



ORIGINAL RESEARCH ARTICLE

OPEN ACCESS

Gastroretentive drug delivery system of a lipid lowering agent

*D. Krishnarajan¹, N. Senthil Kumar², Rajesh Yadav³

¹Department of Pharmaceutics, JKK Munirajah Medical Research Foundation College of Pharmacy, Ethirmediu, B.Komarapalayam, Namakkal-638183, Tamilnadu, India

²Department of Pharmaceutical Chemistry, JKK Munirajah Medical Research Foundation College of Pharmacy, Ethirmediu, B.Komarapalayam, Namakkal- 638183, Tamilnadu, India

³Department of Pharmacy, Sunrise Univercity, Alwar, Rajasthan-301030, India

ABSTRACT

The objective of this study was to develop mucoadhesive tablets of Simvastatin using natural polymers. Simvastatin has short biological half-life and high first pass metabolism hence which was designed to increase the gastric residence time which prolong the drug release. The tablets were prepared by wet granulation technique using Carbopol-934, guar gum, xanthine gum and chitosin as polymers. Formulations were evaluated for different parameters like hardness, friability, uniformity of weight, swelling characteristics, *in vitro* dissolution and kinetic studies. The dissolution was carried out for 12 hours in which the formulation with guar gum has shown highest dissolution release profile (F9). Thus the present study concludes that mucoadhesive tablets of simvastatin can be a good way to pass the extensive hepatic first pass metabolism and to improve the bioavailability of simvastatin.

Key Words: Simvastatin, Mucoadhesive, Carbopal-934, Gastric residence time, swelling characters.

INTRODUCTION

In recent years, there has been increasing interest on the use of bioadhesive polymers. Per oral drug delivery has been the most widely utilized route of administration for the systemic delivery of drugs. The lack of efficacy of certain drugs due to decreased bioavailability, unpredictable and erratic absorption, GI intolerance or pre-systemic elimination has prompted the examination of other potential routes for administration. Moreover, the recent development of a large number of peptides as drugs has intensified investigation of mucosal delivery of drugs (Vinod *et al.*, 2012). Such routes exploring other absorptive mucosa include the oral, nasal, buccal, rectal, vaginal and ocular to a limited extent, pulmonary routes amongst the various route of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, per oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GIT, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosa is considered as potential sites for drug administration (Vyas and Khar, 2002).

Simvastatin is HMG Co-A (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors widely used in the treatment of hyper cholesterolemia, as it reduces levels of low-density lipoproteins and triglycerides, and raises high-density lipoprotein levels. Simvastatin undergoes extensive first pass metabolism in liver due to which the oral bioavailability is less dose size i.e., in few mg. Hence, it is suitable candidate for mucoadhesive drug delivery (Goud *et al.*, 2011).

In this study, the main objective is to develop and evaluate mucoadhesive tablets of Simvastatin by employ-

ing various natural hydrophilic bioadhesive polymers such as xanthan gum, chitosin, guar gum and carbopol for prolonged gastrointestinal absorption. The prepared tablets were evaluated for different parameters such as hardness, friability, weight variation, swelling index, *in vitro* residence time and *ex-vivo* adhesive time.

MATERIALS AND METHODS

Simvastatin was collected as a gift sample from Aurobindo Pharma Ltd., Hyderabad, polymers were purchased from Yarrow Chem Products, Mumbai and all remaining excipients were purchased from Scientific Lab, Erode.

IR studies of Simvastatin with natural polymers Infrared spectra analysis

Compatibility of the drug with the excipients was determined by subjecting the physical mixture of the drug and polymer of the main formulation to infrared spectral analysis. Any changes in chemical composition of the drug after the combining it with the polymers were investigated with IR spectral analysis (Harry, 2006). Infrared spectrum of simvastatin was determined on Fourier transform infrared spectrophotometer using KBr pellet method. The base line correction was done using dried potassium bromide. Then the spectrum of the dried mixture of the drug and potassium bromide was done.

Preparation of the bio-adhesive tablet

Simvastatin bioadhesive oral tablets were prepared by the wet granulation method. In all the formulations, amount of the active ingredient was 20mg. All the ingredients of the tablet were granulated to obtain uniform mixing. All the tablets were stored in airtight containers at room temperature for further study (Deshmukh *et al.*, 2009).

Evaluation of the bio-adhesive tablets

Uniformity of weight

The weight variation test was done by taking 20 tablets randomly and weighed accurately. The composite weight divided by 20 provides an average weight of tablet. Not more than two of the individual weight deviates from the

*Corresponding Author:

D. Krishnarajan, Department of Pharmaceutics
JKK Munirajah Medical Research Foundation College
of Pharmacy, Ethirmediu, B.Komarapalayam
Namakkal - 638183, Tamilnadu, India
E-mail: krishnarajand@yahoo.com
Contact No.: +91 99420 47499



Table 1: Composition of simvastatin mucoadhesive tablets.

Batch number	Amount of ingredients (in mg)						
	Simvastatin	Carbopol	Xanthan gum	Chitosin	Guar gum	Lactose	Citric acid
F1	20	20	20	-	-	40	10
F2	20	20	40	-	-	20	10
F3	20	20	60	-	-	-	10
F4	20	20	-	20	-	40	10
F5	20	20	-	40	-	20	10
F6	20	20	-	60	-	-	10
F7	20	20	-	-	20	40	10
F8	20	20	-	-	40	20	10
F9	20	20	-	-	60	-	10
F10	20	20	30	30	-	20	10
F11	20	20	-	30	30	20	10
F12	20	20	30	-	30	20	10

All the formulation contains 5mg magnesium stearate & 5mg talc, total weight of each tablet=120mg

average weight by 10% and none should deviate by more than twice that percentage. The average weight and standard deviation of the tablets were calculated.

Hardness test

There is a certain requirement of hardness in tablets so as to withstand the mechanical shocks during handling, manufacturing, packaging and shipping. For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester. Monsanto hardness tester was used to measure hardness of the tablets. The whole experiment was performed in triplicate and the results are expressed in kg/cm² unit.

Friability test

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for 4 minutes, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. Generally considered and acceptable limit is loss of less than 1% in weight. Percent friability (%F) was calculated.

In-vitro swelling study (water uptake study)

The tablets of each formulation were weighed individually (designated as W₁) and placed separately in petri dishes containing 2% agar gel. At regular intervals (1, 2, 3, 4, 5, 6, 7 and 8 hr), the tablets were removed from the petri dishes and excess water was removed carefully by using filter paper (Ramana *et al.*, 2007). The swollen tablets were reweighed (W₂), the swelling index of each formulation was calculated using the formula

$$\% \text{ Swelling Index} = \frac{w_2 - w_1}{w_1} \times 100$$

Where, W₂- weight of tablet after particular time interval
W₁- initial weight of tablet

Evaluation of bio-adhesive strength of tablet

Measurement of adhesion force was determined by using goat gastric mucus membrane. The tissues were washed thoroughly with phosphate buffer solution (pH 6.8) then the membrane was tied to the glass slide using rubber band. The glass slide was kept in a beaker which was

filled with phosphate buffer solution at 37±1°C in such way that buffer just reaches the surface of mucosal membrane and kept it moist. The tablet to be tested was stuck on the mucus membrane and allow for 5min for swelling and then by using clip to attach the tablet. Then the weight on the left hand side was slowly added in an increment of 0.5g till the tablet separated from the membrane (Gupta *et al.*, 1993). From bio-adhesive strength, the force of adhesion was calculated using the formula.

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

Ex-vivo mucoadhesion time

The *ex-vivo* mucoadhesion time was examined after application of tablet over excised goat mucosa for 30sec after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing around 750ml of phosphate buffer, pH 6.8 at 37±1°C. The paddle of the dissolution apparatus was adjusted at a distance of 5cm from the tablet and rotated at 25rpm. The time for detachment from the mucosa was recorded (Chowdary, 2008).

In-vitro drug release studies

The dissolution test apparatus (USP II) was used and the whole assembly was kept in a jacketed vessel of water maintained at 37±1°C. Bio adhesive tablet was stuck on to the bottom of the flask (so as to allow one sided release from the tablet). The beaker was filled with 900ml of phosphate buffer and was maintained at 50rpm under stirring conditions by means of a paddle fabricated for the purpose in a dissolution apparatus. At various time intervals samples of dissolution medium were withdrawn and filtered through Whatman filter paper no: 42. It was replaced immediately with an equal amount of fresh buffer. The samples were then analyzed UV spectrophotometrically at 238nm. Absorbance measured and % drug release was determined (Balamurugan *et al.*, 2008).

Stability studies

The selected F9 formulation was packed in PVC blister pack then they were stored at three different temperatures 4±2°C, 27±2°C and 45±2°C for 30days at RH 75±5%. At 15 days interval, the tablets were evaluated for their physical appearance, hardness, friability, in-vitro drug release (Matthews, 1999).

Drug release kinetics

To study the release kinetics of *in-vitro* drug release, data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas.

Zero order

Drug dissolution from dosage forms that do not disaggregate and release the drug slowly can be represented by the equation:

$$C = k_0 t$$

K₀ - is the zero order release constant

To study the release kinetics, data obtained from in vitro drug release studies were plotted as cumulative amount of drug released versus time.

First order

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism on a theoretical basis.

Table 2: Physical parameter of simvastatin mucoadhesive tablet.

Formulation Code	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Weight variation (%)
F1	2.66±0.10	1.8±0.25	0.01±0.03	0.118
F2	2.54±0.12	1.81±0.25	0.03±0.07	0.119
F3	2.01±0.15	1.79±0.27	0.032±0.08	0.12
F4	2.61±0.07	1.7±0.20	0.002±0.07	0.121
F5	2.97±0.08	1.9±0.27	0.012±0.01	0.119
F6	2.86±0.14	1.75±0.25	0.011±0.04	0.12
F7	3.03±0.07	1.2±0.20	0.23±0.04	0.122
F8	3.11±0.08	1.41±0.19	0.31±0.02	0.118
F9	3.07±0.08	1.49±0.27	0.36±0.02	0.12
F10	2.86±0.12	1.71±0.20	0.21±0.04	0.119
F11	3.01±0.13	1.8±0.12	0.24±0.02	0.118
F12	2.98±0.11	1.76±0.17	0.04±0.02	0.121

All results are average of three measurements

The release of the drug which followed first order kinetics can be expressed by the equation

$$\log C = \log C_0 - Kt/2.303$$

where,

C_0 - is the initial concentration of drug

K - is the first order constant

t - is the time in hrs.

The data obtained were plotted as log cumulative percentage of drug remaining vs. time which would yield a straight line with a slope of $-K/2.303$.

Higuchi

It describes the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion.

$$Q = Kt^{1/2}$$

Where, K is the constant reflecting the design variables of the system. Hence drug release rate is proportional to the reciprocal of the square root time (Biswas *et al.*, 2008).

Korsmeyer Peppas

It derived a simple relationship which described drug release from a polymeric system equation. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas model.

$$\frac{M_t}{M_\infty} = K. t^n$$

Where, M_t / M_∞ - is a fraction of drug released at time t , k - is the release rate constant and n is the release exponent.

Table 3: Mucoadhesion study data.

Batch no.	Muco-adhesive strength (gm)	Muco-adhesion force	In vitro residence time	Ex vivo mucoadhesion time
F1	20.41	2.133	>3 hours	>6 hours
F2	20.50	1.966	>3 hours	>6 hours
F3	20.90	1.814	>3 hours	>6 hours
F4	18.5	1.814	1 hours	2 hours
F5	18	1.765	1 hours	2 hours
F6	17.15	1.711	1 hours	2 hours
F7	20.05	1.966	>3 hours	>6 hours
F8	19.50	1.912	>3 hours	>6 hours
F9	21.75	2	>3 hours	>6 hours
F10	18.5	1.814	2 hours	3 hours
F11	18.25	1.79	2 hours	3 hours
F12	20.5	1.966	>3 hours	>6 hours

RESULTS AND DISCUSSION

All the formulations were evaluated for physical properties and hardness of the tablet in the range of 1-2kg/cm². Percentage weight loss in the friability test was less than 0.4% in all the formulation batches. Thicknesses of all the formulation was less than 3.5mm. Overall, the prepared tablet batches were of good quality with regard to hardness, friability, and thickness.

Bio-adhesive strength

All the formulation showed good mucoadhesion. The *in-vitro* bioadhesive strength study was performed on the modified physical balance to measure the force (N) required for detaching the tablet. The bioadhesion characteristics were affected by the type and concentration of the bioadhesive polymers. Viscosity of the polymer also affected the bioadhesive strength of the tablet. Chitosin batch (F4, F5, F6) showed very low bioadhesive strength, xanthan gum (F1, F2, F3) showed good mucoadhesion and guar gum (F7, F8, F9) showed highest adhesive strength.

Ex-vivo mucoadhesion time

Ex-Vivo Mucoadhesion time of all formulation (F1-F12) calculated by modified dissolution apparatus. In all the formulation *Ex-vivo* mucoadhesive time increased more than 6 hrs except formulations F4, F5, F6, F10, F11 it was decreased because of chitosin which displayed a much lower hydration capacity and a higher rate of erosion.

Swelling index

Batch F1-F3 showed 700% swelling in 8 hrs, batch F4-F6

Table 4: In vitro drug release data.

Batch no.	Percent release of simvastatin from different test batches					
	1 hour	2hour	4 hour	8 hour	10 hour	12 hour
F1	19%	24.3%	48.4%	78.2%	93.11%	-
F2	16.3%	21.5%	45.9%	75.5%	82.2%	93.36%
F3	12.7%	19.7%	40.21%	70.87%	81.98%	94.7%
F4	22.1%	29.8%	58.8%	97.6%	-	-
F5	18.4%	27%	55.5%	89.5%	94.2%	-
F6	16%	26.23%	52.23%	86.05%	96.49%	-
F7	17.9%	23%	35.07%	67.34%	84.62%	93.4%
F8	14%	21.05%	32.1%	66.5%	81.76%	95.38
F9	12.02%	19.2%	30.9%	64.78%	87.34%	97.98%
F10	21%	29%	48%	85.62%	91.32%	-
F11	20.4%	28.4%	46.11%	88.68%	94%	-
F12	13.4%	20.32%	38%	69.23%	84.1%	94.22%

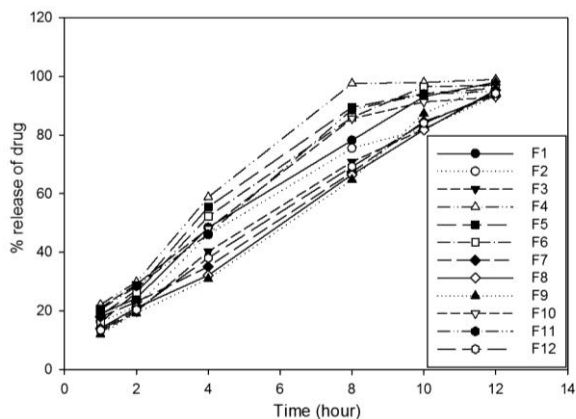


Figure 1: Graph showing *in vitro* drug release profiles.

showed good swelling (more than 800%); F7-F9 batch swelling index was 400% on 8 hr.

In-vitro drug release

From the overall dissolution profiles, it was concluded that the drug release rate decreased as the concentration of the polymer increased, in batch (F1-F6) which was also affected by the type of polymer used. And batch (F7-F9) guar gum with high concentration act as disintegrant and showed extended drug release which is the best in all the formulations.

Drug release kinetics

The straight line of linear regression analysis indicates zero order of the data yields the equation of best line with R^2 value 0.994 and the slope of line corresponds to the zero order rate constant was 8.33. The best linearity was found in zero order equation plot ($R^2 = 0.994$) indicating the release from system where release rate is concentration dependent.

According to Korsmeyer, where n is the release exponent, indicative of mechanism of drug release. Fickian diffusional release and a case-II relaxation release are the limits of this phenomenon. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxation release is the drug transport mechanism associated with stresses and state transition in hydrophilic glassy polymers which swell in water or biological fluids. This term also includes polymer disentanglement and erosion. The value of the release exponent in Simvastatin extended release was obtained as 0.588 which follows Anomalous transport ($0.45 < n < 0.89$).

Stability study

According to ICH guidelines, 30 days stability study at $4 \pm 2^\circ\text{C}$, $27 \pm 2^\circ\text{C}$ and $45 \pm 2^\circ\text{C}$ for 30 days at RH $75 \pm 5\%$ of optimized formulation (F9) was carried out. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference in the drug content between initial and formulations stored at $4 \pm 2^\circ\text{C}$, $27 \pm 2^\circ\text{C}$ and $45 \pm 2^\circ\text{C}$ for 45 days at RH $75 \pm 5\%$ for 30 days.

Table 5: Stability study data for optimized batch (F9).

Sl. no.	Parameters	Observations
1	Physical appearance	No change
2	Weight variation	0.115g
3	Hardness	1-2kg/cm ²
4	Friability	0.342%
5	<i>In-vitro</i> drug release	96.27%
6	Mucoadhesive strength	21.32g

CONCLUSION

Literature review indicates that gastroretentive drug delivery systems can be used to increase the gastric residence time of dosage form, which led to an increased bioavailability of various drugs. Thus, in the present investigation, an attempt was made to deliver simvastatin via an oral bio-adhesive drug delivery system to the vicinity of the absorption site by prolonging the gastric residence time of the dosage form. For the formulation of the oral bio-adhesive tablet, various hydrophilic polymers and their combinations were used in varying concentrations.

Tablets were subject to various evaluation parameters such as hardness, friability and drug content, bio-adhesive strength study and *in-vitro* drug release study. It was revealed that tablets of all batches had acceptable physical parameters. Tablets of batch F9 have good mucoadhesion along with *in-vitro* drug release and thus were selected as an optimized batch. The present study shows that the hydrophilic gums obtained from natural sources can be used for designing a bio-adhesive controlled release drug delivery system.

ACKNOWLEDGEMENT

Authors are sincerely thankful to the management of JKKMMRF's College of Pharmacy, Kommarapalem, Namakkal dist., Tamilnadu for providing the needful facilities and moral support to carry out this research work.

REFERENCES

- Balamurugan M, Saravanan VS, Ganesh P, Senthil SP, Hemalatha PV and Sudhir Pandya. (2008) Development and In-vitro evaluation of mucoadhesive buccal tablets of domperidone research j. pharm. and tech.; 1(4).
- Biswas, B.K., Md. Safiqul Islam, Farida Begum and Abu Shara Shamsur. (2008) In vitro Release Kinetic Study of Esomeprazole Magnesium from Methocel K15M and Methocel K100 LVCR Matrix Tablets AAPS.
- Chowdary K.P.R, G.B. (2008) Sundari Design and evaluation of bioadhesivecontrolled release oral tablets of glipizide, IJPS.
- Deshmukh VN, Harsulkar AA, Sakarkar. (2009) Formulation and in-vitro evaluation of bioadhesive tablets using hydrophilic gum blends. Int J Pharm Res.; 1(1): 16-22.
- Goud A. B, Kumara Swamy S, Praveen Kumar V. (2011) Formulation and evaluation of bioadhesive buccal tablets of simvastatin. JAPS/ vol 1/ Issue 1
- Gupta A, Garg S, Khar RK. (1993) Measurement of bioadhesive strength of mucoadhesive buccal tablets: Design of an in vitro assembly. Indian Drugs.; 30:152-155.
- Harry.G.Brittain (2006) Analytical profiles of Drug substances and Excipients, Volume 23, 53-58.
- Kumar P.S, B.Srikanth, T.Satyanarayana, G.Shaji, S.Navaneetha Krishnan, P.Saranya. (2011) Formulation and evaluation of nebigolol mucoadhesive buccal tablet pharmacologyonline.; (3): 869-885.
- Matthews B. R. (1999) Regulatory aspects of stability testing in Europe. Drug dev Ind Pharm.; 25(7): 831-856. [DOI](#) PMID:10459489
- Ramana M.V., C Nagda, M Himaja (2007) Design and evaluation of bioadhesivebuccal drug delivery systems containing metoprolol tartrate, IJPS.
- Vinod KR, Rohit Reddy T, Sandhya S, David Banji, Venkatram Reddy B. (2012) Critical Review on Mucoadhesive Drug Delivery Systems. Hygeia.J.D.Med.; vol.4 (1).
- Vyas S.P, and R.P Khar. (2002) Controlled drug delivery system, Concepts and advances; 1st edition, 257-295.