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Bioadhesive and release studies on riboflavine granulations prepared from cissus gum coprecipitated with gelatin

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ABSTRACT
Mucosa-adhesive polymers can be used as useful means of delivering drug to mucosal membranes, and in particular intestinal and gastric mucosa. Cissus gum from Cissus vogelii has not been studied as mucosa-adhesive material, but being a good local soup thickener, it might be a good candidate for drug targeting based on mucosa-adhesive properties. Its adhesive strength and that of varying admixtures of gelatin coprecipitates were examined for bioadhesiveness in this study. Cissus-gelatin hydrophilic polymer containing either one or the two with a total polymer concentration of 2.5 %w/v were prepared and coprecipitated using analytical grade of acetone and tested for their mucosa-adhesive strength on freshly excised hog intestinal ileum (as a model mucosa) using simulated intestinal fluid of pH 7.5 and also the modified Lecomte Du Nouy Tensiometer. Release studies on riboflavine granulations prepared with the co-precipitated cissus-gelatin gum were also investigated. It was established that cissus gum possesses bioadhesive properties which could be used in gastrointestinal tract drug delivery. The bioadhesive properties of cissum gum were modified when coprecipitated with gelatin.

Keywords: *Bioadhesion, release studies, riboflavine, granules, cissus gum-gelatin coprecipitate*

Introduction

The use of bioadhesive polymers and co-polymers as means of delivering therapeutically active drugs, to or via mucous membrane has been the focus of attention in recent years [1-5]. The term bioadhesion is defined as the attachment of synthetic or natural macromolecules to a biological tissue [6-8]. When applied to mucosal epithelium, bioadhesive interactions occur primarily with the mucus layer, and this phenomenon is referred to as mucosa-adhesion [9-11].

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The materials with this property are generally hydrophilic macromolecules that contain numerous hydrogen bond forming groups, and hydrates and swell when placed in contact with an aqueous solution. These materials need to hydrate to become adhesive, but over-hydration usually results in the formation of a slippery mucilage and loss of adhesive properties [12]. Intimate contact between the adherents is a prerequisite for a strong adhesive bond. As a result, static adhesion behaviour has been described as a function of the spreading coefficient,

S_{12}; this thermodynamic parameter has been suggested as the driving force for the wetting process [2].

$$S_{12} = Y_{23} - Y_{13} - Y_{12} \quad \ldots\ldots 1$$

The specific work of adhesion, W_{12}, can be described by the Dupre's equation [12].

$$W_{12} = Y_{13} + Y_{23} - Y_{12} \quad \ldots\ldots 2$$

Here, W_{12} represent the energy required to reversibly separate two substrates to infinite separation. When the two substrates are identical, this expression reduces to

$$W_{12} = W_{11} = 2Y_{13} \quad \ldots\ldots 3$$

This occurs when the spreading coefficient is maximized; i.e. when

$$Y^{p}_{1}/Y_{1} = Y^{p}_{2}/Y_{2} \quad \ldots\ldots 4$$

Wetting of a substrate is best when the measured contact angle approaches zero [13].

Delivering mucosa-adhesive dosage forms offers the advantage of good drug absorption as a result of increase in resident time, enhanced patient acceptance and compliance. This phenomenon has been used in several occasions like in the local application of steroids for the treatment of mucosal ulceration, and can remain at its site of application for 15 to 150 min [1].

In this study, attempts were made to establish the mucoadheisives and bioadhesiveness of cissus gum prepared from *Cissus vogelii* (Fam.Ampelidaceae) [14], alone and in combination with an auxiliary animal gum (gelatin) co-precipitated.

Cissus vogelii is extensive herbaceous climber, setose on the young parts, and the leaves and stem often purple tinged, flower greenish, and ripe fruit black [14].

Gelatin is a protein obtained from collagenous material such as animal skins, tendons, ligaments, and bones. There are two types of gelatin: Type A is gelatin obtained from an acidic treated precursor (gelatin obtained from an acidic treated precursor (with isoelectric point between 7 and 9), and Type B is gelatin derived from an alkali treated or hydrolysis of precursor from animal bone (with isoelectric point between 4.7 and 5.2)

Usually gelatin is soluble in hot/warm, but insoluble in cold water. However, when placed in cold water, gelatin softens and gradually absorbs about 5 – 10 times its own weight of water. It has been proved to be insoluble in alcohol, chloroform, ether, fixed or volatile oil, but readily soluble in biological fluid at body temperature. It is a good film forming material and non-toxic. It is a widely employed in foodstuffs, as tablet film coats and binders.

The research work is aimed at evaluating the release of riboflavine from drug loaded granules prepared from a gelatin-cissus gum coprecipitate. It also looks into usefulness of cissus gum in bioadhesive drug delivery system and its role in in-vitro release of drug from encapsulated granules when coprecipitated with gelatin.

MATERIALS AND METHODS

Type B gelatin (BDH England), acetone analytical grade (BDH, England), concentrated hydrochloric acid (BDH Chemicals Ltd, England), sodium

hydroxide pellet (BDH, England), potassium dihydrogen orthophosphate (BDH, England), sodium chloride (BDH, England), riboflavine sample (Sigma, USA). All laboratory reagents were freshly prepared.

METHODS

Precipitation of Cissus Gum

The method of Adikwu *et. al.* (16) for the preparation of prosopis gum was used. Roots of *Cissus vogelii* were collected, washed, dried and weighed before grinding. Its particle size was reduced by grinding into a fine powder. The powder was passed through 1.7 mm sieve. The powder was soaked in distilled water for 24 h, to allow for proper hydration. The hydrated mass was passed through a muslin cloth and the filtrate was collected. The mucilaginous material was subsequently precipitated with 5000 ml of acetone. This volume of acetone was five times the volume of the mucilage. The precipitate was washed severally with fresh acetone and decanted until no slight change in colour was noted. The gum was air-dried and comminuted into fines with an end-runner mill (Model 331245G, Erweka, England). The fines of the gum were passed through 250 µm sieve and were weighed to be 248 g of processed cissus gum.

Coprecipitation

Aqueous dispersions containing 2.5 % w/v of the polymer gums (cissus/gelatin) were made into ratios of cissus–gelatin of 1:1, 1:4, 1:6, 1:10, 0:1, 1:0 combinations. The mucilage was prepared by separately stirring of weighed cissus and gelatin gums in appropriate quantity in different beakers containing water. The gelatin was warmed to facilitate effective dissolution, but was brought to the same temperature with the cissus mucilage before mixing them in one beaker. The mixture was stirred for 5 min., before the mixed mucilage was precipitated with 150 ml of analytical grade of acetone and was air-dried. The co-precipitated gum was pulverized and passed through sieve 250 µm. The yield of the 2.5 g w/v was 1.23 g w/v after precipitation.

Preparation of Coprecipitated Polymer Dispersion

Different ratios of the co-precipitated polymer gums (cissus:gelatin) were each dissolved in 20 ml of distilled water and allowed to hydrate for 24 h before use in the determination of bioadhesion. The mucilage used for coating of beads, was prepared by dispersing 1.25 g of the co-precipitated gum in 10 ml of distilled water was allowed to stand for 24 h before coating the beads.

Measurement of Bioadhesion of Coprecipitated Polymer Gums Ratios

Use of Tensiometer

The concentration of 0.0625 g/ml each of the dispersion of the co-precipitated polymer were each poured into a watch glass. The tensiometer (model NR 3124, Akruss Hamburg, Germany) was properly zeroed and the weightless film properly attached. The glass plate was hung on the lever of the tensiometer in each case, while the platform was gradually lowered to make contact between the dispersion and the weightless film. Contact time was allowed for seven min to allow for film-polymer interaction to take place. The glass plate was lifted by means of screw until it detached from the surface of the dispersed polymer. The force required to remove the glass plate containing the

weightless object was read off from the microform balance in degrees and adequate conversion of this force to tension was obtained from the equation:

$$T = \frac{Mg\,F}{2L} \quad \ldots . 5$$

T = tension equivalent to the bioadhesive strength

M = weight required to return the lever pointer to its original position

L = perimeter of the glass plate

F = a constant dependent on the perimeter of the plate with a value of 0.94

G = acceleration due to gravity.

Averages of three readings were taken in each case.

Preparation of Simulated Intestinal Fluid without Pancreatin (pH 7.5)

A 6.8 g quantity of potassium dihydrogen orthophosphate was dissolved in 250 ml of distilled water. Then, 190 ml of 0.2 N NaOH and 400 ml of water was added. The mixture was stirred and adjusted to the pH of 7.5, and was made up to required volume (1000 ml).

Preparation of Simulated Gastric Fluid without Pepsin

The method described by Adikwu *et. al.* [18] was followed: A 2.0 g quantity of NaCl was dissolved in sufficient distilled water and 7.0 ml of concentrated HCl was added. The pH was adjusted to 1.3 with the solution of HCl, using pH meter and was made up to 1000 ml with distilled water. The volume needed for the test was prepared accordingly.

Bioadhesion of Coated Beads on Isolated Intestinal Mucus Surface

A separatory funnel were clamped on a retort stand with a rubber tube attached to the end of the funnel. Everted support slanted at an angle of 45° at the base of the retort stand with the height between the tube and the ileum being 10 cm was prepared. Freshly isolated and excised hog ileum (2.5 x 15 cm) was pinned on a plastic. Glass beads of average diameter and mass of 3 mm and 60 mg respectively, were thoroughly cleaned with distilled water and then with acetone to maximize the roughness factor. The beads were immersed in the aqueous dispersion of 2.5 %w/v of the polymer to ensure uniform coating. Coated beads were air dried and weight to note the amount of gum that adhered and for uniformity of the coatings. 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 8 min period.

Simulated intestinal fluid without enzyme (500 ml) was then allowed to drop over the beads at the rate of 30 ml/min. The number of detached beads was noted and used as a measure of mucoadhesion. The procedure was repeated three times in each case and average value recorded.

Preparation of Granules

The co-precipitated gums were ground in a mortar with a pestle and passed through 1.0 mm sieve. Wet granulation method of granule preparation was used and the granules were air-dried. Each batch of approximately 1.6 g of the gum coprecipiatae was prepared with 15 mg of riboflavine as the model drug. The granules were dried at 60 °C for 1 h. After the granulation, the granules were encapsulated using no. 1 capsules shells (300 mg) with an average weight of the empty capsule shell being 77 mg.

Absolute drug content measurement of the granules

A 200 mg quantity of each of the batches of granules were soaked in SIF or SGF and allowed to stand for 12 h to allow for proper hydration and leaching out of the drug from the granules. At the end of 12 h, serial dilutions of each were prepared to obtain 0.1 mg % to 1.0 mg% i.e. 10 fold dilutions, after filtering. Absorbance of the dilutions was taken in each case and the reading recorded accordingly.

Dissolution Studies on the Granules

In vitro release of the riboflavine from the encapsulated granules was measured according to the USP XXIII paddle apparatus (Model 1324R Erweka Dissolution Apparatus) at 37 ° C $\pm$ 1 °C and at 50 rpm using 500 ml of SGF or SIF in each batch as the dissolution medium. Samples (10 ml) were withdrawn at predetermined time intervals of 5, 10, 15, 20, 25, 30, 60, 90, 120, 150, 180, and 210 min. Absorbance of the corresponding samples was read spectrophotometrically at the wavelength of 446 nm and 445 nm in SGF and SIF respectively [18]. An equal volume of fresh dissolution medium, maintained at the same temperature, was added after withdrawing each sample to maintain the initial volume constant. Percentage of drug dissolved at different time intervals was calculated using the equation generated from the standard curve.

Statistical analysis

The significant of the results was done using the Student's t-test at the 95% confidence interval ($p < 0.5$).

RESULTS

Table 1 shows the results of the mucoadhesive studies obtained from intestinal mucus surface. The highest percentage was recorded in *cissus* gum alone while 1:10 ratio of cissus: gelatine recorded the lowest.

Table 2 shows the result of bioadhesion carried out with a tensiometer and it tallied with that of mucoadhesive study using coated beads. The study showed that both polymer gums had bioadhesive properties but cissus gum showed greater adhesion. This confirms that cissus gum has good bioadhesive property and it is possible for it to be used in bioadhesive controlled drug delivery. From the tables, increase in gelatine concentration decreased the level of adhesion of the polymers onto the intestinal mucosa. When surface tension was evaluated as shown in Table 2, gelatine alone decreased the surface tension more than the other polymer combination. These, may be related to the greater solubility of gelatine than cissus gum. The differences in the results were statistically significant ($p < 0.5$).

In-Vitro Release Studies

Figure 1 and 2 are the normal release profiles for the drug loaded granules (encapsulated) in SIF and SGF respectively. In Figure 1, the maximum percentage release among the batches was recorded with cissus: gelatin ratio of 1:6. All the batches showed a gradual decrease in percentage amount released within 30-60 min.

In Figure 2, the cissus:gelatine ratio of 1:6 alone showed the greatest release while the gelatin that showed highest in SIF showed less in SGF. In SGF, 1:10 ratio showed the minimum release while 1:4 showed minimum release. Figures 3 and 4 are the Higuchi's plots for the release of

the drug from the granules using SGF and SIF respectively. These plots are essential to evaluate the mechanism and order of release of the drug from the granules.

Finally, Figures 5 and 6 show the plots of the log of fraction released against the log of time (min) (in SIF and SGF) respectively. The slope of this plot gives a release exponent, n, which is indicative of the mechanisms which they represent or even the order of release. These plots were used to interpret the mechanisms. Tables 3 and 4 show the n exponent of the batches classified according to Fickian release mechanism based on the values of "n".

In SIF Batches (cissus:gelatin) 1:1, 1:10, 1:4, and cissus alone released through super case II transport diffusion mechanism, while gelatin alone is released based on Fickian principle. Then, the 1:6 ratio is released through non-Fickian mechanism. In SGF, 1:1 showed that the drug was released through super case II transport diffusion mechanism and 1:10 ratio, gelatin alone and 1:6 ratio, were non-Fickian in their release. Only cissus alone (1:0) had a Fickian diffusion release mechanism. Other batches could not be analyzed using these models.

DISCUSSION

Bioadhesive strength

Bioadhesion/mucoadhesion is expressed as the force required for detaching 50% of particles [15]. Cissus gum alone showed highest bioadhesive strength with the percentage mucoadhesion of 90% as shown in Table 1.As the simulated intestinal fluid comes in contact with the coated beads attached to the mucus tissue, the polymer swells, thereby causing the beads to adhere to the mucosal surface and retarding the release of the beads. The cissus : gelatin gum in 1:1 combination showed a convincing high bioadhesive property. Gelatin is known to possess good bioadhesive properties. Bioadhesive force occurs between the mucus surface and the polymer. The stronger the bioadhesive interaction between a polymer and a mucus membrane, the greater the force required to detach the polymer film from the mucus.

Cissus:gelatin in 1:10 ratio gave very low bioadhesion of 40% and this can be accounted for by the fact that gelatin was in a minute quantity and the combination absorbs water to form a tacky film which exhibits a maximum bioadhesion but when it is over-hydrated it forms a slippery mucilage, thus releasing the beads and providing an easy glide of the beads from the intestinal mucus surface [16]. From the results of the experiment in Table 2 and Figure 2, it showed that cissus gum alone gave the highest tension result of 2.65×10^{-4} $Nm.^{-1}$ This can be attributed to the ready hydration properties of the cissus gum which facilitated fast spreading over the mucosal surface to produce an interpenetrating layer and entanglements.

The ratio combination of 1:4, also exhibited a high tension result than gelatin alone, 1:1, 1:6 and 1:10 cissus:gelatin combinations. Gelatin showed lower bioadhesive values than the cissus gum alone and its combinations.

Gelatin alone showed an appreciable level of bioadhesiveness from the study.

However, it takes a longer period to gel than cissus gum to gel. This may be responsible for the low bioadhesive values recorded for the material. Other combinations gave varying bioadhesion as recorded in Tables 1 and 2. Ratio 1:4 gave 60% bioadhesion, while 1:6 gave 50 %; thus, the more the gelatin in the system less the bioadhesive value. In the use of this gum as a bioadhesive agent in combination with gelatin, less of the gelatine should be included in a system where a high adhesion is desired. Similarly more of the gelatin should be incorporated where little adhesion is desired.

Drug Release from encapsulated granules

From the results in Figures 5 and 6, it shows that gelatin alone released faster and highest in SGF, while the release was slower in SIF. Cissus:gelatin in the ratio of 1:6 released highest in SIF which shows the effect of pH in the release mechanism and pattern of polymers. The type B gelatin used showed higher water uptake than cissus gum and its combinations.

In the Log Mt/Mx against Log time, the release mechanism was determined from Figures 7 and 8. In SIF ratios of the coprecipitates containing cissus:gelatin 1:1, 1:10, 1:4, and cissus gum alone released through super case II transport diffusion mechanism, while gelatin alone released based on the Fickian principle. In the use of polymers in drug formulations it is often essential to use combinations to modify the effect of each of the polymers in the formulations. Many of such combinations may be physically made in the dry state.

However, this could lead to non uniform mixing or it may need longer mixing or kneading time. The method of gelatination of cissus gum using coprecipitation is novel. This is because the aqueous dispersions when mixed together before drying can lead to molecular mixing and interactions. At this level a lot of electrostatic forces such as hydrogen bonding may occur resulting in a product that has properties which is intermediate between the two compounds. In this study this purpose was achieved since the bioadhesive studies of the coprecipitates resulted in materials which had properties that were intermediate between gelatin and cissus gum. The idea of coprecipitation is interesting as an "intermediate" polymer was formed from an animal and plant mucilage conferring some properties of the gelatin on the plant gum and vice versa. This also affected the mechanisms of drug release from the polymer granules since the mechanism of release is dependent on the hydrophobicity of a material [17, 18]. The more hydropobic a material is the more it follows the Higuchi diffusion model in terms of drugs release [19].

CONCLUSION

This study showed that cissus gum alone has the highest bioadhesive strength when examined on intestinal hog ileum. Similarly, the gum co-precipitated with gelatin gave a good result in terms of adhesion at the ratios of 1:1 and 1:4 cissus: gelatin.

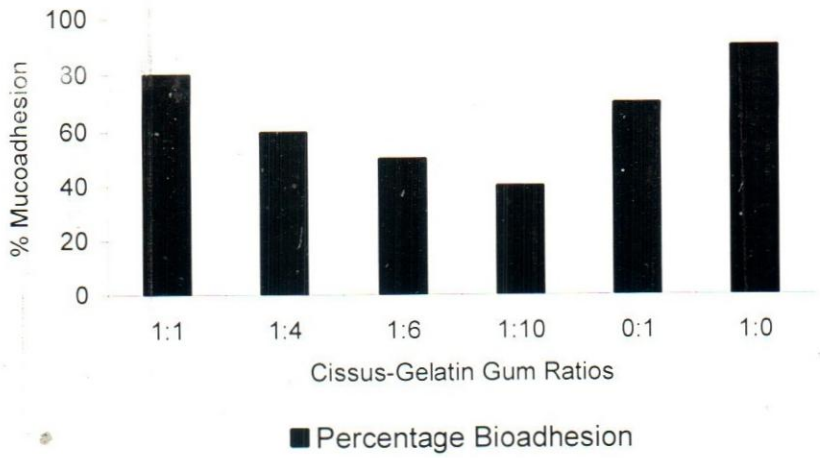

Fig. 1. Bioadhesive studies on the coprecipitated gum using glass beads

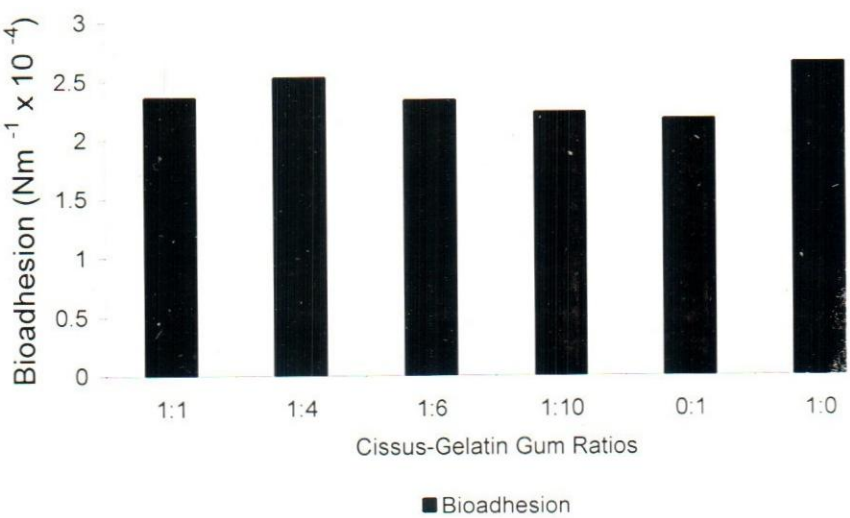

Fig. 2. Bioadhesive studies on the coprecipitated gum using a tensiometer

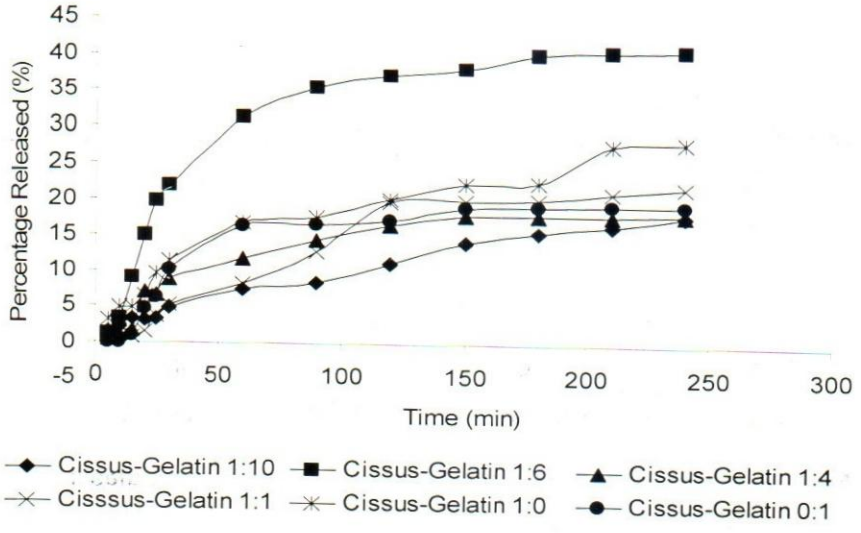

Fig. 3. **Release of riboflavine from the bioadhesive granules in simulated intestinal fluid**

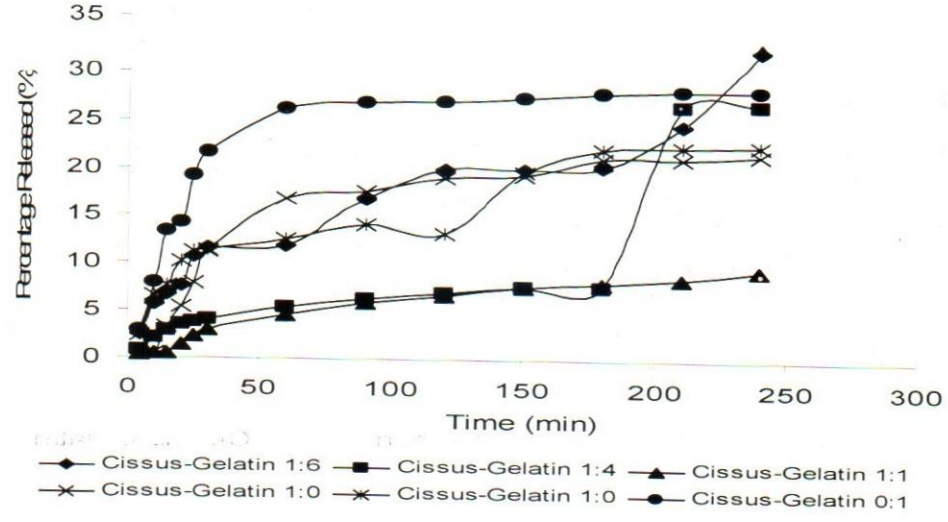

Fig. 4. **Release of riboflavine from the bioadhesive granules in simulated gastric fluid.**

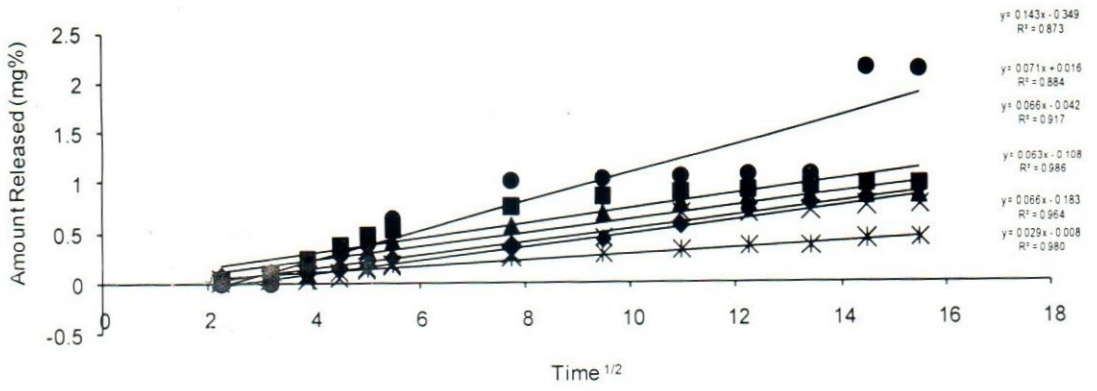

Fig. 5. Higuchi plots of the release of riboflavine from the granules in simulated intestinal juice

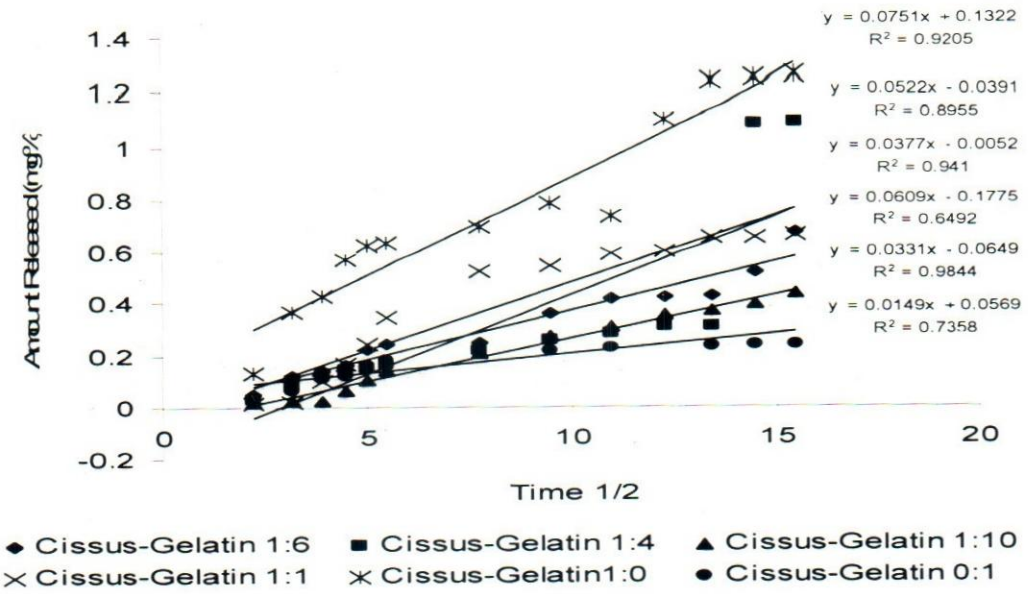

Fig. 6. **Higuchi plot of the release of riboflavine from the granules in simulated gastric fluid**

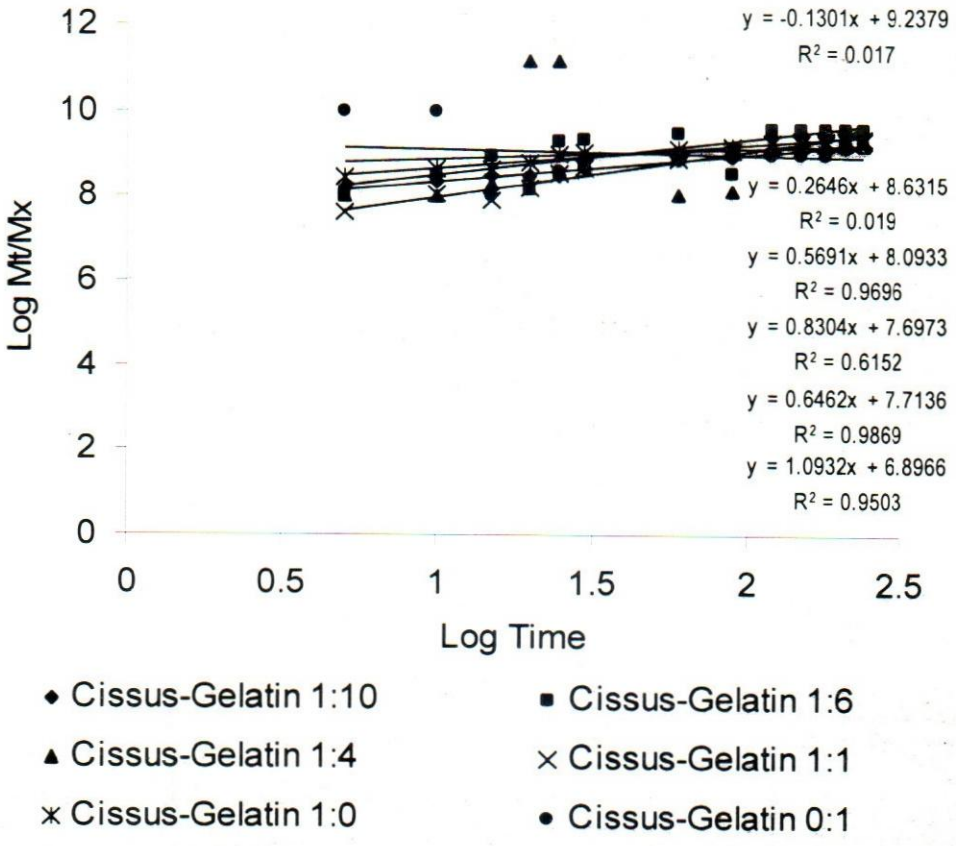

Fig. 7. **Plot of log Mt/Mx against log of time for the release of riboflavine from the granules in simulated intestinal fluid**

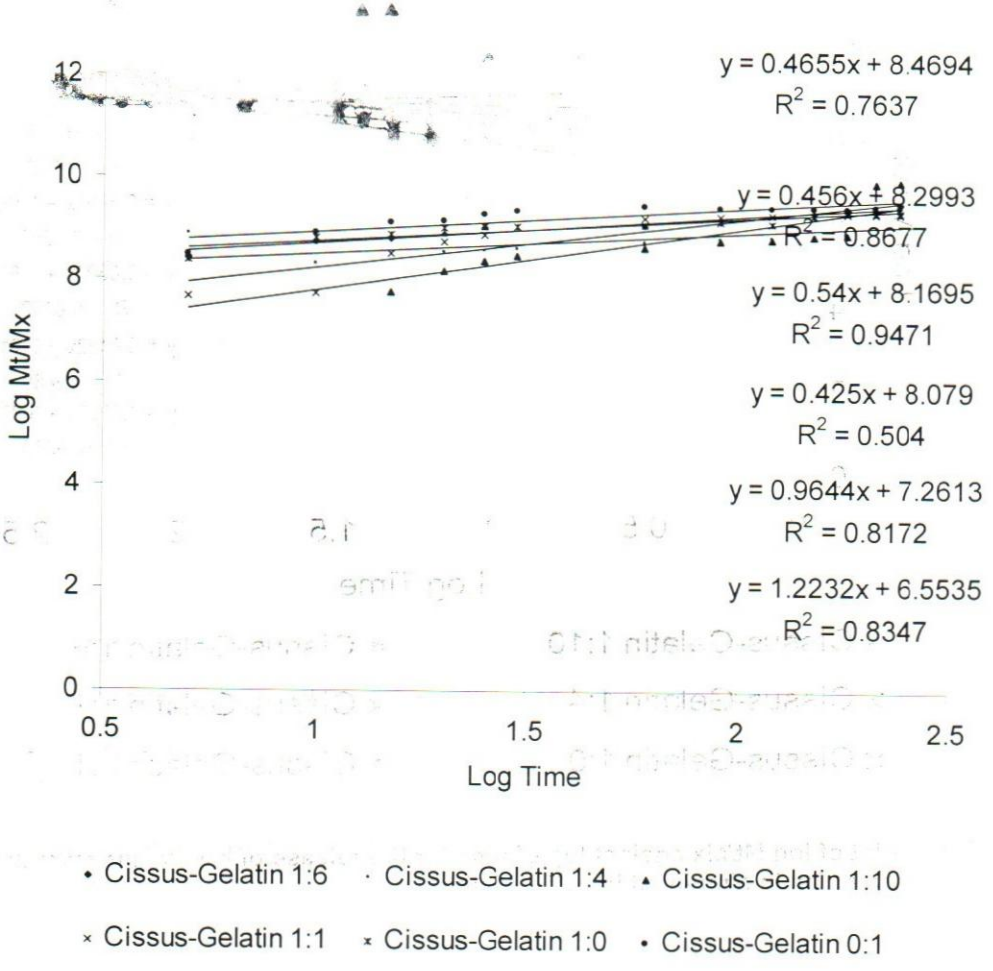

Fig. 8. Plot of log Mt/Mx against log of time for the release of riboflavine from the granules in simulated gastric fluid

Table 1: **Results of bioadhesive strength studies determined by test of coated beads on intestinal mucus surface**

Batch No	Cissus:gelatin Composition	Total No of Beads	No of Detached Beads	No of Undetached Beads	Percentage of Bioadhesion
1	1:1	10	2	8	80
2	1:4	10	4	6	60
3	1:6	10	5	5	50
4	1:10	10	6	4	40
5	Gelatin alone	10	3	7	70
6	Cissus gum alone	10	1	9	90
7	Uncoated beads	10	10	0	100

Table 2: Results of Bioadhesive Strength Studies of the Aqueous Dispersion of the Polymers and their combinations determined by Tensiometry

Batch No	Polymer gum	Polymer gum (auxiliary)	Compositions/ratios	Average forces obtained	Calculated tension in (Nm^{-1})
1	Cissus	Gelatin	1:1	35.8	2.35×10^{-4}
2	Cissus	Gelatin	1:4	38.5	2.53×10^{-4}
3	Cissus	Gelatin	1:6	35.0	2.33×10^{-4}
4	Cissus	Gelatin	1:10	34.0	2.23×10^{-4}
5	Cissus	Gelatin	0:1	33.0	2.17×10^{-4}
6	Cissus	Gelatin	1:0	40.3	2.65×10^{-4}
7	Water	Distilled water	Distilled water	42.0	2.76×10^{-4}

Table 3: Values of "n" Exponent for Release Mechanism Determination in SIF.

Batch Number	Batch Compositions	"n" Values from the Slope
1	1:1	1.0934
2	1:4	0.2649
3	1:6	0.8328
4	1:10	0.6465
5	CISSUS	0.1316
6	GELATIN	0.5671

Table 4: Values of "n" Exponent for Release Mechanism Determination in SGF.

Batch Number	Batch Composition	"n" Values from the Slope
1	1:1	0.9648
2	1:4	0.4245
3	1:6	0.5400
4	1:10	1.2223
5	CISSUS	0.4562
6	GELATIN	0.4658

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