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Evaluation of the bioadhesive property of Grewia gum in indomethacin tablet formulation in pig gastric mucus

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Abstract
The bioadhesive property of grewia gum for sustained release of Indomethacin from tablets was evaluated using pig gastric mucus as substrate. The tablets formulated by wet granulation contained 75 mg of the drug and 15 or 20 $\%^{w}/_{w}$ of the gum. Similar tablets made differently with carbopol 934, tragacanth and sodium carboxymethylcellulose (SCMC) were used as basis for comparison. Hydration of tablets and substrate surfaces was done using 0.1N hydrochloric acid and phosphate buffer providing pH values of 1.2 and 7.4 respectively. The force required to detach the tablets from substrate surface was determined in a testometric material testing machine. Drug release from polymer matrix tablets was fastest for tragacanth and slowest for carbopol 934. The detachment force of tablets from substrate was found to increase in the order: carbopol 934 > SCMC > grewia gum > tragacanth. The detachment force was affected by the pH of the hydration medium. On the basis of these grewia gum may find application as bioadhesive polymer for sustained release tablet formulation.

Keywords: Indomethacin; Pig gastric mucus, Grewia gum, Bioadhesive performance

Introduction

Plant gums or polymers with gummy or mucilaginous characteristics have been used in Pharmacy as binders (Udeala and Chukwu, 1985), suspending (Chukwu and Nwankwo, 1991) and emulsifying (Gaind *et al.*, 1968) agents, while others have found application as matrices for the controlled-release of medicaments (Huber and Christenson, 1996; Talukdar and Vercamen, 1993; Sujja-areevath *et al.*, 1996). Natural or synthetic materials capable of adhering to a biological substrate for an extended period of time sufficient enough to allow for a reduction in dosage frequency compared to conventional, non-adhesive dosage forms are called bioadhesive polymers (Gu *et al.*, 1988; Helliwell, 1993). They are employed in tablet formulations to enhance drug bioavailability through a prolonged and intimate contact with the absorbing membrane (Pritchard *et al.*, 1996). This is a method of achieving sustained release of medicaments. Indeed, bioadhesive polymers have been studied for most accessible routes of drug absorption (Middleton *et al.*, 1990; Illium *et al.*, 1987; Nagai and Konishi, 1987; Helliwell and Sektere, 1993). The bioadhesive properties of a wide range of materials have been evaluated. It has been reported that carbopol, polycarbophil, carboxymethylcellulose, tragacanth and sodium alginate display

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excellent bioadhesion when tested *in vitro* (Richardson *et al.*, 1992).

Grewia gum is a polysaccharide derived from the inner stem bark of the edible plant *Grewia mollis,* Juss (Family, Tiliaceae). The plant is a savannah shrub, which grows widely but is usually cultivated. The leaves and bark of the plant contain mucilage. In Nigeria, the dried and pulverized inner stem bark is used as thickening agent in some local dishes. The gum contains glucose, rhamnose and galacturonic acid, and has a molecular weight of approximately 320,000 (Okafor *et al.*, 2001). The rheological properties of the gum (Okafor, 2001a) and its use in sustained-release formulation have also been studied (Okafor, 2001b). The binding property of the gum in tablet formulation has been reported (Okafor and Chukwu, 2003).

In this report, the bioadhesive property of grewia gum for the delivery of indomethacin from tablet is evaluated in pig gastric mucus.

Experimental

Materials. Hydrochloric acid (FSA Lab. Ltd., Poole, England), sodium hydroxide and magnesium stearate (BDH Ltd., England), sodium carboxymethylcellulose, M.W. 700,000 (F.M.C. Corp., Philadelphia), carbopol 934 (BF Goodrich, Cleveland-Hounslow, UK), tragacanth (Merck, Darmstadt, Germany), indomethacin (Sigma Chemicals Co., St. Louis, Mo.), Lactose (M & B, Dagenham, UK.). Grewia gum was extracted in our Laboratory as previously reported (Okafor *et al.*, 2001). All other materials were of analytical grade and used as obtained.

Preparation of granules and tablets. Tablets containing 15 or 20 $\%^{w}/_{w}$ of grewia gum, tragacanth, sodium carboxymethylcellulose, or carbopol 934 were prepared by wet granulation according to the formula in Table 1. Eight batches of tablets were prepared. To weighed amounts of indomethacin, lactose and gum or polymer was added a predetermined quantity of distilled water followed by mixing in a laboratory kneader. Moist granules passing through sieve No.10 were obtained, and dried at 60^{0}C in a hot air oven (Gallenkamp) until a constant dry weight was achieved. The dried granules were further passed through stainless steel sieve No.16 and fines discarded before compression. The granules were compressed on a single punch tabletting machine (Eagle Scientific, England) fitted with a 6mm flat faced punch. The average tablet weight was 100±2 mg. Compacts of the respective pure polymers were made by direct compression to give 100 ± 2 mg compacts.

Physical properties of tablets. The uniformity of weight test was determined according to the B.P (1998) method. Tablet hardness was measured in a Monsanto tablet hardness tester (CT 40 Engineering systems Ltd., England). Tablet friability was measured in a Roche friabilator (Erweka GmbH, Germany). Tablet thickness and diameter were measured by means of a micrometer. The disintegration time of tablets was monitored in the Erweka disintegration apparatus (Erweka Apparatebau ZT4 model), with 0.1 N hydrochloric acid as the medium.

Substrate Preparation. The adhesiveness of grewia gum was assessed in pig gastric mucus. The mucus was obtained by gently scraping the stomach of freshly slaughtered pig with a wooden spatula. The gel mixture obtained was mixed with an equal volume of distilled water, stirred slowly for 24 hours at 4^{0}C, and then centrifuged at 10,000 rpm for 30 minutes (Mst, MIWW centrifuge, UK). The supernatant and sedimented solids were discarded and the middle gel layer retained. This was stored at 4^{0}C until required (Smart *et al.*, 1984).

Dissolution studies. Drug release from the tablets was studied using the magnetic stirrer, hot plate dissolution apparatus (Baun and

Walker, 1969). The temperature was kept at 37±1^{0}C. The dissolution medium was 1000 ml of 0.1N hydrochloric acid (pH 1.2). The test was carried out for 8 hours. Samples of 5 ml were withdrawn at 1-hour intervals for analysis and replaced with 5ml of fresh 0.1N hydrochloric acid after each sample collection. The drug concentrations of the samples were determined using Spectronic 21 (Milton Roy Co. England) at 318 nm. All experiments were carried out in triplicates and the average values obtained.

Determination of in vitro bioadhesion. Bioadhesive performance of grewia gum and the reference polymers was assessed by measurement of the detachment force using the testometric machine U-4000 (Testometric Co. Ltd., Rochdale-Lankershire, England) equipped with a 25 Newton transducer. The machine measures the detachment force, which is the force required to separate surface of bioadhesive tablets from substrate. The bioadhesive tablet was attached to the upper arm of the machine, using cyanoacrylate gum (super glue). The substrate was smeared on the lower arm. Hydration of tablet surface was done with 0.1 ml of 0.1 N hydrochloric acid (pH 1.2) or phosphate buffer solution (pH 7.4). The upper arm of the tensile apparatus containing the bioadhesive tablet was lowered at a speed of 20mm/minute to an impact of 1.0 Newton with the pig gastric mucus on the lower arm of the machine. After a contact time of 5 minutes, the upper arm was raised at the predetermined detachment speed of 20 mm/min. At the point of separation between tablet and substrate, the detachment force was read-off the screen of the tensile machine. All experiments were carried out five times per formulation using fresh tablet and substrate for each determination.

Results and Discussion

Physical properties of tablets. Weight of tablets from all batches was relatively uniform. Tablet friability was quite low, and tablet hardness was adequate. All batches of tablets were non-disintegrating even after 2 hours in 0.1N hydrochloric acid.

Dissolution studies. The effect of type of polymer on the release of indomethacin from tablets is shown in *Figure 1.* Tablets containing tragacanth showed the highest release of indomethacin at any given time except at 1-hour interval where the amount of drug released was same as for tablets containing grewia gum. Tablets containing carbopol 934 released the least amount of drug at any given time except at 2-hour interval where amount of drug released was same as that for SCMC. Tablets containing grewia gum released more of the drug than tablets containing SCMC for over 6-hour interval. However, the release of drug from tablets containing grewia gum was lower than for tablets containing SCMC after 7-hour interval. The dissolution parameters are shown in *Table 2.* The time taken for 50% of drug to be released from tablet ($t_{50\%}$) containing 15% $^w/_w$ of polymer was 1.7 hr for grewia gum. The corresponding values for tablets containing 15% each of tragacanth, SCMC and carbopol 934 were 1.4, 2.5 and 2.7 hr respectively. After 8 hours, the amount of drug released from batches of tablets (C_{max}), was 78.2% for tablets containing grewia gum. The corresponding values for tablets containing tragacanth, SCMC and carbopol 934 were 95.9, 76.6 and 70.5% respectively.

Table 1: Formula for indomethacin tablets

	Quantities of ingredients (g) used in batch:							
Ingredients	I	II	III	IV	V	VI	VII	VIII
Indomethacin	11.25	11.25	11.25	11.25	11.25	11.25	11.25	11.25
Grewia gum	2.25	3.00	-	-	-	-	-	-
Tragacanth	-	-	2.25	3.00	-	-	-	-
SCMC	-	-	-	-	2.25	3.00	-	-
Carbopol 934	-	-	-	-	-	-	2.25	3.00
Lactose	1.35	0.60	1.35	0.60	1.35	0.60	1.35	0.60
Magnesium stearate	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15

SCMC-sodium carboxymethylcellulose. Each batch formula is for 150 tablets. Each tablet weighs 100mg ± 2 mg

Table 2: Effect of selected polymer and concentration on dissolution parameters of indomethacin tablets

Gum conc. ($\%^w/_w$)	Grewia gum		Tragacanth		Sodium CMC		Carbopol 934	
	$t_{50\%}$ (hrs)	C_{max} (%)	$t_{50\%}$ (hrs)	C_{max} (%)	$t_{50\%}$ (hrs)	C_{max} (%)	$t_{50\%}$ (hrs)	C_{max} (%)
15%	1.7	78.2	1.4	95.9	2.5	76.6	2.7	70.5
20%	3.3	70.5	3.0	74.6	5.2	54.4	*	47.5

* Less than 50% released

Table 3: Effect of selected polymer on the detachment force (N) of its pure compacts from pig gastric mucus

Gum compact	Detachment Force (N) in:	
	0.1N HCl (pH 1.2)	Phosphate buffer (pH 7.4)
Grewia gum	3.201 ± 0.46	3.020 ± 0.42
Tragacanth	2.865 ± 0.61	2.685± 0.65
Sodium CMC	3.510 ± 0.73	3.245± 0.58
Carbopol 934	3.659 ± 0.69	3.490± 0.30

Table 4: Effect of selected polymer and concentration on the detachment force (N) of indomethacin tablets from pig gastric mucus

Gum conc. ($\%^w/_w$)	Detachment force (N) in 0.1N HCl (pH 1.2)	Detachment force (N) in phosphate buffer (pH 7.4)
Grewia gum		
15%	0.980± 0.25	0.760 ±0.21
20%	1.095± 0.12	0.908 ±0.15
Tragacanth		
15%	0.536 ± 0.18	0.427± 0.31
20%	0.867±0.29	0.675±0.18
Sodium CMC		
15%	1.075± 0.15	0.895 ±0.14
20%	1.162±0.23	0.998±0.15
Carbopol 934		
15%	1.595 ±0.20	1.340±0.32
20%	1.832±0.17	1.605±0.21

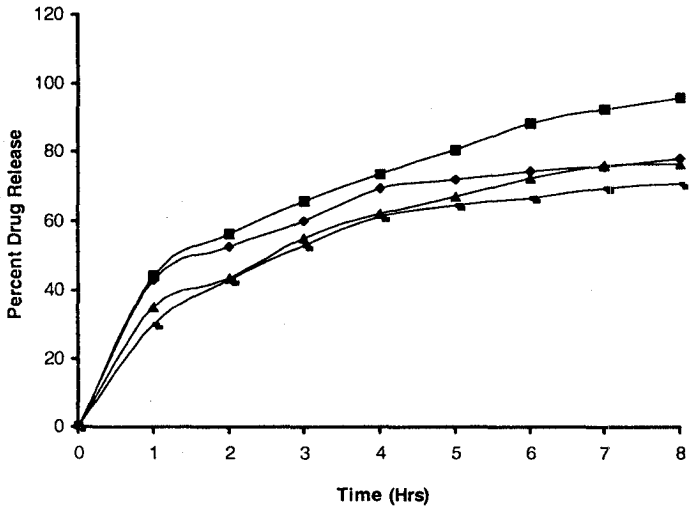

Figure 1 - Percent drug released (%) / Time (Hrs) for Indomethacin tablets containing 15 %w/w of the selected polymers in 0.1 N HCl at 37°C

Grewia — Tragacanth — Sodium CMC — Carbopol 934

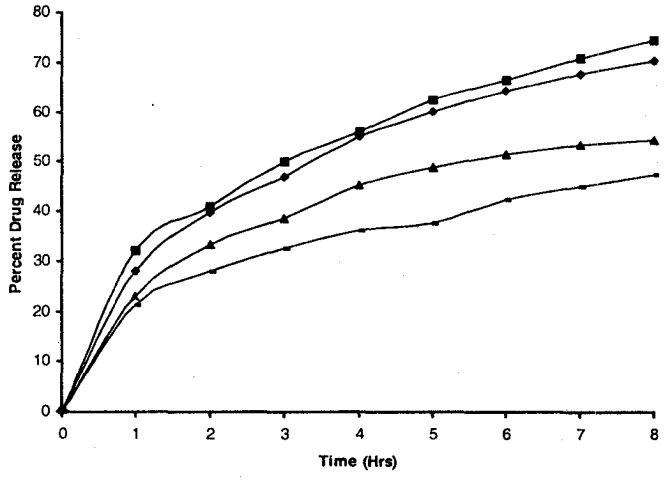

Figure 2 - Percent drug released (%) /Time (Hrs) for Indomethacin tablets containing 20 %w/w of the selected polymers in 0.1 N HCl at 37°C

Grewia — Tragacanth — Sodium CMC — Carbopol 934

The effect of polymer concentration on the release of indomethacin is shown in *Figure 2*. Tablets containing tragacanth (20% $^{w}/_{w}$) exhibited the higher release of drug than grewia gum. The amount of drug released however, was affected by the concentration of the polymer as can be seen from the values of Cmax and $t_{50\%}$ given in *Table 2*. The $t_{50\%}$ value for tablets containing grewia gum was 3.3 hr. This is higher than 1.7 hr obtained when gum concentration was 15% $^{w}/_{w}$. The corresponding $t_{50\%}$ values were 3.0, and 5.2 for tragacanth and SCMC respectively. Carbopol 934 did not give up to 50% of drug release therefore no $t_{50\%}$ value was calculated for it. In each case however, the $t_{50\%}$ value increased with a corresponding increase in the concentration of the polymer. Similar results were obtained for the Cmax where amount of drug released decreased with an increase in polymer concentration for all batches. The ability of the polymers to delay the release of indomethacin was in the order: carbopol 934 > SCMC > grewia gum > tragacanth. A previous report has shown that the concentration of a polymer plays a dominant role in determining drug release rate from polymer matrix tablets (Sujja-areevath *et al.*, 1996). The release of drugs from such polymer matrices is affected by factors such as excipients, the viscosity of the polymer and the type and nature of polymer (Mitchell *et al.*, 1990; Cheong *et al.*, 1992). Some polymers are water soluble, swellable or erodible. The rates at which these processes occur influence the rate of release of drug from the polymer matrix.

Bioadhesive performance of polymers. The detachment force recorded when 100% polymer were in each case compacted is shown in *Table 3*. The detachment force, which is indicative of the bioadhesive strength of the polymer, was highest for compacts of carbopol 934 and lowest for compacts of tragacanth. The bioadhesive strength of the pure polymer compacts, increase in the order: carbopol 934 > SCMC > grewia > tragacanth. This order was the same for the different hydration media used. The effect of the type and concentration of polymer on the detachment force are shown in *Table 4*. For all batches of tablets, an increase in polymer concentration from 15% to 20% $^{w}/_{w}$ resulted in a corresponding increase in the detachment force of the formulation in either hydration media. It was also observed that detachment force was higher when the tablet/substrate surfaces were hydrated with 0.1 N hydrochloric acid than when phosphate buffer (pH 7.4), was used irrespective of the polymer type. Generally, the bioadhesive strength of the polymers increased in the order: carbopol 934 > SCMC > grewia gum > tragacanth.

The rate and extent of hydration and swelling of polymers have been shown to be largely pH dependent. The faster the hydration, the faster the initiation of the bioadhesive process while excessive swelling will result in abrupt drop in the bioadhesive strength (Leung and Robinson, 1990). It is probable therefore that for all the polymers used in this study, hydration of the polymer matrix tablets with phosphate buffer resulted in excessive swelling with a consequent drop in the bioadhesive strength. Okafor *et al.*, (2001), showed that for grewia gum, hydration with phosphate buffer (pH 7.4) results in excessive swelling. The results also agree with other findings, which showed that for solid dosage forms, the higher the concentration of polymer the stronger the bioadhesion (Pritchard *et al.*, 1996; Saettone *et al.*, 1989; Nep and Okafor, 2005). Leung and Robinson, (1990) advanced that, the nature of hydrophilic functional groups of the polymers, the extent of chain interpenetration and the expanded nature of the polymer account for observed variations in bioadhesive performance of different polymers.

Conclusion

Grewia gum exhibits bioadhesive performance superior to tragacanth. Bioadhesive performance is in the order- carbopol 934 > SCMC > grewia gum > tragacanth. It may be preferable to tragacanth where bioadhesion is indicated.

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