Drug Development and Industrial Pharmacy, 34:807–816, 2008

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040801925768

informa
healthcare

Evaluation of Mucilage of *Hibiscus rosasinensis* Linn as Rate Controlling Matrix for Sustained Release of Diclofenac

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This article reports the exploitation of novel hydrophilic excipient, that is, mucilage from *Hibiscus rosasinensis* Linn, for the development of sustained release tablet. Swelling ratio and flow properties analyses of dried mucilage powder were carried out. A 3^2 full factorial design was used. In factorial design, amounts of dried mucilage and dibasic calcium phosphate (DCP) were taken as independent factors and percentage drug release in 60 and 300 min and time for 80% drug release as dependent variables. Matrix tablet containing dried mucilage and diclofenac sodium (DS) was prepared through direct compression techniques. DS tablets were evaluated for hardness, friability, weight variation, in vitro drug release and water uptake, and mass loss study. The dried mucilage powder shows superior swelling capacity and excellent flow properties. Prepared tablets have acceptable hardness, friability, and uniformity in weight. It was found that batch HD8 fulfills all selected criteria. Drug release kinetics from these formulations corresponded best to the zero-order kinetics. Water uptake was independent whereas mass loss was dependent on agitation speed. The concept of similarity factor (f_2) was used to prove similarity of dissolution profile in distilled water and phosphate buffer and was found to be 90.68. It was concluded that mucilage can be used as release-retarding agent for 12 h when the drug–mucilage ratio was 1:1.5. So, matrix tablet containing dried mucilage is most suitable for sustained release of DS.

Keywords *Hibiscus rosasinensis* Linn; mucilage; factorial design; diclofenac sodium; sustained release; hydrophilic polymer

INTRODUCTION

In recent years, the value of hydrophilic polymer-based matrix tablets as vehicles for controlled release has been increasingly demonstrated with the publication of numerous patents, research papers, and their utilization in new products in the market place. In part, the widespread and successful use of such polymeric systems can be attributed to their ease of manufacturing, relatively low cost, free availability, nontoxicity, their favorable in vivo performance, and their versatility in controlling the release of drugs with a wide range of physicochemical properties. Though a variety of polymeric substances are available to serve as release-retarding matrix material, there is a continued need to develop new, safe, and effective release-retarding material. Oral drug delivery systems continue to dominate the market despite the advancements made in newer drug delivery systems such as transdermal, liposomes, microspheres, and so on.

Hibiscus (Malvaceae) is a genus of herbs, shrubs, and trees. Its 250 species are widely distributed in tropical and subtropical regions of the world. The leaves of *Hibiscus rosasinensis* Linn of Malvaceae family are known as *jasud*, *jabakusum*, *jasuva* in Gujarati; *japa*, *ondrapuspi* in Sanskrit; *jasum*, *jasut*, *java*, *odhul* in Hindi; *cemparatti* in Malayalam; *dasindachaphula*, *jaswand* in Marathi; *joba* in Bengali; *mandaro* in Oriya; and shoe-flower plant, china rose, Chinese hibiscus in English (Anjaria, Parabia, & Dwivedi, 2002). It is cultivated in garden, and about 40 species are found in India. *H. rosasinensis* Linn is a native of China and is a potent medicinal plant. It is a common Indian garden perennial shrub and often planted as a hedge or fence plant (Mudgal, 1974).The parts used are leaves, flower, roots, and buds. Traditionally, this drug is attributed to antifertility activity in Ayurvedic literature, where leaves are used in traditional system of medicine as emollient, aperients, and in the treatment of burning sensation, skin disease, and constipation (Ivan, 1999; Kirtikar & Basu, 1999; Pullaiah, 2006).The petroleum ether extracts of the leaves and flower have been shown to potentiate hair growth in vivo and in vitro (Adhirajan, Ravikumar, Shanmugasundram, & Babu, 2003). They also possess hypoglycemic activity (Sachdewa & Khemani, 2003; Sachdewa, Nigam, & Khemani, 2001). The mucilage of the leaf has anticomplementary activity. The plant contains the cyclopropanoids, methyl sterculate, methyl-2-hydroxysterculate, 2-hydroxysterculate malvate, and ß-rosasterol. Representative mucilage, called Hibiscus-mucilage RL, was isolated from the leaves of *H. rosasinensis* Linn. The major constituent is an

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acidic polysaccharide composed of L-rhamnose, D-galactose, D-galacturonic acid, and D-glucuronic acid in the molar ratio of 5:8:3:2. Methylation analysis, partial hydrolysis, and nuclear magnetic resonance studies indicated its main structural features including a unique backbone chain composed of alpha-1,4-linked D-galactosyl alpha-1,2-linked L-rhamnosyl alpha-1,4-linked D-galacturonic acid units (National Institute of Science and Communication, 2002; Shimizu, Tomoda, Suzuki, & Takada, 1993). The leaves contain carotene (7.34 mg/100 g of fresh material) and are used as cattle feed (National Institute of Science and Communication). It also contains moisture, protein, fat, carbohydrate, fibers, calcium, and phosphorous (Duke & Ayensu, 1985).

Many natural materials, such as guar gum (Thomas & Reza, 2002), modified guar gum (Toti & Aminabhavi, 2004), isaphgulla husk (Gohel & Patel, 1997), olibanum and its resins (Chowdary, Mohapatra, & Murali Krishna, 2006), crosslinked high-amylose starch (Jerome, Pomplia, & Mircea, 2004), ulmus fulva (slippery elm mucilage) (Beveridge, Stoddart, Szarek, & Jones, 1969), pectin (Nurjaya & Wong, 2005), peums boldus dry plant extract (Santiago et al., 2002), galactomannon from mimosa scabrella (Ughini, Andreazza, Ganter, & Bresolin, 2004; Vendruscolo, Andreazza, Ganter, Ferrero, & Bresolin, 2005), ficus awkedsong (jelly fig extract) (Yasunori, Shigeru, & Kozo, 2004), honey locust gum (*Gleditsia triacanthos* Linn) (Melike & Turan, 2004), karaya and xanthan gum (Munday & Philip, 2000), gellan gum and alginates (Wataru, 2003), Xanthan gum (Helton, Francisco, Eugenia, & Joao, 2005), sesbania gum (Bharadia, Patel, Patel, & Patel, 2004) mucilage from pods of *Hibiscus esculent* (Baveja, Ranga Rao, & Arora, 1988), tamarind seed gums (Sumathi & Ray, 2002), gum copal and dammar (Morkhade, Fulzele, Satturwar, & Joshi, 2006), and modified ispaghula husk and modified guar gum (Gohel, Patel, & Amin, 2003), have been studied as sustained release in formulation.

Diclofenac sodium (DS) is a nonsteroidal drug having potent anti-inflammatory, analgesic, and antipyretic properties. It is an inhibitor of prostaglandin synthetase. It is used for the relief of pain and inflammation in conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout following some surgical procedures. It has an unpleasant taste and causes gastric irritation. DS is mainly absorbed from gastrointestinal tract. DS is a phenyl acetic acid derivative with a pK_a value of 4.0; it is practically insoluble in acidic solution but dissolves in intestinal fluid and water. It is generally known that DS reaches blood within 30 min and reaches the maximum blood concentration (C_{max}) within 1.5–2.5 h following oral administration of an enteric-coated tablet. The oral bioavailability is around 60% with an excretion half-life between 1.1 and 1.8 h (Fowler, Shadforth, Crook, & John, 1983; Hardman & Limbrid, 1995; Willis, Kendall, & Jack, 1981). To diminish DS gastrointestinal irritation, which is a common problem with all nonsteroidal anti-inflammatory agents, effective enteric-coated dosage forms have been developed. The benefits of administering DS in a sustained release dosage form have been demonstrated (Ayhan, Yalem, & Askin, 2005). In several investigations, the feasibility of development of a modified release dosage form has been studied using matrix-type formulations, which appears to be a very attractive approach from process development and scale up point of view.

Presently, mucilage of *H. rosasinensis* Linn has not been explored as pharmaceutical excipient. In this study, attempt was made to extract mucilage from leaves of *H. rosasinensis* Linn and study its physicochemical properties. On the basis of the results obtained from physicochemical properties, mucilage was incorporated into tablets to evaluate the effect of polymer blends in rate and kinetics of release from matrix tablet. Drug release mechanism was studied. A formulation variable, such as amounts of mucilage and diluents, was optimizing for prepared tablets. Furthermore, water uptake and mass loss studies of pure mucilage and matrix tablet containing drug–mucilage were carried out. A comparison of drug release profile of optimized batch and market preparation (Voveran-SR tablet) was carried out. Finally, stability study of optimized batch was done for 3 months.

MATERIALS AND METHODS

Materials

DS was received as a generous gift from Beacon Pharmaceuticals Pvt. Ltd. Ahmedabad, India. The leaves of *H. rosasinensis* Linn were collected from our medicinal garden. Dibasic calcium phosphate (DCP) IP, Talc IP, and Magnesium stearate IP were used as such. All other solvents and chemicals were of AR grade. Deionized double-distilled water was used throughout the study.

Methods

Extraction of Mucilage

The fresh leaves of *H. rosasinensis* Linn were collected, washed with water to remove dirt and debris, and dried. Then they were powdered and soaked in water for 5–6 h, boiled for 30 min, kept aside for 1 h for complete release of mucilage into water. The material was squeezed in an eightfold muslin cloth bag to remove the marc from the solution. Then, three times volume of acetone was added to filtrate, to precipitate the mucilage. The mucilage was separated, dried in an oven at a temperature less than 50°C, collected, dried, powdered, passed through sieve no. 80, and stored for further use in desiccators (Wahi, Sharma, Jain, & Sinha, 1985).

Acute Oral Toxicity Test (LD_{50})

The acute toxicity of dried mucilage of *H. rosasinensis* Linn was determined in overnight-fasted wistar rats by following fixed dose method as per OECD guideline no. 425.

Swelling Ratio

The study was carried out in 100 mL stopper-graduated cylinder. The initial bulk volume of 1 g dried mucilage was noted and

then water was added in sufficient quantity to yield 100 mL uniform dispersion. The sediment volume of the swollen mass was noted after 24 h of storage at room temperature. The edge of the swelled sediments clearly differentiated from the water phase. The swelling ratio was calculated by taking the ratio of the swollen volume to the initial bulk volume. Swelling ratio study was carried out in distilled water, simulated gastric fluid (0.1 N HCl), and phosphate buffer (pH 6.8) (Bowen & Vadino, 1984).

Angle of Repose

The angle of repose (Φ) was determined using the fixed height funnel method and calculated as follows:

$$\Phi = \tan^{-1}\frac{h}{r}, \quad (1)$$

where h is the height of the powder heap and r is the radius of the powder heap. Comparisons were made between dried mucilage, guar gum, and ispaghula husk.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) thermograms were obtained using a differential scanning calorimeter (Model TA-60, Shimadzu, Japan) of pure DS, pure dried mucilage, and a mixture of DS and dried mucilage. About 2 mg of sample was scanned in a hermetically sealed standard aluminum pan and heated at a temperature between 100 and 400°C at a heating rate of 10°C/min under constant purging of nitrogen at 40 mL/min. An empty sealed aluminum pan was used as a reference. The characteristic peaks and specific heat of the melting endotherm were recorded.

Preparation of DS Tablets

The required quantities of DS and dried mucilage powder (80#) were physically admixed. DCP was used as diluent. The powder blend was then lubricated with 1% wt/wt talc and 2% wt/wt magnesium stearate. Lubrication was done in a glass jar for 2 min. Each tablet contained 100 mg of the drug (Gilbert & Neil, 1987). The tablets were prepared by direct compression on a rotary tablet press (Cadmach, Ahmedabad, India), fitted with concave punches of 9 mm diameter. The turret was rotated at a fixed speed of 0.5 rps. The composition of the preliminary batches (A1–A3) and its results are summarized in Table 1. The experimental design was 3^2 full factorial designs, and nine formulations were prepared. The two independent variables were amount of dried mucilage powder (X_1) and amount of DCP (X_2). The low (–1), medium (0), and high (+1) values of X_1 were 100, 150, and 200 mg, respectively; the low (–1), medium (0), and high (+1) values of X_2 were 0, 50, and 100 mg, respectively. The compositions of the nine batches of the factorial design are summarized in Table 2.

Hardness and Friability Tests

Hardness test was carried out by using Monsanto Hardness Tester, and friability was evaluated as the percentage weight loss of 20 tablets tumbled in a friabilator (Model EF2, Electrolab, Mumbai, India) for 4 min at 0.416 rps. The tablets were dedusted, and the loss in weight was recorded as percentage friability.

TABLE 1
Formulation and Results of Preliminary Batches Containing Dried Mucilage and Diclofenac Sodium

Batch Code	Amount of Mucilage (mg)	Amount of DCP (mg)	Y_{60}	Y_{300}	t_{80}
A1	100	0	30.67	69.33	388
A2	150	0	26.70	65.23	420
A3	200	0	22.38	55.40	480

Each tablet contains 100 mg of diclofenac sodium.

TABLE 2
Formulation and Dissolution Characteristics of Batches in a 3^2 Full Factorial Design of Diclofenac Sodium Tablets

	Variable Level in Coded Form		% Drug Release in Distilled Water		
Batch Code	X_1	X_2	Y_{60}	Y_{300}	t_{80}
HD1	–1	–1	30.67	69.33	388
HD2	0	–1	26.70	65.23	420
HD3	1	–1	22.38	55.40	480
HD4	–1	0	27.20	65.89	405
HD5	0	0	24.52	53.89	482
HD6	1	0	19.76	47.52	555
HD7	–1	1	25.42	58.20	480
HD8	0	1	23.97	44.45	555
HD9	1	1	17.56	43.55	585

Uniformity of Weight

The weight variation test was performed. Twenty tablets were weighed individually and average weight was calculated.

Dissolution Rate Study

The drug release study was carried out using USP XXIII paddle-type dissolution test apparatus (Model TDL-08, Electrolab, Mumbai, India) at 37 ± 0.5°C and at 0.833 rps using 900 mL of distilled water or phosphate buffer (pH 6.8) as dissolution medium (n = 5). Five milliliters of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45-μm membrane filter, diluted suitably, and analyzed spectrophotometrically at 276 nm using a Shimazdu-1,700 UV-Visible double beam spectrophotometer. Equal amounts of fresh dissolution medium were replaced immediately after withdrawal of a test sample. The percentage drug dissolved at different time intervals was calculated using regression equation generated from the standard curve. A comparison of optimized batch and market preparation was also made.

Full Factorial Design

A 3^2 randomized full factorial design was utilized in this study. In this design, two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The ratio of mucilage ($X1$) and amount of DCP ($X2$) were selected as independent variables. The time required for 80% drug dissolution ($t80$) and percentage drug released in 60 min ($Y60$) and 300 min ($Y300$) were selected as dependent variables.

Water Uptake and Mass Loss Studies

Mass loss (erosion) and water uptake of the formulated tablets were determined under conditions identical to those described above for dissolution testing. Water uptake and mass loss (erosion) were determined gravimetrically according to the following equations:

$$\%\ \text{water uptake} = 100\,\frac{\text{wet weight} - \text{remaining dry weight}}{\text{remaining dry weight}}, \quad (2)$$

$$\%\ \text{mass loss} = 100\,\frac{\text{remaining dry weight}}{\text{original dry weight}}. \quad (3)$$

Three tablets were used per time point. At the predetermined times, the ring mesh assemblies supporting the partially hydrated tablets were carefully removed, and the tablets were lightly blotted with tissue paper to remove excess surface water. After determining the wet weight, the tablets were dried at 70°C for 1 day, before reweighing to determine the remaining dry weight. Test was performed at different speeds of 0.833 rps and 1.666 rps. Placebo tablets consisting of pure mucilage were tested in the same way. All studies were carried out in triplicate.

Radial and Axial Swelling of Tablet

The initial diameter and thickness of the tablets were measured, and the tablet was then kept in dissolution media. Tablet was kept on a glass slide, and the increase in diameter and thickness were measured at different time intervals in stationary condition by vernier calipers. Tablet was kept on glass slide. To evaluate the relation, the equilibrium degree of swelling (Q) was calculated from radial and axial swelling ratio (Colombo et al., 1990).

$$Q = \frac{V_t}{V_0} = \left(\frac{R_t}{R_0}\right)^2 \times \left(\frac{I_t}{I_0}\right) \quad (4)$$

where V_t and V_0 are volumes; R_t and R_0 are radii at time t and zero, respectively. I_t and I_0 are thicknesses at time t and zero, respectively.

Stability Study

To study the effect of storage on in vitro release profile, stability study of best formulation (HD8) was carried out at 40°C and 75% relative humidity (RH) in a humidity oven. Samples were withdrawn after a 3-month interval and evaluated for change in in vitro drug release profile.

Statistical Analysis

The drug release analysis of DS (optimized batch HD8) was carried out in two different dissolution media (distilled water and phosphate buffer pH 6.8) for 12 h. It was compared using U.S. FDA specification, f_2 value, a similarity factor. A comparison of dissolution profile of optimized batch (HD8) was carried out with market preparation (Voveran-SR tablet). A comparison of dissolution profile of optimized batch (HD8), that is, before and after its stability study was carried out. As per U.S. FDA guidelines for f_2 value, two dissolution profiles are considered as identical if calculated f_2 value is greater than or equal to 50. Thus, ±10% range from ideal profile has been used for arbitrary selection of the optimal batch. A value of f_2 greater than or equal to 50 is necessary for similarity in dissolution profile at 10% difference (Shah, Tsong, Sathe, & Liu, 1998).

RESULTS AND DISCUSSION

The results of acute oral toxicity test (LD_{50}) show that LD_{50} dose for dried mucilage of *H. rosasinensis* Linn was found to be 3,000 mg/kg, and one-tenth of the dose of $LD_{50,}$ that is, 300 mg/kg, was considered safe for use as the metabolic rate in animals will be 5–10 times more than the human individual.

The swelling capacity of mucilage was found to be 9, 10, and 9 in distilled water, simulated gastric fluid (0.1 N HCl), and phosphate buffer (pH 6.8), respectively. It was concluded that swelling of mucilage is pH independent and mucilage may be considered nonionic. The angle of repose of a powder provides an insight into the magnitude of the cohesiveness of the powder and hence its flowability. Mildly cohesive powders have angles of repose between 40 and 60 when measured by any of the standard methods. A comparison was made between dried mucilage, guar gum, and ispaghula husk. Dried mucilage has an angle of repose of 27.83 while guar gum and ispaghula husk have 42.27 and 38.79, respectively. The dried mucilage has excellent flow properties when compared with guar gum and ispaghula. It could be inferred that dried mucilage powder being less cohesive has superior flow property. It can be concluded that dried mucilage has flow properties suitable for use in a direct compression formulation.

The average crushing strength of the prepared tablets was found to be 5 kg/cm^2, which shows good strength obtained from tablets. Friability study shows that it was less than 1%, that is, between 0.7 and 0.9%. All tablets pass the standard for uniformity in weight. From all the above results, it was concluded that tablets prepared from mucilage can be used as directly compressible vehicle because of good hardness, less friability, and uniformity in tablet weight because mucilage has good binding capacity and flowability.

To check the compatibility between drug and excipient, DSC was carried out. Figure 1 depicts the DSC of pure DS (A), pure dried mucilage extracted from *H. rosasinensis* Linn (B), and a mixture of DS and dried mucilage (C). The thermogram of pure DS (A) exhibits a sharp melting endotherm at 112.18°, 291.26°, and 323.25°C. DSC thermogram of pure dried mucilage (B) shows melting endotherm peaks at 105.50° and 356.79°C. A DSC thermogram of mixture of pure DS and dried mucilage (C) exhibits melting endotherm peak at 112.00°, 125.10°, and 278.00°C, indicating that there is no alteration in the thermal features of DS and pure mucilage. It was observed that there was no major change in peak and intensity of DS indicating no chemical changes. It was concluded that there was compatibility between drug and excipient.

It was observed from dissolution study of preliminary batches (batches A1–A3) that a complete drug release was obtained within 9, 10, and 11 h with different proportions of mucilage and DS. Data are summarized in Table 1. It was concluded that mucilage was suitable as a sustained release matrixing agent for DS tablet. Four criteria were established for the desired drug release profile: (a) a release of 20–25% drug within the first hour, (b) drug release after 5 h was 40% < Y_{300} < 60%, followed by (c) prolonged drug release of the remaining drug over 12 h, preferably at a relatively constant rate, and (d) time to release 80% drug was 490 < t_{80} < 590 min (Gohel et al., 2003; Peck, Johnson, & Anderson, 1990).

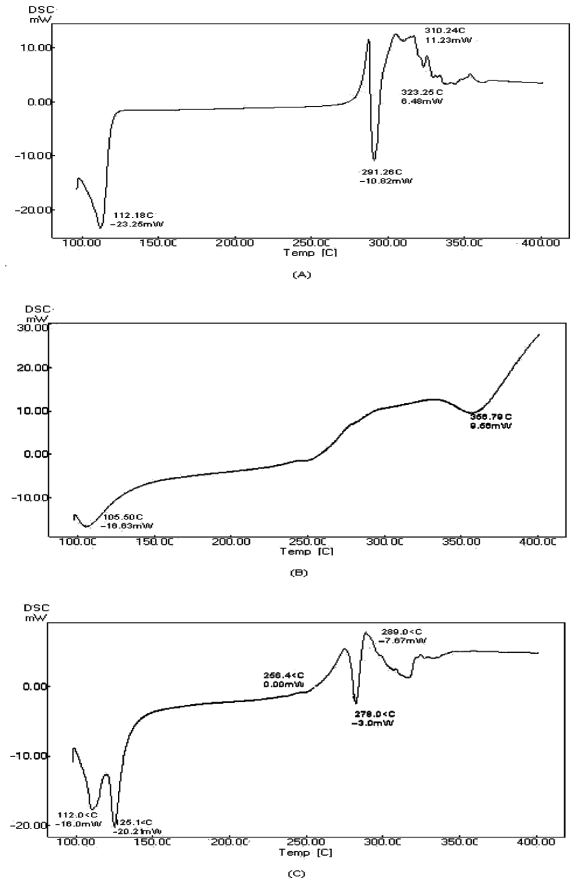

FIGURE 1. A DSC thermogram of pure diclofenac sodium (A), pure dried mucilage (B), and a mixture of diclofenac sodium and dried mucilage (C).

Factorial Design

A 3^2 full factorial design was constructed to study the effect of dried mucilage powder (X_1) and amount of DCP (X_2) on the drug release of DS tablets. The dependent variables chosen were Y_{60}, Y_{300}, and t_{80}, that is, percentage drug release in 60, 300 min and time to release 80% of the drug. A statistical model incorporating interactive and polynomial terms was used to evaluate the response.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2, \qquad (5)$$

where Y is the dependent variable, b_0 is the arithmetic mean response of the nine runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed (Sanford & Charles, 2004).

The $Y_{60,}$ Y_{300}, and t_{80} values for the nine batches (HD1–HD9) showed a wide variation from 17.56 to 30.67%, 43.55 to 69.33%, and 388 to 585 min, respectively. The data clearly indicate that the values are strongly dependent on the selected variables. The fitted equation relating the response $Y_{60,}$ $Y_{300,}$ and t_{80} to the transformed factor is shown in Equations 6, 7, and 8.

$$Y_{60} = 24.64 - 3.93\,X_1 - 2.13\,X_2 - 1.23\,X_1^{\,2} + 0.62\,X_2^{\,2} + 0.11\,X_1X_2 \quad (r^2 = .9845, df = 8, F = 38.28) \tag{6}$$

$$Y_{300} = 54.35 - 7.82\,X_1 - 7.29\,X_2 + 2.12\,\vec{X}_1^{\,2} + 0.26\,X_2^{\,2} - 0.18\,X_1X_2 \quad (r^2 = 0.9523, df = 8, F = 12.00) \tag{7}$$

$$t_{80} = 483 + 57.83X_1 + 55.33X_2 - 3.50X_1^{\,2} + 4.00\,X_2^{\,2} + 3.25X_1X^2 \quad (r^2 = .9666, df = 8, F = 17.38). \tag{8}$$

The value of correlation coefficient was found to be .9845, .9523, and .9662, respectively, indicating a good fit. Equations 6, 7, and 8 may be used to obtain reasonable estimate of the response because small error of variance was noticed in the replicates. The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, that is, positive or negative. The data demonstrate that both the factors (X_1 and X_2) affect the drug release Y_{60}, Y_{300}, and t_{80}. The low value X_1X_2 of coefficient also suggests that the interaction between X_1 and X_2 is not significant.

Batches HD3, HD5, and HD8 met the set criteria of Y_{60}, that is, 20% < Y_{60} < 25%. Batches HD3, HD5, HD6, HD7, HD8, and HD9 met the set criteria of Y_{300}, that is, 40% < Y_{300} < 60%. Batches HD6, HD8, and HD9 met the set criteria of t_{80} between 490 to 590 min. Only HD8 fulfilled all the selection criteria including prolonged drug release of the remaining drug over 12 h. So, batch HD8 was selected as optimized batch. The results of multiple linear regression for the response Y_{60}, Y_{300}, and t_{80} are summarized in Table 3. The high values of r^2 indicate good fit.

The dissolution data of batch HD8 were compared with the ideal release profile using f_2 statistics. An f_2 value of 70.13 indicates that the release profile of batch HD8 was comparable with the ideal batch. A value of f_2 greater than or equal to 50 is necessary for similarity in dissolution profile at 10% difference. The drug release analysis of the optimized batch (batch HD8) was also conducted in phosphate buffer (pH 6.8). Figure 2 depicts the dissolution profiles of batch HD8 in both media. The dissolution data of batch HD8 in distilled water were compared with the dissolution data in phosphate buffer (pH 6.8). An f_2 value of 90.68 indicates that the release profile of batch HD8 in distilled water and phosphate buffer is comparable. Finally, the dissolution of batch HD8 was compared with market preparation in distilled water. Figure 3 shows the dissolution profiles of batch HD8 and market preparation in distilled water. Dissolution data of both were compared using f_2 statistics. An f_2 value of 78.47 indicates that the release profile of batch HD8 and market preparation were comparable.

Kinetics of Drug Release

The method of Bamba and Puisieusx (Bamba & Puisieusx, 1979) was adopted for study of kinetics of drug release for the most appropriate model. The dissolution data of best batch HD8 were fitted to zero-order, first-order, Higuchi, Hixson–Crowell, Korsemeyer and Peppas, and Weibull models. The results of *F*-statistics were used for the selection of the most appropriate model. The release profile of the best batch HD8 fitted best to zero-order equation (F = 14.3), showing the least residual sum of square as compared with Higuchi (F = 52.57) and Korsmeyer and Peppas (F = 39.23) model. This superiority is, however, statistically insignificant among these three models as shown by the goodness of fit test (*F*-ratio test). But the priority should be given to the model with the least *F*-value. Thus, it may be concluded that the drug release from hydrophilic matrix of DS tablets is best explained by zero-order model. The values of slope and intercept for the zero-order model are 0.1275 and 8.8855, respectively.

TABLE 3
Results of Regression Analysis for Dependent Variables of Optimized Batch HD8

Dependent Variable	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}	r^2
Y_{60}	24.65	−3.93	−2.13	0.11	−1.23	0.62	.9845
Y_{300}	54.35	−7.82	−7.29	−0.18	2.12	0.26	.9523
t_{80}	483.00	57.83	55.33	3.25	−3.50	4.00	.9666

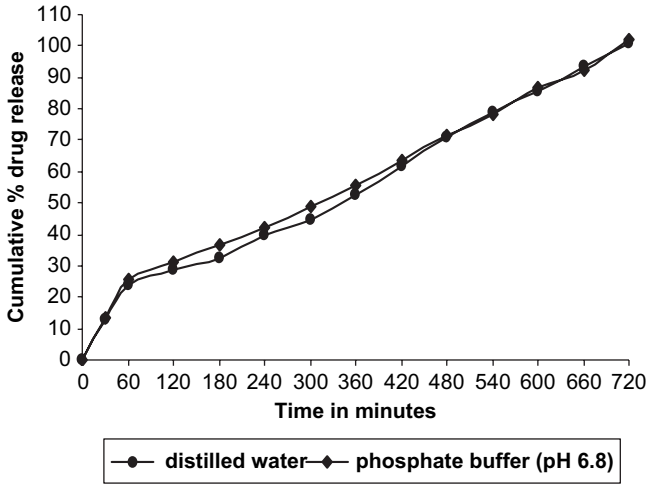

FIGURE 2. Comparison of cumulative percentage drug release of optimized batch (HD8) in distilled water and phosphate buffer (pH 6.8).

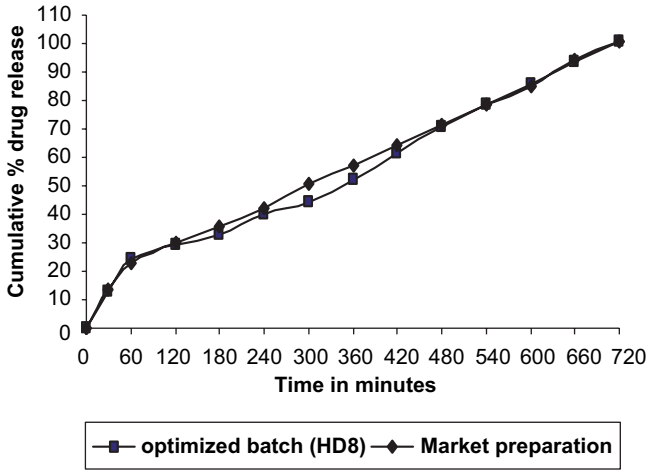

FIGURE 3. Comparison of cumulative percentage drug release of optimized batch (HD8) and market preparation (Voveran-SR tablet) in distilled water.

Water Uptake and Mass Loss

Pure Mucilage Matrices

The water uptake indicates the rate at which this formulation absorbs water and swells. The changes in weight, characteristic of water uptake and swelling, started from the beginning and continued until 6 h of experiment. These matrices showed a high ability to swell. Visual observation denoted that the matrices appeared swollen almost from the beginning, a viscous gel mass was created when they came into contact with the liquid. The matrix erosion measured the weight loss from matrix tablets immersed in dissolution media as a function of time. Mass loss from the tablets was in constant progression until the end of 6 h of experiment (Billa & Yuen, 2000; Thomas & Reza, 2002).

The percentage increase in weight of the hydrated pure gum matrices at various time intervals up to 6 h is shown in Figure 4. There was a high degree of water uptake by the mucilage powder (~1,107% weight increase after 6 h), but it was noteworthy that there was little difference in water uptake into the mucilage powder at different agitation speeds (<10% weight difference at 100 and 50 rpm after 6 h). Water uptake of mucilage was independent of agitation speed for this study. The large increase in weight was due to the very strong water uptake of mucilage powder coupled with very little simultaneous weight loss due to erosion.

Mass loss (erosion) was greatly influenced by agitation speed. Figure 5 shows that approximately 54% mass of the mucilage was lost after 6 h at 50 rpm, whereas after the same time period at 100 rpm, mass loss was found to be approximately 74%. As mass loss (erosion) occurred quite readily

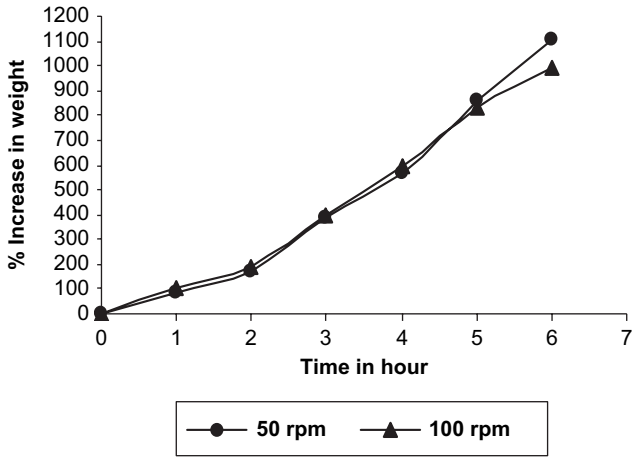

FIGURE 4. Percentage increase in weight resulting from water uptake by the pure mucilage matrices at various time intervals after contact with aqueous medium using two agitation speeds.

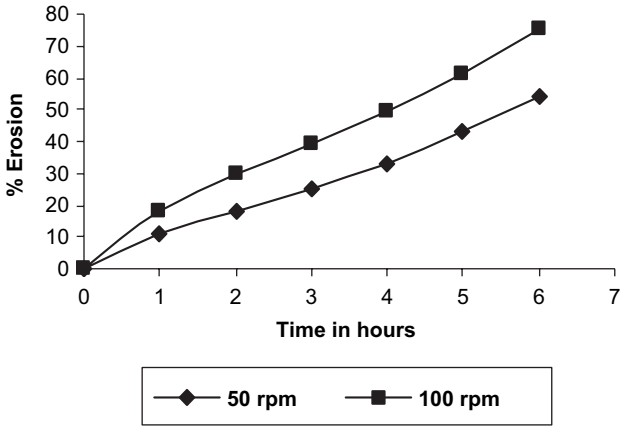

FIGURE 5. Percentage erosion (mass loss) in the pure matrices after relaxation of mucilage strands in aqueous medium at various time intervals using two agitation speeds.

from compressed mucilage matrices highly influenced by agitation speed, it is clear that the weight difference with time was a measure of both the water uptake and the mass loss processes occurring simultaneously. Mass loss of mucilage gradually increases as the time increases.

Drug–Mucilage Mixture

In case of matrix tablets containing dried mucilage and DS (optimized batch HD8) in proportions of 1:1.5 of drug : mucilage, it was observed that there was increase in weight resulting from water uptake in distilled water. There was no significant difference in weight gain (i.e., water uptake) between matrices containing drug at the two different agitation speeds (Figure 6). When matrices containing a lower proportion of mucilage [drug: mucilage (1:1)] was prepared, it showed a lower degree of weight gain with time. Significant differences in weight gain were shown only for matrices containing different proportions of mucilage. This was expected because the lower proportion of mucilage would decrease the ability of the matrix to absorb water. The dynamic balance between weight gain due to water uptake and mass loss due to mucilage erosion and drug dissolution is further illustrated by scrutiny of the profiles for mucilage matrices containing DS at both agitation speeds.

Figure 7 shows percentage mass loss of optimized batch HD8 containing 1:1.5 proportion of drug : mucilage into distilled water at two different agitation speeds. There was an initial rapid uptake of water by the dry matrices during the first 2 h, following gradual increase in rate of mass loss from matrix tablet at both speeds. This may be due to the amount of drug release in 2 h. It follows, therefore, that the hydrated mucilage network maintains its tight integrity with drug release by erosion and dissolution of the drug for most of the mass loss during the remainder of the experimental time period. In the first hour, due to solubility of the drug, interparticulate adhesive forces between the dry mucilages became weakened. Hydration of mucilage occurs when hydrogen-bonding forces maintain the integrity of the hydrophilic mucilage matrix during the remainder of the experimental time period (Dale & Philip, 2000). In hydrophilic matrix tablets, hydration of the polymer results in the formation of a gel layer, followed by matrix bulk hydration, swelling, and erosion. Initial mass loss of the matrix may be caused by dissolution of drug.

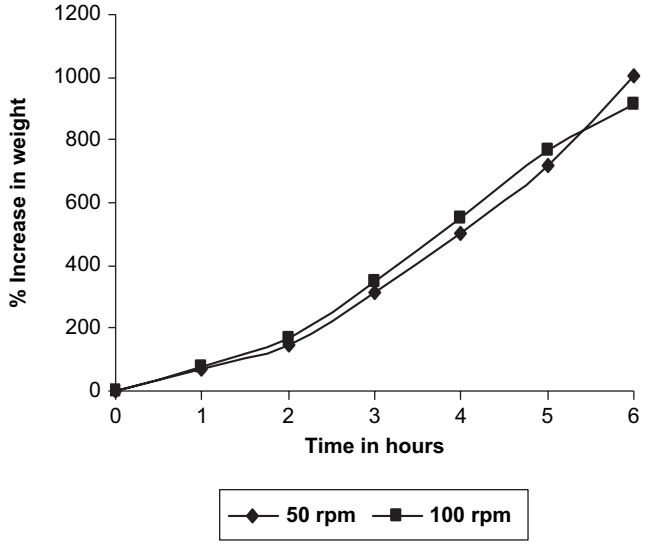

FIGURE 6. Percentage increase in weight resulting from water uptake of drug–mucilage formulations in aqueous dissolution medium at various time intervals using two agitation speeds.

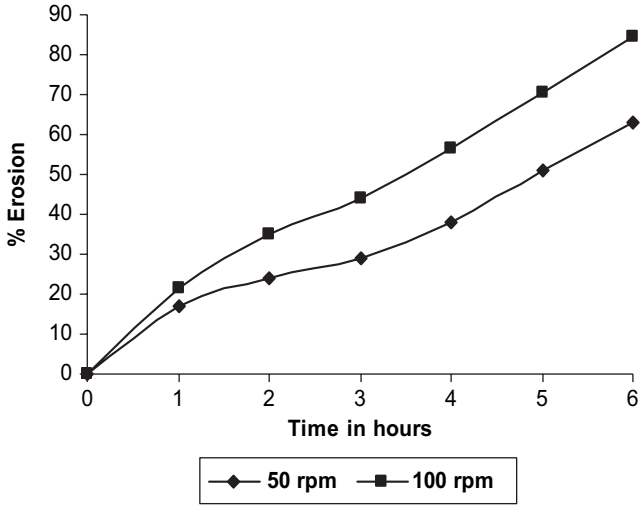

FIGURE 7. Percentage erosion (mass loss) of drug–mucilage formulation into aqueous medium at various time intervals using two agitation speeds.

Table 4 shows results of radial and axial study from the data, it was concluded that increase in diameter and thickness was proportionate with time, but there was more swelling in axial as compared to radial.

To determine the change in in vitro release profile on storage of batch HD8, it was carried out at 40°C in a humidity oven having 75% RH for 3 months. After storage, there was no physical change in the tablets, but the tablet was slightly softened because of hydrophilic nature of mucilage. Results of dissolution study shown that there was a insignificant difference in drug release profile. Data are shown in Table 5. The value of similarity factor was 94.11 indicating good similarity of dissolution profile before and after stability studies. The calculated *t*-value (0.974) was smaller than tabulated value (2.577), indicating insignificant difference in the dissolution profile before and after stability study. It was concluded that formulation HD8 was stable.

TABLE 4
Radial and Axial Swelling Study of Optimized Batch HD8 in Distilled Water

Time (h)	Diameter(mm)	Thickness(mm)	Normalized Diameter	Normalized Thickness	Normalized Volume
0	09	5.0	1.00	1.00	1.00
1	10	6.5	1.11	1.30	1.60
2	12	8.0	1.33	1.60	2.84
3	13	9.0	1.44	1.80	3.76
4	14	10.0	1.56	2.00	4.84
5	16	11.5	1.78	2.30	7.27
6	17	13.0	1.89	2.60	9.28

TABLE 5
Percentage Diclofenac Sodium Release of Optimized Batch HD8 Matrix Tablet, Before and After Storage at 40°C/75% relative humidity for 3 Months

Time(min)	% Drug Release Before Stability	% Drug Release After Stability
00	00.00	00.00
60	23.97	23.02
120	28.96	27.95
180	32.56	33.56
240	39.93	40.93
300	44.45	45.45
360	52.26	52.99
420	61.60	61.65
480	70.95	71.85
540	78.59	79.95
600	85.52	86.55
660	93.65	93.95
720	100.54	99.96

Similarity value (f_2) = 94.11. Dissimilarity value (f_1) = 01.46. Student's *t* test: tabulated value = 2.577; calculated value = 0.974.

CONCLUSIONS

From this study, it was concluded that a novel hydrophilic excipient, that is, mucilage extracted from *H. rosasinensis* Linn, can be used for the development of sustained release tablets. The dried mucilage powder shows superior swelling capacity and is pH independent. DS tablets can sustain their drug release up to 12 h. There was no significant effect of agitation speed on water uptake and mass loss of prepared tablets. Stability study of optimized batch showed that there was no significant effect of storage on in vitro dissolution profile. The mucilage can be further explored as disintegrating agent, gelling agent, and modified release dosage form.

ACKNOWLEDGMENTS

Authors are grateful to Dr. P. Deshmukh, Mr. R. Posia, and Mr. M. Dalal for their help to carry out Acute Oral Toxicity Study and also thank Jai Research Foundation, Vapi, Gujarat, India, for providing its facilities for the above-mentioned study.

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