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FORMULATION AND EVALUATION OF MUCOADHESIVE CIPROFLOXACIN TABLET USING SIDA ACUTA GUM

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ABSTRACT

Mucoadhesion is the adhesion or sticking together of two or more materials, at least one of which is a mucosal surface. This study was carried out to formulate and evaluate mucoadhesive ciprofloxacin matrix tablets using *Sida acuta* gum as polymer. *Sida acuta* gum was extracted from the dried powdered leaves of *Sida acuta* plant by isopropyl alcohol precipitation of the filtrate obtained from its maceration in distilled water. Different concentrations of *Sida acuta* gum (10%, 20%), carbopol (10% and 20%) and combination of both (10%/10%) were used respectively as mucoadhesive polymer matrix former. The mucoadhesive matrix tablets were prepared using the direct compression technique. The prepared tablets were evaluated for hardness, weight uniformity, friability, *in vitro* drug release and mucoadhesive strength. The study showed that the formulations had hardness values ranging from 9.87 to 16.55 kgf while the friability ranged from 0.1 to 0.4 %. About 70 % of their drug contents were released between 0.75 and 8 h. Tablets from all the formulations were able to adhere to the tissue with the duration of adhesion ranging from 4.03 to > 9 h. The kinetics of release showed that Higuchi, first order, Hixson-Crowell and Korsmeyer-Peppas models were in operation but Higuchi was dominant in F2 and F5 while first order and Hixson-Crowell were dominant in F3 and F4 respectively. The mechanism of release was anomalous (non – Fickian) diffusion. *Sida acuta* gum could be used as a polymer in the formulation of mucoadhesive ciprofloxacin matrix tablets that are comparable to that formulated using carbopol.

KEYWORDS: ***Ciprofloxacin, matrix tablet, mucoadhesive property, Sida acuta gum***

INTRODUCTION

Bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, stick together for an extended or a prolonged time period by means of interfacial forces [1- 4] The term bioadhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa and may be referred to as mucoadhesion where the bond is formed with mucus.[3]

The potential use for mucoadhesive systems as drug carriers lies in its prolongation of the residence time at the absorption site, allowing intensified contact with the epithelial barrier. [5] Mucous membranes of human organism are relatively permeable and allow fast drug absorption. Their epithelial layer's surfaces are covered by mucus. The mucus contains glycoproteins, lipids, inorganic salts and 95% water by mass, making it a highly hydrated system. Mucin is the most important glycoprotein of mucus and is

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responsible for its structure. [1] The mucous site most used for drug administration and absorption is gastrointestinal but other routes, including nasal, ocular, buccal, vaginal, rectal, oral, and periodontal have also been studied. [2, 5 - 8]

Polymers used in mucosal delivery system may be of natural or synthetic origin. Synthetic polymers include poly (acrylic acid) polymers (carbomers, polycarbophil), cellulose derivatives (methylcellulose, ethylcellulose, hydroxypropylmethylcellulose, and sodium carboxymethyl -cellulose), polylactic acid and polyglycolic acid while natural polymers include xanthan gum, soluble starch, tragacanth, sodium alginate, gelatin, pectin, chitosan, albumin, etc. Newer generation polymers such as lectins, thiolated polymers and Polyox WSRA are also available. [3]

The mechanism of adhesion of certain macro-molecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must dominate. [2] Thus, the mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage

No technology has still been developed specifically to analyze mucoadhesion. Most of the tests available were adapted from other preexisting techniques but are useful and necessary for selecting the promising candidates as mucoadhesives as well as in elucidating their mechanisms of action.

Ciprofloxacin hydrochloride, a broad-spectrum fluoroquinolone antibacterial agent, is indicated for the treatment of infections such as urinary tract infections, acute uncomplicated cystitis in females, chronic bacterial prostatitis, lower respiratory tract infections, acute exacerbations of chronic bronchitis, acute sinusitis, skin and skin structure infections, bone and joint infections, complicated intra-abdominal infections (used in combination with metronidazole), infectious diarrhea, typhoid fever (enteric fever), uncomplicated cervical and urethral gonorrhea. It is more absorbed from the stomach and the proximal part of the small intestine. Oral bioavailability is about 70% and reaches the peak plasma concentration of 2.5 μg/ml in 1 to 2 h after administration of 500 mg. Ciprofloxacin has a relatively short elimination plasma half-life of 4 h. As the tablet passes down the GIT, the decrease absorption is the draw back with sustained release dosage form of ciprofloxacin hydrochloride. This calls for a drug delivery system that will prolong the gastric residency time.[9]

Sida acuta gum is derived from the powdered dried leaves of *Sida acuta* by isopropyl alcohol precipitation of the filtrate from its maceration in distilled water. [10] *Sida acuta* gum has recently been used in tablet formulations as binder [11], as hydrophilic polymer matrix former [12], and as a suspending agent in formulation of suspensions [13].

This study was carried to formulate a mucoadhesive matrix tablet of ciprofloxacin which will prolong the residence time of ciprofloxacin in the stomach leading to higher bioavailability.

MATERIALS AND METHOD

Materials

Ciprofloxacin (Changsh Huagang Pharm. Co, China), acetone, isopropyl alcohol (Guangxing Guanghua Chemical, China), absolute ethanol (May & Baker, Dagenham, England), microcrystalline cellulose (MCC), talc, magnesium stearate (BDH Chemicals Ltd Poole England). Wistar rats were obtained from the animal house of the Department of Pharmacology, Faculty of Basic Medical Science, Delta State University Abraka. *Sida acuta* leaves were collected from the botanical garden, Faculty of Pharmacy, Delta state university, Abraka, Nigeria.

Isolation and purification of *Sida acuta* Gum

Sida acuta gum was isolated from powdered dried leaves of *Sida acuta* using the method applied by previous researchers [10]

Precompression evaluations

Bulk density

A 10 g quantity of the powder blend was weighed and poured into a 100 ml measuring cylinder and the volume occupied (bulk volume) was recorded. The bulk density was then determined using the equation 1

$$Bulk\ density = \frac{Mass\ of\ powder\ (g)}{Bulk\ volume\ (ml)} \dots\dots\dots\dots\dots\dots\dots 1$$

Tapped density

The graduated cylinder containing the powder blend was then tapped 100 times from a height of 20 mm

and the volume occupied by the tapped powder blend (tapped volume) was recorded. The tapped density was then calculated using the equation 2

$$Tapped\ density = \frac{Mass\ of\ powder\ (g)}{Tapped\ volume\ (ml)} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 2$$

Carr's index

This was calculated using equation 3

$$Carr's\ index = \frac{Tapped - Bulk\ density}{Tapped\ density} * 100 \ldots\ldots\ldots\ldots\ldots 3$$

Hausner's ratio

This was calculated using equation 4

$$Hausner = \frac{Tapped\ density}{Bulk\ density} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 4$$

Preparation of mucoadhesive matrix tablets of Ciprofloxacin

Ciprofloxacin mucoadhesive matrix tablets were prepared by direct compression technique using the drug and variable concentration of the polymers (*Sida acuta* gum and carbopol 940p), microcrystalline cellulose (MCC), magnesium stearate and talc according to the formula on the Table 1. The drug and respective polymers with the optional additives were blended thoroughly using pestle and mortar. The powder blend was then lubricated with magnesium stearate and talc and compressed into the respective tablets using a CJD 316 sixteen station rotary tablet press (Clit Jemkay Engs. Pvt, Ltd. Ahmedabad, India) having a 13 mm punch.

Evaluation of mucoadhesive matrix tablets

Weight uniformity:

From each formulation, 20 tablets were randomly selected and their individual weight determined using an analytical weighing balance. The mean weight and the percentage weight difference for each tablet were determined.

Table 1: Composition of ciprofloxacin formulations F1 to F5

INGREDIENT (mg)	F1	F2	F3	F4	F5
Ciprofloxacin	250	250	250	250	250
Sida acuta gum	60	-	120	-	60
Carbopol	-	60	-	120	60
Magnesium stearate	3	3	3	3	3
Talc	6	6	6	6	6
Microcrystalline cellulose	281	281	221	221	221
Total weight of tablet	600	600	600	600	600

Key: F1 (10% *Sida acuta* gum), F2 (10% Carbopol), F3 (20% *Sida acuta* gum), F4 (20% Carbopol) and F5 (10% *Sida acuta* gum and 10% Carbopol)

Friability

Ten (10) tablets were weighed and then transferred into a friabilator (Veego friability test apparatus, India) and rotated 100 times thereby subjecting the tablets to a series of free-fall shocks. The tablets were removed from the friabilator, dusted and re-weighed. Friability was calculated using equation 5

$$Friability\ (\%) = \frac{w1 - w2}{w1} * 100 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 5$$

Where $w1$ = initial weight and $w2$= final weight

Tablet thickness, diameter and hardness:

Five (5) tablets were selected at random from each of the formulations. Their individual weight was determined using an analytical weighing balance. Thereafter, the thickness, diameter and hardness of each of the tablet were determined by placing them in the digital tester machine (VEEGO digital hardness tester apparatus).

Dissolution rate test

This was carried out using USP XX type 1 (Rotary basket) apparatus. One tablet of ciprofloxacin was weighed and placed in the basket of a single unit

Copley dissolution test apparatus (Erweka Apparatebau GMBH, Heusengtamm, Germany). The basket was inserted into the dissolution chamber that contained 0.1 N HCl maintained at 37 ± 1^0C as the dissolution medium and rotated at a speed of 100 rpm. A 5 ml sample was withdrawn and replaced with 5 ml of fresh pre- heated dissolution medium after of 5, 10, 15, 30, 45 min, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 h. The withdrawn samples were analyzed spectrophotometrically using a UV/Visible spectrophotometer at a wavelength of 272 nm.

Mucoadhesive test

The test was carried out using the method of [14] with little modification. A 50 ml plastic container with a drip fixed to its tip to allow flow of liquid and a plastic stage clamped at an angle of 30º below the outlet of the drip set were used. Freshly excised wistar rat ileum of about 1 cm by 6 cm was pinned onto the plastic stage. A clean container was placed directly below the set up to collect the 0.1N HCl that flowed through the drip set onto the stage. One tablet was weighed and placed on the exposed mucus surface of the tissue. A period of fifteen minutes was allowed for mucus-polymer interaction. The 50 ml plastic container was then filled with 0.1N HCl and this was allowed to flow over the tablet at a rate of 10 ml/min. The burette was refilled with 0.1N HCl after each 50 ml was exhausted. The quantity of 0.1N HCl used and the time taken for the tablet to fall off or completely disintegrate was noted and used as a measure of bioadhesion.. The test was carried out in triplicate for all the formulations.

Weight of solvent = Volume of solvent × density of solvent ---------- 6

Bioadhesive strength was recorded as the weight of the solvent in g that was required to pull off the formulation from mucus tissue [15]

Determination of content uniformity of mucoadhesive ciprofloxacin tablet

Five tablets were weighed and crushed using a mortar and pestle. Thereafter, quantity of powder equivalent to 100 mg of ciprofloxacin was weighed and dissolved in 100ml of 0.1N HCl. Serial dilutions were made and the samples analyzed at a wavelength of 272nm using a UV spectrophotometer. The percentage content was determined using the equation from the calibration curve.

In vitro drug mechanism and kinetics of release

The dissolution kinetics of ciprofloxacin from the mucoadhesive matrix tablets in
0.1 N HCl solution were determined by fitting the drug release data into zero order [16,
17, 18], first order [16, 17, 18], Higuchi [18, 19, 20] and Hixson – Crowell's cuberoot law [21] plots. The mechanism of drug release was obtained by fitting the first 60% drug release data into the Korsmeyer – Peppas model [22, 23] as shown in equations 7 – 12.

Zero order model

$$C = K_0\, t \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 7$$

C = % Release, K_0 = Zero Order rate constant expressed in units of concentration/time (t).

First order model

$$LogC_r = LogC_0 - \frac{K_1}{2.303} t \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 8$$

Cr = % drug remaining, C_0 = Initial concentration of drug, K_1 = First order constant, t = Time

Higuchi's square root law model

$$Q = K_H t^{½} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 9$$

Q = % drug released, K_H = Constant reflecting design variables of the system, t = Time

Hixson – Crowell's cuberoot law model

$$\left[\frac{100 - f}{100}\right]^{\frac{1}{3}} = 1 - K_{HC}\, t \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 10$$

f = % Drug released, K_{HC} = Rate constant, t = Time

Korsmeyer – Peppas model

$$\frac{M_t}{M_\infty} = Kt^n \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 11$$

$$Log\ {M_t}/{M} = Log\ K + n\ Log\ t \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots 12$$

Where, Mt / $M\infty$ is the fraction of drug released at time t, k is the rate constant and n is the release exponent. The n value is used to characterize different release mechanisms for cylindrical shaped matrices [22, 23, 24] as given on Table 2.

Table 2: Diffusion exponent and solute release mechanism for cylindrical shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

RESULTS AND DISCUSSION

Precompression evaluation

From the result on Table 3, the powder blend for formulations F1 and F4 had Carr's index and Hausner's ratio values that signify poor flow. F2 had values which signify very very poor flow. F3 had values that signify passable flow while F5 had values that signify fair flow [25]. For direct compression technique to be used effectively in the formulation of tablets, the flow properties of the powder blend for formulations F1, F3, F4 and F5 could be improved upon by the addition of glidants such as aerosol or talc. Formulation F2 that had a very very poor flow needs the incorporation of an agitator or vibrator to the hopper of the tableting machine if direct compression technique is to be used. Alternatively the formulation should be produced using non – aqueous wet granulation method.

Table 3: Precompression evaluation

Formulation	Bulk Density	Tapped Density	Carr's Index	Hausner Ratio
F1	0.37	0.52	28	1.41
F2	0.22	0.40	45	1.82
F3	0.34	0.45	24	1.32
F4	0.21	0.30	30	1.41
F5	0.33	0.40	18	1.21

Evaluation of Mucoadhesive Ciprofloxacin Tablets

The quality of the different formulations of the mucoadhesive Ciprofloxacin tablets were evaluated based on uniformity of weight, drug release rate, uniformity of content, hardness and friability. All the formulations complied with the compendia standard for the uniformity of weight as shown on Table 4.

Hardness test is a test that shows the ability of tablets to withstand pressure or stress during handling, packaging and transportation. The hardness of tablets from all the formulations ranged from 9 to 16 kgF, as shown on Table 4. Therefore, they would be able to surmount pressure or stress of handling, packaging and transportation.

The friability of the tablets from the different formulations was found to be within the range of 0.1 to 0.4. Friability is another mechanical property of a tablet with a compendia specification of not more than 1%. This showed that all the formulated tablets conformed to the specification for friability. They will be able to withstand the effects of forces of abrasion during further handling and transport.

Uniformity of content

From the results shown on Table 4 the drug content of formulations F1 to F5 ranged from 98.35 to 109.38%. There were all within the normal range for ciprofloxacin.

In vitro Drug Release

From Figure 1, Formulation F1 (10 % SAG) behaved like a conventional release tablet as it released 67.67 and 91.67 % of its drug content at 45 and 60 min respectively. It had no sustained release property. Formulation F2 (10 % Carbopol) released 77.03 and 98.63 % of its drug contents within 3 and 8 h respectively. It showed a poor sustained release property as majority of the drug content (77.03%) were released in 3 h. Formulation F3 (20 % SAG) released 67.67 % of its drug content after 8 h. It showed that it has a good drug release retardant effect. It could be used in the formulation of sustained release drugs that can be administered once daily. F4 (20 % Carbopol) released 72.23 and 91.43 % of its drug contents in 5 and 8 h respectively. It has a fair drug retardant effect. F5 (10/10 % SAG/Carbopol) released 79.43 and 101.03 % of its drug content at 4 and 8 h respectively. It showed a fair drug retardant effect.

Table 4: Evaluation of mucoadhesive ciprofloxacin tablets

F	Weight (g)	Thickness (m)	Diameter (m)	Hardness (m)	Friability (%)	% content of drug
F1	0.59 ± 0.01	3.22 ± 0.25	12.80 ± 0.22	9.87 ± 1.42	0.2	99.49
F2	0.60 ± 0.01	3.33 ± 0.13	13.02 ± 0.17	9.62 ± 7.89	0.4	100.15
F3	0.60 ± 00	3.18 ± 0.04	12.75 ± 0.00	10.81 ± 1.33	0.3	98.56
F4	0.60 ± 0.00	3.31 ± 0.13	12.94 ± 0.15	10.73 ± 2.94	0.1	98.35
F5	0.59 ± 00	3.19 ± 0.17	12.75 ± 0.17	16.55 ± 3.59	0.1	109.38

Key: F = Formulation

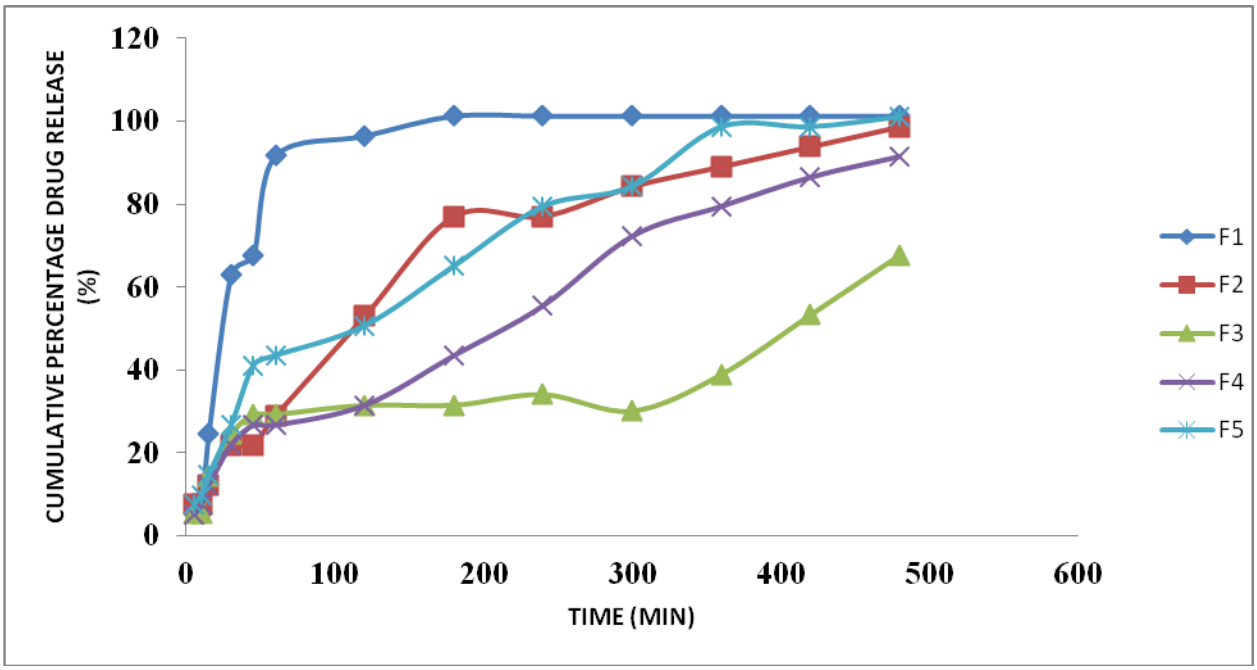

Fig 3.1: Cumulative Percentage drug release profile for batches F1 - F5

Key: F1 = SAG (10 %), F2 = Carbopol (10 %), F3 = SAG (20 %), F4 = Carbopol (20 %), F5 = SAG/ Carbopol (10/10 %)

Mucoadhesive Test

The results on Table 5, showed that tablets from all the formulations (F1 – F5) were able to adhere to the tissue. Tablets from all the formulations adhered for up to 8 h except for F1 (4.33 h) and F2 (5.08 h). This shows that tablets from formulations F3, F4 and F5 are good candidates for formulation of mucoadhesive drug delivery systems. Greater force (indirectly, weight of solvent) will be required to detach tablets from formulation F3, F4 and F5 from the tissue than that required for formulations F1 and F2.

Table 5: Mucoadhesive strength of ciprofloxacin tablets

Formulation	Volume of solvent used (ml)	Bioadhesive strength (Weight of solvent used (g))	Duration of bioadhesion (hours)
F1	2600	3042	4.33
F2	3050	3568.5	5.08
F3	4900	5733	8.17
F4	4800	5616	8.00
F5	5400	6318	> 9.00

Kinetics and mechanism of release

From the result on Table 6, the kinetics of release for formulations F2 and F5 was dominated by Higuchi model though strong influence from first order, Hixson - Crowell and Korsmeyer – Peppas were observed. For formulations F1, F3 and F4, Korsmeyer – Peppas model was dominant though pronounced input from first order, Higuchi and Hixson – Crowell models were observed. Higuchi model is used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs [26]. First order model can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water soluble drugs in porous matrices. Hixson – Crowell model is applicable to different pharmaceutical dosage form such as tablets, where the dissolution occurs in planes which are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a way that the initial geometrical form keeps constant all the time [26]. The mechanism of release was anomalous (non – Fickian) diffusion.

Table 6: Kinetics of release of mucoadhesive ciprofloxacin matrix tablets

		F1	F2	F3	F4	F5
Zero order	R^2	0.710	0.796	0.435	0.901	0.729
First order	R^2	0.747	0.945	**0.788**	0.961	0.920
Higuchi model	R^2	0.585	**0.986**	0.784	0.963	**0.981**
Hixson-Crowell cube-root model	R^2	0.641	0.974	0.618	**0.975**	0.965
Korsmeyer-Peppas model	R^2	**0.849**	0.833	0.783	0.955	0.958
	n	0.619	0.526	0.461	0.608	0.579

CONCLUSION

Mucoadhesive ciprofloxacin tablets were successfully produced by direct compression using *Sida acuta* gum as mucoadhesive polymer. It is therefore concluded that *Sida acuta* just like the standard polymer (Carbopol), has potential mucoadhesive properties and could be used alone or in combination with carbopol as polymer in the formulation of sustained release mucoadhesive ciprofloxacin tablets.

CONFLICT OF INTEREST

The authors has no conflict of interest in conducting and reporting of this work

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