough Ditab® as direct composition filler/binder. The polymers, the drug and Ditab® were mixed thoroughly in specimen bottles. The powder mixtures were lubricated with 1% magnesium stearate prior to direct compression in an F-3 Manesty single punch electric tableting machine fitted with 12.50 mm punches. Tablets were compressed to hardness of 3.3-3.7 kgf.

The bioadhesive test on the tablets was as described earlier under the use of tensiometer except that the metronidazole bioadhesive tablets were attached to the glass plate by means of a super glue and isolated pig ileum was used in place of I-mucin.

**Dissolution Studies**

The dissolution profiles of the tablets were studied using the static-basket-magnetic stirrer assembly [16]. A tablet from each batch was placed inside the basket (aperture size 320 mm), which was immersed half way in the dissolution medium. The dissolution medium was freshly prepared SIF maintained at 37 ± 1°C. Agitation was maintained at 100 rpm by switching on a thermostated hot plate. Samples were withdrawn at predetermined time intervals and analysed for metronidazole at 277nm in UV-Vis Spectrophotometer; (Milton Roy Spectronic 1201).

**RESULTS AND DISCUSSION**

The results of the tensiometric determination of the bioadhesive strength of the dispersion of Carbopol 940, Tacca starch and their admixtures are shown in Table 2 while Figure 2 shows the bioadhesion of coated glass beads on intestinal mucus surface. Carbopol 940 exhibited the highest bioadhesive strength in two methods employed in the assessment of bioadhesive

strength. This is expected since Carbopols are highly negatively charged and are known to produce negative zeta potential that results in an increase in bioadhesion [17].

**Table 2: Tension values of polymer- mucin interactions and tablets-isolated pig ileum interactions**

Polymer	Admixture (ratio)	Tension Nm-1 102
TS -Cp	Polymer	Tablet
5 : 0	5.30 + 0.706	6.67 + 0.021
1 : 1	6.26 + 0.014	—
3 : 7	6.44 + 0.090	8.54 + 0.162
7 : 3	5.37 + 0.593	—
3 : 2	6.08 + 0.004	—
2 : 3	6.42 + 0.078	8.51 + 0.410
0 : 5	7.12 + 0.960	9.65 + 0.340

In addition, Carbopol 940 contains groups, which gave high capacity of hydration to the polymer [18]. It has now been established that Carbopols interact with the glycoprotein component of the mucus gel to form a strengthened network [19]. If this interaction results to the molecular inter penetration, the interfacial layer of the muco-adhesive joint will be strengthened and this increases the chances of a dosage form formulated with such polymer to be retained at the site of application. Tacca starch, on the other hand, exhibited the least bioadhesive strength. It is evident from Table 2 and Figure 2 that bioadhesion of the admixtures decreased with increasing proportion of Tacca starch. This is an indication of the absence of inter polymer complexation between the two polymers. The reduction in bioadhesion observed could therefore, be attributed to the formation of slippery film by the over wetting of the Tacca starch component of the hydrogel. For maximum bioadhesion to occur, the hydration of a polymer coat to form a "tacky" film is necessary, while slippery mucilage, usually leads to poor adhesion [20]. This is because in the presence of excess moisture, the adhesive material becomes over-hydrated, equilibrium is lost and a slippery film results leading to reduction or loss of adhesion. The interaction between dispersion of Tacca starch or the coated glass beads and the mucin of isolated pig intestine was relatively weak resulting in lower tensions and easy detachment

of coated beads.

The bioadhesive strengths of the tablets were higher than that obtained with the polymer dispersions. This is related to the difference in hydration of the polymer coats in I-mucin slurry and actual mucus surface and on slippery films that are normally formed by polymers in the presence of I-mucin slurry as a result of overhydration [21]. Results of the present study indicate that a strong attachment of the bioadhesive tablets to the intestine in vivo could be achieved with these polymer admixtures. The results of tensiometric measurement (Table 2) and detachment of coated beads (Figure 2) are in close agreement and TS-CP admixtures (ratios 3:7, 2:2 and 1:1) possess very good bioadhesive properties. In the 1980s it was believed that: (a) Strong hydrogen-bonding groups (-OH, -COOH), (b) Strong anionic charges, (c) High molecular weight and (d) Sufficient chain flexibility are responsible for bioadhesion [22]. This theory, however had to be modified at the beginning of 1990s, when Hassan and Gallo [23] demonstrated that positively charged polymer, chitosan also displays strong bioadhesion. In most cases, single polymer, may not possess all of the five listed properties and use of polymer combinations or admixture may result in blends with optimum bioadhesive properties and an added advantage of economy. Tacca starch is readily available and could be sourced locally in Nigeria. Its combination with some more expensive synthetic polymer such as Carbopol 940 will have the added advantage of economy while still achieving good bioadhesion.

The release profile of metronidazole from the compressed tablets containing the TS:CP admixtures, ratios, 5:0, 0:5, 3:7, and 2:3 are shown in Figure 3. The release of the drug from all the systems under investigation followed sustained release pattern. It is evident from the two figures that Carbopol 940 exerted more retardant effect on metronidazole release than Tacca starch and the admixtures. The retardant effect of the admixture apparently increased with increase in the proportion of Carbopol 940. Carbopols exhibit maximum viscosity in the pH range of 5 to 10 [24] and at pH 7.5 of SIF, high

viscous gel formed by Carbopol 940 led to slow diffusion of metronidazole across the gelled layers. The release pattern of the drug further indicates a direct relationship between bioadhesive strength of the polymers and dissolution profile of the incorporated drug. Thus polymer mobility (swelling and viscosity) may play major role in the degree of attachment of the dosage form to intestinal mucus surface in vivo.

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