ORIGINAL ARTICLE

# Development Optimization and Evaluation of Dual Mechanism Based Gastro Floatable and Bioadhesive Drug Delivery System for Simvastatin

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## Abstract

**Aim:** The objectives of this investigation were to develop gastroretentive floating bioadhesive drug delivery for simvastatin to increase gastric residence time and reduce the dose frequency. To explore Badams gum's sticking property in floating bioadhesive drug delivery of simvastatin. **Materials and Methods:** Floating bioadhesive tablet was formulated with Badam gum and hydroxypropyl methylcellulose (HPMC) K 15 M polymers, sodium bicarbonate, and citric acid as the gas generating agents to reduce floating lag time. Tablets were prepared by direct compression method. Optimization study was conducted using $3^2$ factorial design. The concentration of polymers was considered as independent variables whereas swelling index, bioadhesive strength and % drug release at 10 h, of the tablets were utilized as dependent variables. **Results and Discussions:** Preformulation study suggests powders blends shows acceptable flow properties. Simvastatin floating- bioadhesive tablet found to be good without chipping, capping, and sticking. Comparing all the formulations, A5 optimized formulation exhibited 98.10 ± 2.10% of drug release in 12 h, floating lag time of 34 ± 3 s, with appropriate bioadhesive property, and total floating time of over 12 h. It was observed that increasing percentage of polymer in formulation the drug release decreased. Developed formulations were stable during stability studies. **Conclusion:** Based on these findings, it was concluded that Badam gum can be used as a bioadhesive as well as release retarding polymer for the floating bioadhesive dosage form of other drugs.

**Key words:** Badam gum, bioadhesive, direct compression floating, gastric residence time, ptimization

## INTRODUCTION

Greater patient compliance associated with oral formulations is due to its ease of administration, low cost, and wide flexibility makes it a significant place among the various dosage forms.[1] Even though oral route is most famous route for drug administration but conventional oral drug delivery has following limitation of unpredictable gastric emptying rate, short gastrointestinal transit time, and intersubject variability leads into less bioavailability.[2] The goal of any drug delivery system is to provide a therapeutic amount of the drug to the proper site in the body to achieve promptly, and then maintain, the desired drug concentration, to ensure the safety of drugs as well as patient compliance which is not achieved by conventional oral drug delivery.[3] Hence, there is need of controlled release drug delivery systems to overcome this problem. This type of oral controlled drug delivery systems releases the drug with constant or variable release rates.[4,5]

Most popular approach of oral controlled drug delivery is gastroretentive drug delivery system (GRDDS) drug delivery system one. GRDDS plays a key role among novel drug delivery systems.[6,7] The retention of oral dosage forms in the upper GRDDS causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug

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**Received:** 29-03-2017
**Revised:** 13-04-2017
**Accepted:** 18-04-2017

administration, potentially reduced dose size and thus patient compliance. The various approaches are available in the GRDDS such as mucoadhesive, hydrodynamically based system, swelling and expanding system, and high-density system. Mostly preferred approaches are floating and bioadhesion.[8,9]

Floating drug delivery system is a type of GRDDS that has appropriate flexibility so as to float over the gastric contents for an extended period of time.[10] Low-density excipients and polymers are used for manufacturing of FDDS.[11,12] These GRDDS approaches have some merits and demerits like FDDS is effective only when the fluid level in the stomach is sufficiently high[13] as the stomach empties and the tablet is at the pylorus, the buoyancy of the dosage form may be impeded. Bioadhesive system it is quite likely that they become dislodged from the stomach wall when the system is full, and the semi-liquid contents are churning around due to the effect of peristalsis and its efficiency can be reduced by the constant turnover of the mucus. A floating -bioadhesive combination approach would overcome these drawback of floating and bioadhesive individual system and improving the therapeutic effect of the drug involved.[14] Design of experiment has been widely used in the pharmaceutical field to study the effect of formulation variables and their interactions on response variables. Design of experiments is a systematic series of tests, in which purposeful changes are made to input factors, so that you may identify causes for significant changes in the output responses.[15]

Hyperlipidemia is a major cause of atherosclerosis and atherosclerosis associated conditions such as coronary heart disease, peripheral vascular disease, and ischemic cerebrovascular disease.[16]

Besides, simvastatin undergo extensive first-pass metabolism in the liver and hence, the availability of the drug to the general circulation is very low (below 5%).[17] Therefore, GRDDS might be advantageous for simvastatin.[18]

Natural polysaccharides are extensively used for development of solid dosage form. Gums and mucilages are interesting polymer for the preparation of pharmaceutical formulations, because of their high water-swellability, non-toxicity, low cost, and free availability.[19,20]

Badam gum the *Terminalia catappa* is obtained from plant of *Terminalia randii* Linn. belong to the family Combretaceae.[21,22]

The aim of this investigation was to develop GRDDS drug delivery of simvastatin to increase its gastric residence time and reduce the dose frequency using floating bioadhesive tablet approach with Badam gum and HPMC K 15 M polymers and sodium bicarbonate and citric acid as the gas generating agents. Furthermore, to utilize Badam gum's sticking nature in floating bioadhesive drug delivery of simvastatin.

## MATERIALS AND METHODS

### Materials

Simvastatin was obtained as a gift sample from Wockhardt Ltd. Aurangabad, India. Badam gum samples were obtained from Local market Rasappa Chetty Street, Park Town, Chennai, Tamil Nadu, India. All other reagents and chemicals were of analytical grade obtained from Research Lab Fine Chem. Ltd. Mumbai India.

### Methods

#### *Experimental design*

Design of experiment has been widely used in the pharmaceutical field to study the effect of formulation variables and their interactions on response variables. The application of experimental design is to obtain the maximum information with the minimum number of experiments.[17]

The objective of this study is to develop GRDDS tablet of simvastatin. For this purpose, optimization study was conducted by using $3^2$ factorial design layout of batches shown in Table 2. The concentration of polymers was considered as independent variables whereas swelling index (SI), bioadhesive strength and % drug release at 10 h, of the tablets were utilized as dependent variables and effect of these on various parameters were studied.[30]

### Formulation of floating bioadhesive tablets of simvastatin

For the preparation of floating bioadhesive tablets of simvastatin all the ingredients according to the formulae shown in Table 3 were passed through sieve no. 40. The drug was geometrically mixed with polymer until a homogenous blend was achieved. Sodium bicarbonate and citric acid was added to the above mixture and mixed for 15 min in a polybag as a gas generating agents. The blend was lubricated with pre-sifted magnesium stearate and talc through sieve no. 60 for 3 min in a polybag. The final blend was then compressed into tablets on a 9 station rotary tablet machine (Rimek Mini Press - II, Karnavati, Ahmadabad, India) using 9mm round plain punches.[23,24]

### Characterizations of GRDF

#### *Determination of pre-compression parameters of simvastatin tablet*

The preformulation studies including bulk density, tapped density, Hausner ratio, and angle of repose were performed of the powder blend of floating bioadhesive formulations.[41]

### *Determination of post-compression parameters*

Following various evaluation tests are performed on developed floating bioadhesive tablets of simvastatin results are expressed as mean values ± standard deviation.

#### *Tablet weight variation*

About 20 tablets were randomly selected and accurately weighed and weight variation was determined as per I.P.

#### *Tablet hardness*

The hardness of tablets from all the batches was determined using the Monsanto hardness tester.

#### *Thickness*

Control of physical dimension of the tablet such as thickness is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using vernier calipers. It is measured in mm in triplicate.

**Table 1:** Layout of batches by $3^2$ full factorial designs

| Batch no. | X1 | X2 |
|---|---|---|
| A1 | −1 | −1 |
| A2 | −1 | 0 |
| A3 | −1 | +1 |
| A4 | 0 | −1 |
| A5 | 0 | 0 |
| A6 | 0 | +1 |
| A7 | +1 | −1 |
| A8 | +1 | 0 |
| A9 | +1 | +1 |

**Table 2:** Translation of coded value in an actual unit

| Coded value | Badam gum (X1) | HPMCK 15 M (X2) |
|---|---|---|
| −1 | 20 | 50 |
| 0 | 30 | 60 |
| +1 | 40 | 70 |

#### *Friability*

Roche friabilator was used for determination of friability of each for each formulation. In this test tablets were subject to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighted tablets was placed in Roche friabilator which was then operated for 100 revolutions, i.e., 4 min. The tablets were then dusted and reweighed.

Percent friability (%F) was calculated as, % F = (loss in weight/initial weight) ×100 (1)

#### *Simvastatin content uniformity*

The tablets were crushed in the mortar, and the powder equivalent to 20 mg of drug was dissolved in 0.1 N HCl. The stock solutions were filtered through an appropriate filter. The solutions were then diluted suitably with 0.1 N HCl. The drug content was analyzed at 238 nm by ultraviolet (UV) spectrophotometer (Shimadzu UV 1800). Each sample was analyzed in triplicate.

#### *SI study*

For each formulation batch, one tablet was weighed and placed in a beaker containing 200 ml of 0.1 N HCl. After each interval, the tablet was removed from beaker and weighed again up to 12 h. The SI study was performed in triplicate and it calculated using following formula.[20]

Swelling index (S.I) = {(wt-wo)/wo}×100 (2)

Where,
S.I. = Swelling index
Wt. = Weight of tablet at time t
Wo = Weight of tablet before placing in the beaker.

**Table 3:** Formulae of optimization batches

| Ingredients (mg) | Formulation batch code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | A1 | A2 | A3 | A4 | A5 | A6 | A7 | A8 | A9 |
| Simvastatin | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Badam gum | 20 | 30 | 40 | 20 | 30 | 40 | 20 | 30 | 40 |
| HPMC K15 M | 50 | 50 | 50 | 60 | 60 | 60 | 70 | 70 | 70 |
| PVP K-30 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Sodium bicarbonate | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 | 40 |
| Citric acid | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Lactose | 75 | 65 | 55 | 65 | 55 | 45 | 55 | 45 | 35 |
| Total | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |

### *In vitro buoyancy study*

The floating behavior of the tablets was visually determined in triplicate. The tablets were placed in a glass beaker containing 200 mL of 0.1 N HCl as a medium, maintained in a water bath at 37±0.5°C. Floating lag time and total floating duration (time during which tablet remains buoyant) were recorded.[25]

### *In vitro drug release studies*

Drug release studies of the prepared floating bioadhesive tablets were performed, in triplicate, in a USP dissolution tester apparatus, type-II (Paddle method) (dissolution tester, electro lab) at 37 ± 0.50°C. The paddles rotated at a speed of 50 rpm. The tablets were placed into 900 mL of 0.1 N HCl solutions (pH 1.2).

Aliquots of 1 mL were withdrawn from the dissolution apparatus at different time intervals and diluted with 0.1 N HCL, filtered. The drug release study was conducted by spectrophotometrically at a wavelength of 238 nm using UV. At each time of withdrawal, 1 mL of fresh medium was replaced into the dissolution flask to maintain sink condition.[30,31]

### *Measurement of bioadhesive strength and force of adhesion*

Bioadhesion strength was determined in terms of force required to detach the tablet from the membrane. For this study, all nine batches of floating bioadhesive dosage form were selected and executed. Bioadhesive strength of the tablets was measured on the modified physical balance. This instrument consists of a modified double beam physical balance in which the right pan has been replaced by a glass slide with copper wire and additional weight, to make the right side weight equal with the left side pan. A Teflon block of 3.8 cm diameter and 2 cm height was fabricated with an upward portion of 2 cm height and 1.5 cm diameter on one side. This was kept in a beaker filled with buffer media 0.1 N HCl pH 1.2, which was then placed below the right side of the balance.

Goat stomach mucosa was used as a model membrane and buffer media 0.1 N HCl pH 1.2 was used as moistening fluid. Fresh goat mucosa obtained from local slaughterhouse kept in a Krebs buffer during transportation and it was cut into pieces washed with distilled water followed by 0.1 N HCl pH 1.2. It was then tied over the protrusion in the Teflon block using a thread. The block was then kept in a glass beaker. The beaker was filled with 0.1 N HCl pH 1.2 up to the upper surface of the goat stomach mucosa to maintain stomach mucosa viability during the experiments. The one side of the tablet was attached to the glass slide of the right arm of the balance, and then the beaker was raised slowly until contact between goat mucosa and floating bioadhesive tablet was established. A preload of 10 g was placed on the slide for 15 min so that tablet adheres to gastric mucosa. The preload and preload time were kept constant for all formulations. After the completion of preload time, preload was removed from the glass slide and water was then added in the plastic bottle in the left side arm by peristaltic pump at a constant rate of 100 drops/min. The addition of water was stopped when floating bioadhesive tablet was detached from the goat stomach mucosa. Mucoadhesive strength (F) was assessed in terms of the weight of water in grams required to detach floating bioadhesive tablet from goat stomach mucosa. From this mucoadhesive strength, the force of adhesion, i.e., the force required for separating the tablet from the tissue surface was calculated using the following formula.[24-31]

$$\text{Force of adhesion } (\text{N}) = \frac{\text{Bioadhesive strength} \times 9.81}{100} \quad (3)$$

### *Kinetic modeling of drug release*

The dissolution profile of all the batches was fitted to zero-order, first-order, matrix, Hixson-Crowell, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release.

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into zero-order, first-order, Higuchi matrix, Pappas, and Hixson–Crowell model using Pcp-Disso - software. Based on the $R^2$-value, shown in Table 9 the best-fit model was selected.[32,33]

### *Selection of optimized batch*

Selection of optimized batch is done on the basis of its drug release profile, *in vitro* buoyancy study, *in vitro* bioadhesion study, and floating lag time.[34,35]

### *Stability study*

Stability study was conducted according to ICH guidelines at 40±2°C and 75±5% RH for 6 months.

## RESULTS AND DISCUSSION

### Evaluation of pre-compression parameters of simvastatin GRDDS tablet

The powder blend of various formulations shows good flow property. Results are shown in Table 4. Results of various formulations revealed that the powder blend can be directly compressed into tablets.

### Evaluation of post-compression parameters of simvastatin GRDDS tablet

#### *Hardness*

Hardness of the formulations F1-F9 was observed within the range of 5.2 ± 0.05 to 5.6 ± 0.11 kg/cm$^2$ as shown in Table 5.

#### *Friability*

The percent friability of all the prepared formulae was <1%. The previous results indicated that all formulations complied with the pharmacopeias limits for these tests.

### *Thickness*

The thickness of all the tablets was found within the range of 4.22 ± 0.09 - 4.56 ± 0.03 mm.

### *Weight variation*

The weight of all the tablets was found within the range of 250 ± 3 mg. Hence, the weight of all formulations was found within the limit.

### *Drug content*

The range of % drug content of the formulations A1-A9 was found between 98.25 ± 1.46 and 100.04 ± 0.35. Physicochemical parameters of the formulation A1-A9 were within the acceptance limit. All the batches passed the pharmacopeias limits. The drug content was found to be within a narrow range as specified in pharmacopeia (90-110%) in all the formulations. Almost all the batches showed uniform thickness and drug content. All batches passed weight variation test and found to be within range (±3%), and friability was <1.0%.

### *In vitro buoyancy study*

The buoyancy lag time also known as floating lag time is most important parameter in floating drug delivery. The buoyancy of floating tablet was studied at 37 ± 0.5 in 200 ml of 1.2 pH buffer.

The mechanism contributing the buoyancy to the composite matrix involves penetration of HCl acid into the interior of the tablet resulting generation of $CO_2$ due to the reaction between $NaHCO_3$ and HCl acid of the simulated gastric fluid. The buoyancy lag time was measured using stop watch and total floating time was observed visually photograph of it shown in Figure 1. This test was performed to cheek floating behavior of floating dosage form. All tablets of each batch floated well and floating lag time observed in between 32± 2 and 57 ± 2 s. Total floating time for all batches observes minimum more than 10 h.

### *Swelling study*

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule, breaking the hydrogen bond and resulting in the swelling of particle.[20] The extent of swelling can be measured in terms of % weight gain by the tablet. The floating bioadhesive tablets of simvastatin made up of

**Table 4:** Evaluation of pre compression parameters of powder blends (A1-A9)

| Batch no. | Bulk density (g/ml) | Tapped density (gm/ml) | Hausner ratio | Carr's index (%) | Angle of repose (θ) |
|---|---|---|---|---|---|
| A1 | 0.232±0.12 | 0.270±0.13 | 1.16±0.02 | 14.07±0.06 | 26.56±1.15 |
| A2 | 0.224±0.14 | 0.263±0.16 | 1.17±0.04 | 14.82±0.08 | 25.64±1.32 |
| A3 | 0.219±0.08 | 0.243±0.12 | 1.10±0.08 | 9.87±0.05 | 27.02±1.11 |
| A4 | 0.212±0.06 | 0.240±0.11 | 1.13±0.09 | 11.66±0.09 | 24.70±2.02 |
| A5 | 0.235±0.11 | 0.273±0.08 | 1.16±0.05 | 13.91±0.06 | 27.02±1.95 |
| A6 | 0.218±0.12 | 0.268±0.13 | 1.14±0.11 | 12.60±0.12 | 32.61±1.23 |
| A7 | 0.215±0.06 | 0.277±0.10 | 1.28±0.02 | 22.38±0.02 | 31.79±1.82 |
| A8 | 0.229±0.10 | 0.263±0.06 | 1.14±0.07 | 12.92±0.04 | 28.81±1.51 |
| A9 | 0.202±0.11 | 0.246±0.15 | 1.21±0.06 | 17.88±0.14 | 29.24±2.21 |

**Table 5:** Evaluation of post compression parameters of floating bioadhesive tablets of Simvastatin (A1-A9)

| Formulations | Weight variation (mg) | Hardness (kg/cm²) | Thickness (mm) | Friability (%) | Drug content (%) |
|---|---|---|---|---|---|
| A1 | 250.35±2.02 | 5.3±0.05 | 4.31±0.05 | 0.34±0.14 | 99.11±1.69 |
| A2 | 248.66±1.54 | 5.4±0.15 | 4.22±0.09 | 0.45±0.02 | 99.26±1.12 |
| A3 | 251.1±0.91 | 5.2±0.11 | 4.52±0.02 | 0.67±0.04 | 98.25±1.46 |
| A4 | 252.02±2.7 | 5.4±0.17 | 4.29±0.09 | 0.28±0.09 | 98.75±0.33 |
| A5 | 250.1±1.91 | 5.3±0.05 | 4.41±0.06 | 0.46±0.07 | 99.22±1.11 |
| A6 | 249.55±2.88 | 5.5±0.10 | 4.31±0.06 | 0.55±0.06 | 100.04±1.35 |
| A7 | 253.82±2.03 | 5.2±0.05 | 4.46±0.02 | 0.65±0.05 | 99.66±1.57 |
| A8 | 247.35±1.81 | 5.4±0.20 | 4.56±0.03 | 0.33±0.02 | 98.55±2.14 |
| A9 | 250.66±0.75 | 5.6±0.11 | 4.48±0.04 | 0.71±0.08 | 99.40±1.32 |

polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug released from the matrix tablet. The floating tablets containing Badam gum and HPMC K15M with showed constant increased in swelling because Badam gum and HPMC K15M showed higher swelling and can maintain their matrix integrity for more than 8-9 h similar observation are reported by Meka, *et al.*[23] this erosion of polymer dominates over water sorption after 8 h hence the reduction in tablet weight occurs after 9 h because of constant due to constant erosion of matrix. It might be due to increased hydration of the formed gel layer with time resulted in chain disentanglement and dissolution of the gel layer (erosion), thus decreased SI.

The swelling ability of the tablets could be attributed to the existence of hydrophilic moieties on both HPMC K15M and Badam gum. SI profile of all formulation between A1-157 ± 2.7% and A9-254 ± 10.0%. From the plots it as from the Figure 2 and 3, it was concluded that the SI increases with increasing polymer concentrations. Previously it was reported that Terminalia matrix containing Lactose exhibited higher water uptake than those containing the other excipients Bamiro *et al*.[22]

All the polynomial equations were found to be statistically significant ($P < 0.01$), as determined using analysis of variance (ANOVA), as per the provision of Design Expert Software. Statistical analysis revealed that the quadratic model showed the maximum adjusted $R^2$-value. As per response surface plot and contour plot shown in Figures 3 and 4, it can be observed that both polymers Badam gum and HPMC K15M facilitates SI of all batches are shown in Figure 6.

Mathematical relationship in the form of polynomial equation for the measured response (SI) was obtained and given below

$$\text{Swelling index} = +154.26+33.17^{*} A+13.56^{*} B \quad (4)$$

The above equation 1 represents the quantitative effect of the process variable and its interaction on the response. For estimation of significance of the model, the ANOVA was determined as per the provision of Design Expert Software. Using 5% significance level, a model is considered significant if the *P* value (significance probability value) is <0.05. Model was found to be significant.

### *In vitro drug released studies*

The tablets with formulations A1-A9 containing combinations of Badam gum with HPMC K 15 M in different ratios were evaluated. The formulations containing lower concentration of Badam Gum with HPMC K 15 M such as A1, A2, and A3 released all drug within 11 h since polymer concentration is low from batch A1 to A3, the hydrated matrix would be highly porous with a low degree of tortuosity leading to low gel strength and rapid diffusion of the drug from the matrix tablet similar finding were obtained by Bamiro *et al.*[22] The formulations A1, A2, A3, and A4, shows cumulative drug release 99.28 ± 3.23, 98.19 ± 2.12%, at 10 h and 99.17 ± 1.32, 99.17 ± 2.88%, at 11 h, respectively.

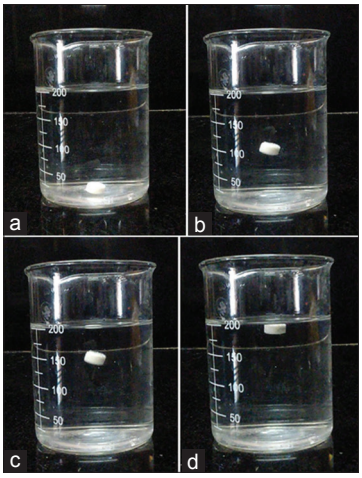


**Figure 1:** Photographs showing the *in vitro* floating behavior of the optimized batch A5. (a) Photograph was taken immediately after placing the tablet into the beaker, (b) photograph taken during the intermediate stage of tablet floating, (c) photograph taken during the intermediate stage of tablet floating near to surface, (d) photograph taken immediately after the tablet floated onto the surface indicating the floating lag time

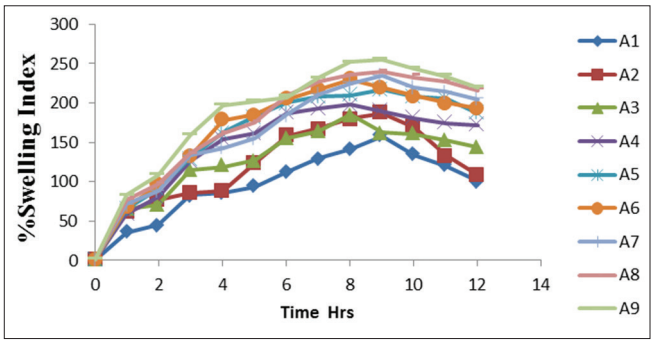


**Figure 2:** Swelling index of simvastatin floating bioadhesive tablets (A1-A9)

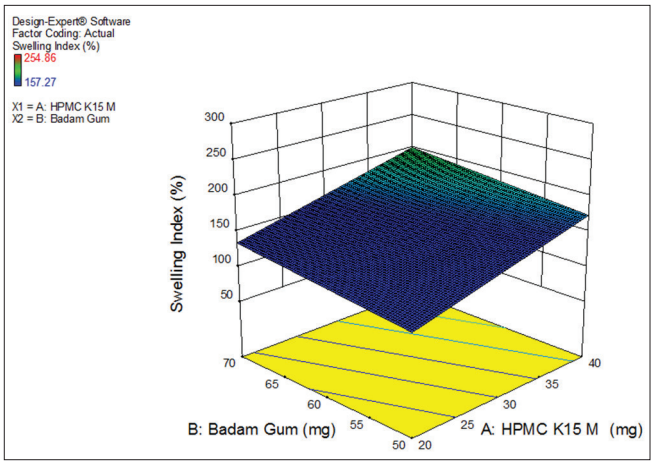


**Figure 3:** Response surface presenting the effects of Badam gum (X1) and hydroxypropyl methylcellulose K15 M amount (X2) on the swelling index

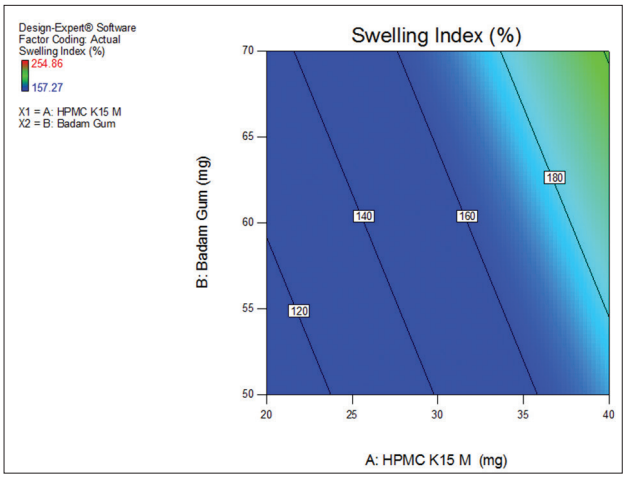


**Figure 4:** Contour plot presenting the effects of Badam Gum (X1) and HPMC K15 M amount (X2) on the swelling index

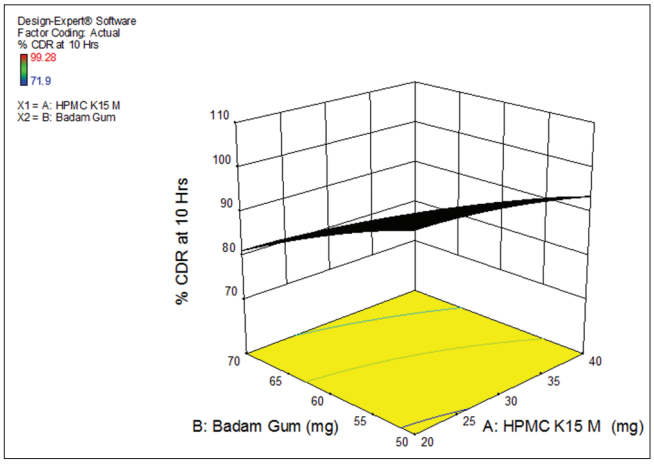


**Figure 5:** Response surface presenting the effects of Badam gum (X1) and hydroxypropyl methylcellulose K15 M amount (X2) on the %CDR

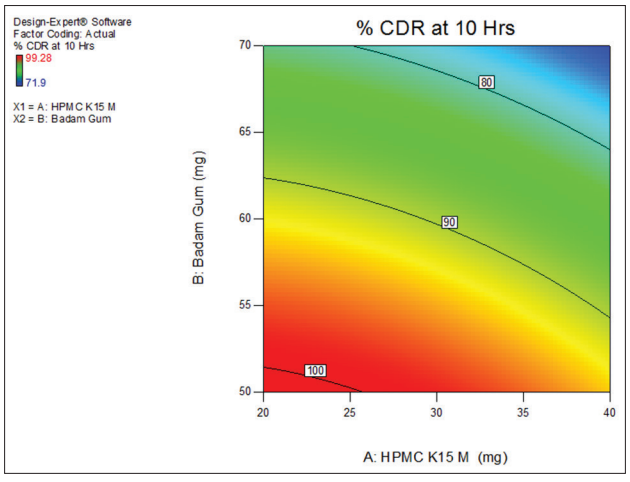


**Figure 6:** Contour plot presenting the effects of Badam Gum (X1) and HPMC K15 M amount (X2) on the %CDR

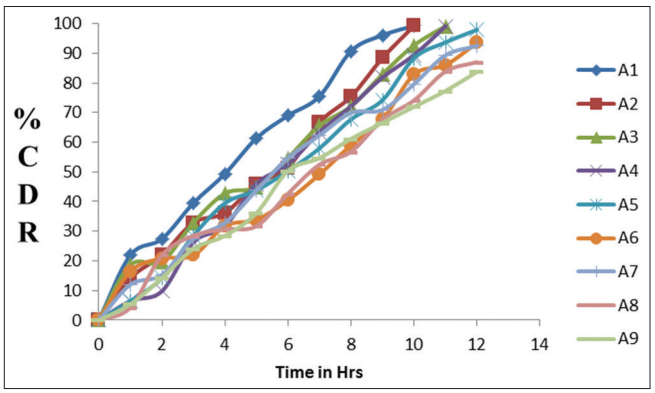


**Figure 7:** Comparative *in vitro* dissolution profiles of all batches ($n$=3, mean ± SD)

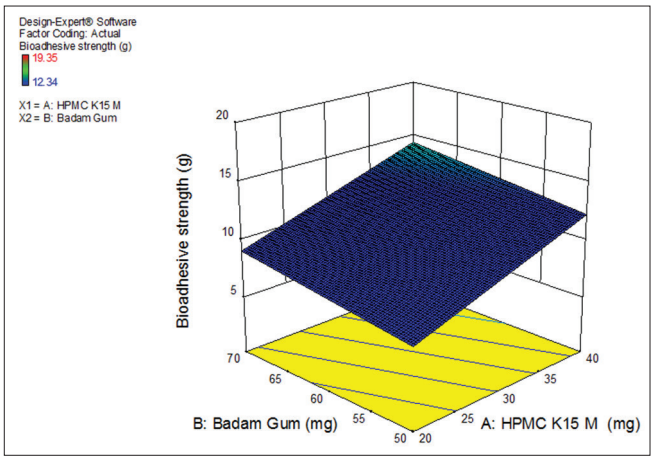


**Figure 8:** Repose surface plot presenting the effects of Badam Gum (X1) and hydroxypropyl methylcellulose K15 M amount (X2) on the bioadhesive strength

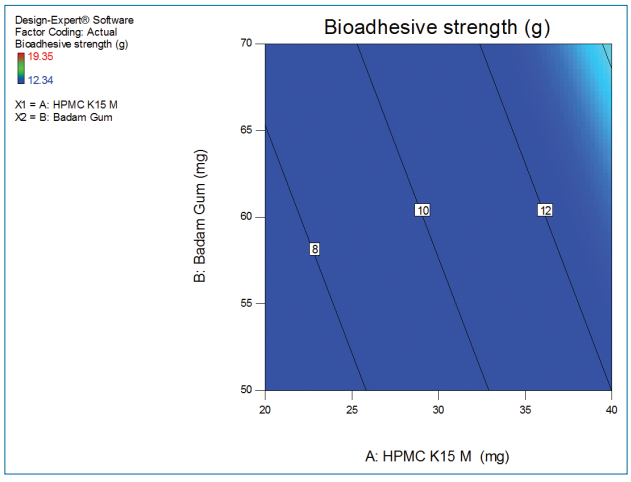


**Figure 9:** Contour plot presenting the effects of Badam Gum (X1) and HPMC K15 M amount (X2) on the Bioadhesive strength

Formulation A5 showed a constant drug release up to 12 h (98.10 ± 2.10%). While formulations A6, A7, A8, and A9 shows 93.61 ± 1.11, 92.52 ± 0.24, 88.16 ± 3.21, and 83.00 ±

0.76 CDR % at 12 h, respectively. It was observed that type of polymer influences the drug release pattern as shown in Figure 7. However, the drug release rate was dependent on the concentration of the investigated polymers. As polymer concentration increases (formulation A1-A9) drug release was decreased.

Mathematical relationship in the form of polynomial equation for the measured response (%CDR) was obtained and given below

$$\text{CDR at 10 h} = +89.71-4.01*A-10.22*B-0.29*AB-1.27*A^2-1.27*B^2 \quad (5)$$

The response surface and contour plots presenting the effects of the independent variables on % cumulative drug release are shown in Figures 5 and 6. From response surface plot and contour plot, it can be observed that both polymers have a significant effect on drug release. Thus, it can be concluded that both polymers HPMC K 15 M and Badam gum have significant release retardant effect, but Badam gum has more pronounced rate controlling behavior as compared to HPMC K15M % CDR of all batches shown in Figure 7.

### *Bioadhesive strength*

Bioadhesive so it is capable to adhere mucous membrane that prevents their passage through the pylorus, and the dosage forms are retained in the stomach for a longer period of time. Floating or bioadhesive approaches have some merits and demerits it can be reduced by the combination of these two different approaches.[13] Floating system means that float over the surface of the gastric contents when the stomach is full after a meal but at the time stomach as empties and the tablet reaches the pylorus the buoyancy of the dosage may be decreased as dosage forms passages through the pylorus and it highly dependent on the presence of food and gastric content. In bioadhesive system, it is quite likely that they become dislodged from the stomach wall when the system is full, and the semi-liquid contents are churning around due to the effect of peristalsis and its efficiency can be reduced by the constant turnover of the mucus. A floating-bioadhesive combination approach would overcome these drawbacks of floating and bioadhesive individual system and improving the therapeutic effect of the drug involved.[14]

Bioadhesion strength was determined for all GRDF. As per Figure 10 all the formulation showed bioadhesive strength in the range of 12.34 ± 1 - 19.35 ± 1 g with varying concentration of different sets of polymer combination. From Table 6 it is found that polymer combination HPMC K 15 M and Badam gum in batch A9 had highest bioadhesion than other batches. Optimized formulation A5 had mucoadhesion strength of 15.30 ± 1 g. The sequential linear model was suggested for relating the bioadhesion strength (Y3) to the investigated formulation factors ($P = 0.0001$).

Mathematical relationship in the form of polynomial equation for the measured response (Bioadhesion) was obtained and given below

$$\text{Bioadhesive strength} = +10.26+2.82*A+1.07*B \quad (6)$$

In this design, bioadhesion strength was one of the factors. HPMC is a non-ionic hydrophilic polymer. Its mucoadhesion could be either due to the formation of physical bonds

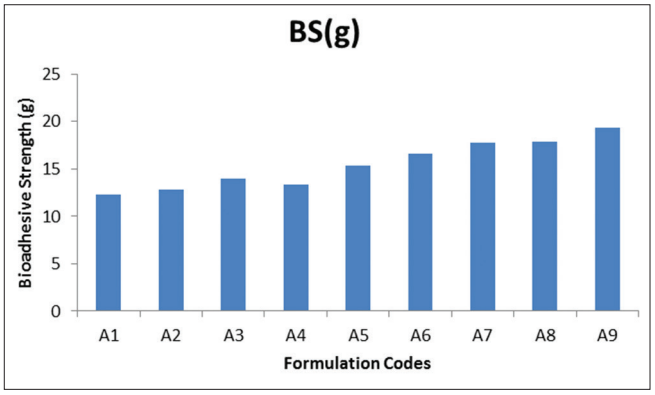


**Figure 10:** Bioadhesive strength of optimized simvastatin bioadhesive tablets (A1-A9)

**Table 6:** Buoyancy and swelling index, Bioadhesion study of GRDFS

| Formulation code | Swelling index (%) | Floating lag time (s) | Total floating time (h) | Bioadhesive strength (g) | Bioadhesive force (N) |
|---|---|---|---|---|---|
| A1 | 157±2.7 | 32±2 | >10 | 12.34±1 | 1.21 |
| A2 | 187±1.6 | 36±3 | >10 | 12.80±1 | 1.25 |
| A3 | 185±8.9 | 39±1 | >12 | 13.16±2 | 1.29 |
| A4 | 197±5.8 | 42±3 | >12 | 13.32±1 | 1.30 |
| A5 | 216±6.6 | 34±3 | >12 | 15.30±1 | 1.50 |
| A6 | 229±7.8 | 44±1 | >12 | 16.60±2 | 1.62 |
| A7 | 234±3.2 | 51±3 | >12 | 17.80±1 | 1.74 |
| A8 | 240±1.5 | 57±2 | >12 | 18.90±2 | 1.85 |
| A9 | 254±10 | 55±2 | >12 | 19.35±1 | 1.89 |

All values are mean±SD of three determinations, SD: Standard deviation

**Table 7:** Summary of result of regression analysis for response for % Swelling index, bioadhesive strength and % CDR

| Parameters | DF | SS | MS | *F* | *P* value | $R^2$ | SD | CV % |
|---|---|---|---|---|---|---|---|---|
| % Swelling index | | | | | | | | |
| Model | 2 | 7704.1 | 3852 | 115.2 | <0.0001 | 0.9584 | 5.8 | 2.71 |
| Residual | 10 | 334.33 | 33.43 | - | - | - | - | - |
| Total | 12 | 8038.4 | 3885.5 | - | - | - | - | - |
| % CDR at 10 hrs | | | | | | | | |
| Model | 5 | 781.32 | 156.26 | 149.1 | <0.0001 | 0.9907 | 1.02 | 1.18 |
| Residual | 7 | 7.34 | 1.05 | - | - | - | - | - |
| Total | 12 | 788.66 | 157.31 | - | - | - | - | - |
| Bioadhesive strength | | | | | | | | |
| Model | 2 | 54.82 | 27.41 | 102.88 | <0.0001 | 0.9537 | 0.52 | 3.3 |
| Residual | 10 | 2.66 | 0.27 | - | - | - | - | - |
| Total | 12 | 57.48 | 27.68 | - | - | - | - | - |

SD: Standard deviation

**Table 8:** Comparison between the experimental and predicted values for the most probable optimal formulation (A5)

| Dependent variable | Optimized Formulation A5 | |
|---|---|---|
| | Experimental | Predicted |
| % Swelling index | 216.66 | 213 |
| % CDR at 10 h | 82.89 | 83.35 |
| Bioadhesive strength (g) | 15.30 | 15.51 |

(entanglement) or hydrogen bonding with mucous tissue.[30] Response surface plots showing the effect of formulation variables on bioadhesion are depicted in Figure 8. From the plots, shown in figures 8 and 9 it was concluded that there was a significant effect of concentration of Badam gum and concentration of HPMC K 15 M on bioadhesion strength. However, the effect of the polymer Badam gum was more pronounced than HPMC K4 M on bioadhesion strength since Badam gum has significant sticking property these findings are in agreement with previously reported results by Meka, *et al.,*[23] who found the Badam gum has remarkable swelling and sticking character in gastric pH.[23-33] This developed floating-bioadhesive combination formulation would overcome the drawback of floating and bioadhesive individual system and improving the therapeutic effect of the drug involved.

### *Optimization data analysis for the floating bioadhesive dosage form*

Responses observed for nine formulations were fitted to Design Expert Software. All values of $R^2$, SD and % coefficient of variance were shown in Table 7. Results of ANOVA in Table 7 for the dependent variables demonstrated that the model was significant for all the three response variables. Comparison between the experimental and predicted values for the most probable optimal formulation

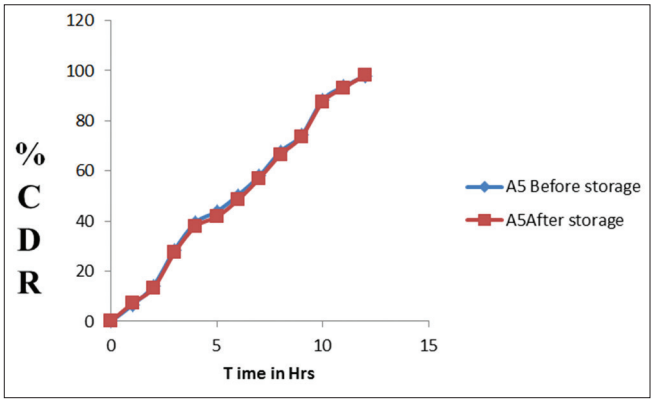


**Figure 11:** Comparative dissolution profile of Batch A5 before and after storage (*n*=3, mean ± SD)

is reported in Table 8. From this it can be concluded that as predicted values agreed well with the experimental values, demonstrating the feasibility of the model in the development of GRDDS floating bioadhesive drug delivery system of simvastatin.

### *Mathematical modeling and release kinetics*

All the formulations were fitted for zero-order release, first-order release, Higuchi matrix model, Hixson-Crowell powder dissolution model, and Korsmeyer-Peppas model. The *in vitro* release profiles of drug from all the formulations could be best expressed Korsmeyer's equation. For matrix tablets, an n value of near 0.5 indicates diffusion control, and an n value of near 1.0 indicates erosion or relaxation control. Intermediate values suggest that diffusion and erosion contribute to the overall release mechanism[36-38]. Based on the $R^2$-value, shown in Table 9 the best-fit model was selected. Optimized formulation A5 showed zero order as best-fit model having $R^2$-value is 0.9966 which indicates that the constant release from systems which is depends on the concentration of polymers confirmed by $R^2$-value. As the diffusion exponent

**Table 9:** Kinetic parameters of Simvastatin tablet batches from (FA1-A9)

| Batch code | Zero-order ($R^2$) | First-order ($R^2$) | Matrix | Korsmeyer-Peppas ($R^2$) | n (release exponent) | Hixson-Crowell |
|---|---|---|---|---|---|---|
| A1 | 0.9810 | 0.8707 | 0.9687 | 0.9900 | 0.7147 | 0.9620 |
| A2 | 0.9944 | 0.7682 | 0.9262 | 0.9901 | 0.8442 | 0.8994 |
| A3 | 0.9925 | 0.8172 | 0.9468 | 0.9784 | 0.7632 | 0.9321 |
| A4 | 0.9962 | 0.8012 | 0.9096 | 0.9896 | 1.2003 | 0.9222 |
| A5 | 0.9966 | 0.8732 | 0.9311 | 0.9929 | 1.0778 | 0.9487 |
| A6 | 0.9889 | 0.8928 | 0.9150 | 0.9604 | 0.7570 | 0.9430 |
| A7 | 0.9931 | 0.9429 | 0.9447 | 0.9908 | 0.8942 | 0.9798 |
| A8 | 0.9923 | 0.9404 | 0.9281 | 0.9650 | 1.0619 | 0.9705 |
| A9 | 0.9948 | 0.9738 | 0.9365 | 0.9935 | 1.0766 | 0.9904 |

**Table 10:** Stability studies of simvastatin floating bioadhesive tablets batch A5

| Parameters | Weight variation (mg) | Hardness (Kg/cm$^2$) | Friability (%) | Drug content (%) | Floating lag time (sec) | % Drug release |
|---|---|---|---|---|---|---|
| Before storage | 250.1±1.91 | 5.3±0.05 | 0.46±0.07 | 99.22±1.11 | 34±3 | 98.10±2.10 |
| After storage | 251.25±2.02 | 5.4±0.44 | 0.47±0.10 | 99.20±2.24 | 52±3 | 97.43±1.65 |

All the values are mean±SD of three determinations

(n) of optimized formulation, A5 showed values >1 (1.0078) so release of drug follows super case II transport due to the swelling of polymer in controlled manner.

### *Selection of optimized batch*[39,40,42]

The optimized formulation must exhibit faster buoyancy, sufficient bioadhesion to ensure gastro retention and maximum drug release at the end of 12 h and the results of the experimental design formulations and drug release kinetic study revealed that formulation A5 satisfies all the desired criteria and hence was selected as optimized formulation.

### *Stability studies*

Stability studies conducted on optimized A5 formulation as per according to ICH guidelines at 40 ± 2°C and 75 ± 5% RH for 6 months (for accelerated testing) to assess their long-term stability. Parameters evaluated are average weight variations, hardness ,friability, drug content, floating lag time, and *in vitro* drug release result of it shown in Table 10.

Analysis of the dissolution data Figure 11, after storage for 6 months, showed no significant change in the release pattern. All other parameters evaluated were comparable with initial values except floating lag time which was increased from 34 ± 3 to 52 ± 3 s after storage this may be due to the reaction of $NaHCO_3$ with the moisture during storage.

## CONCLUSION

Dual mechanism based gastro floatable and bioadhesive drug delivery system for simvastatin with shorter lag time was successfully prepared by direct compression method using Badam gum and HPMCK15M as a polymers and sodium bicarbonate, citric acid as a gas generating agents. Optimized floating bioadhesive tablets of simvastatin were formulated well in terms of hardness, thickness, weight variation, and content uniformity.

Comparing all the formulations, formulation A5 was considered as an optimized formulation which exhibited 98.10 ± 2.10% of drug release in 12 h, floating lag time of 34 ± 3 s, with appropriate bioadhesive property, and total floating time of over 12 h. It was observed that increasing percentage of polymer in formulation the decreased drug release pattern, which was dependent on the type of polymer used in the formulation. The observed independent variables were found to be very close to predicted values of most satisfactory formulation which demonstrates the feasibility of the optimization procedure in successful development of this dosage form. Developed formulations were stable during stability studies. Badam gum's sticking nature in gastric pH was successfully utilized in floating bioadhesive drug delivery of simvastatin.

The most significant finding from this study is developed floating bioadhesive of simvastatin is most promising GRDDS dosage form to improve the bioavailability of simvastatin by increasing gastric residence time. Based on these findings, it was concluded that Badam gum can be used as a bioadhesive as well as release retarding polymer for the floating bioadhesive dosage form of other drugs.

## ACKNOWLEDGMENT

The authors are thankful to Hazrat Maulana G.M. Vastanvi sahab, President, Akbar Patel sir Coordinater

and Dr. G.J. Khan principal of Jamia Islamia Ishaatul Uloom's Ali Allana College of Pharmacy Akkalkuwa Dist. Nandurbar Maharashtra for providing the necessary facilities to carry out this research work and we are very thankful to Syed Noor Aga research scholar, Annamalai University, Tamil Nadu, India, for bringing Badam gum sample from Chennai.

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**Source of Support:** Nil. **Conflict of Interest:** None declared.