Indian Journal of Pharmaceutical Education and Research | Association of Pharmaceutical Teachers of India

Development and Evaluation of Novel Mucoadhesive Multipartculate Drug Delivery System of Simvastatin

Naga Phani J.V.V and Mohan Varma M*

Shri Vishnu College of Pharmacy, Vishnupur, Bhimavaram - 534202, A.P., India.

ABSTRACT

Submitted: 22/03/2012 Revised: 25/08/2012 Accepted: 17/12/2012

The objective of the present study was to prepare the mucoadhesive microspheres of simvastatin to provide oral controlled release.Mucoadhesion had been a topic of interest in the design of drug delivery system to prolong the residence time of the dosage form with the underlying absorption surface to improve and enhance the bioavailability of drugs. The simvastatin loaded mucoadhesive microspheres were prepared by the Orifice – Ionic gelation method using mucoadhesive polymers such as Sodium alginate, Carbopol, HPMC K100, Sodium CMC, Ethyl cellulose, Methyl Cellulose, Guar gum, and Xanthan gum in different ratios.The calcium chloride was used as the cross linking agent.The microspheres were discrete, spherical, free flowing, exhibited drug content uniformity and high entrapment efficiency.The simvastain release from the microspheres was slow and extended up to 8 hours.The drug release from the optimized formulation(drug-sodium alginate-methyl cellulose;1:2:1 ratio) followed zero order kinetics and exhibited non-fickian diffusion. The microspheres exhibited good mucoadhesive property in the in vitro wash-off test.The FTIR analysis of drug, polymers and the optimized formulation indicated the compatibility of the drug with the polymers.The sphericity and smoothness of microspheres were confirmed by scanning electron microscopy(SEM).The differential scanning calorimetry(DSC)studies indicated the absence of drug-polymer interaction in the microspheres.The present study concludes that the mucoadhesive microspheres can be considered as a promising oral controlled release dosage form for simvastatin.

Keywords: Simvastatin, Mucoadhesive microspheres, In-vitro wash off method.

INTRODUCTION

For systemic delivery, the oral route has been the preferred route of administration for many drugs. When administered by the oral route, however, many therapeutic agents have been reportedly subjected to extensive presystemic elimination by gastrointestinal degradation and/or hepatic metabolism.The results of low systemic bioavailability, short duration of therapeutic activity, and/or formation of toxic and inactive metabolites have been often reported. Further, the quick passage of dosage forms through the absorptive segment of GIT often leads to unutilized drug, particularly in case of extended delivery of narrow absorption window drugs.

The mucoadhesive drug delivery systems are delivery systems which utilized the property of mucoadhesion of certain polymers which become adhesive on hydration and hence can be used for targeting a drug to particular region of the body for extended period of time.[1] The pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because it provides the possibility of avoiding either destruction by gastrointestinal contents or hepatic first-pass inactivation of the drug.

Simvastatin is an antihyperlipidemic drug with poor oral bioavailability (<5%) due to the first pass metabolism. The possible methods to avoid first pass metabolism include transversal, buccal, rectal and parenteral routes of administration. The oral route is the most commonly used and preferred route of choice for the delivery of drugs, although several factors like pH of GIT, residence time and solubility can affect the drug administration by this route. Simvastatin, a crystalline compound, is practically insoluble in water and hence poorly absorbed from the GI tract.[2] It is a potent and specific inhibitor of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG CoA) reductase, which catalyzes the reduction of HMG CoA to mevalonate. Thus, simvastatin arrests a key step for cholesterol biosynthesis in the liver and is widely used in the treatment of hypercholesterolemia and dyslipidemia as an adjunct to diet. After, oral administration, simvastatin is metabolized to its β-dihydroxy acid form (simvastatin acid) by the cytochrome-3A system in the liver, where it inhibits the rate-limiting step in cholesterol biosynthesis. This leads to up-regulation of low-density lipoprotein (LDL) receptors and an increase in catabolism of LDL cholesterol. The physiological properties of drug like short half life (2 to 3 h), dose size (5 to 80 mg) and low molecular weight (418.57) makes it a suitable candidate for formulation by mucosal route.[3,4] The ionotropic gelation technique was selected to prepare the simvastatin loaded mucoadhesive microspheres due to its simplicity and low cost.The aim of the present study was to prepare and evaluate the mucoadhesive microspheres as a new oral controlled release system for simvastatin.

***Address for Correspondence:**

M.Mohan Varma, Shri Vishnu College of Pharmacy, Vishnupur, Bhimavaram - 534202, A.P., India.

E-mail: mohan_pharm@rediffmail.com

MATERIALS AND METHODS

Materials

Simvastatin was obtained as gift sample from Alembic Pvt.Ltd., Baroda, Gujarat. Sodium alginate and all other

polymers were obtained from S.D. Fine chemicals, Mumbai. All the chemicals were of analytical grade.

Methods

Preparation of mucoadhesive microspheres

The mucoadhesive micrrospheres were prepared by the ionic gelation method.[5-7] The coating material (sodium alginate, 1 g) and mucoadhesive polymers (1 g) were dissolved in distilled water (32 ml) to form a homogenous polymer solution. The core material (Simvastatin, 2 g) was added to the polymer solution and mixed to form a viscous dispersion. The resulting dispersion was added drop wise into 40 ml of calcium chloride solution(10%w/v) through a syringe fitted with a needle of 18 gauge. The added droplets were retained in the calcium chloride solution for 2 h to complete the curing reaction and to produce spherical rigid microspheres. The microspheres were collected by decantation and the product thus separated was washed repeatedly with water and dried at 45^0C for 12 h. The prepared microspheres were stored in a desiccator until further use.The composition of the different batches of the microspheres prepared is indicated in Table 1b.

EVALUATION OF MICROSPHERES

Estimation of drug content

Initially, the microspheres were powdered using mortar and pestle. Then powder equivalent to 10 mg of Simvastatin was dissolved in 20 ml methanol and the volume was made up to 100 ml with pH7.0 phosphate buffer containing 0.5%SLS. The Solution was filtered through Whatman filter paper no. 41 to obtain the stock Solution A. The Stock Solution A (1 ml) was diluted to 10ml to obtain the stock Solution B .The absorbance[7] of the resulting solution is observed at λmax 239nm using the U.V. Spectrophotometer(Lab . India).

Entrapment efficiency

Entrapment efficiency was calculated using the following formula:

$$\text{Bulk Density} = \frac{\text{Weight}}{\text{Volume}}$$

The flow property of microspheres was evaluated using Carr's Index. The results were averaged from three determinations (Table no: 4).

$$\text{Carr's Index} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times 100$$

The angle of repose of the granules was determined by the fixed funnel and the free standing cone method.The Hausner ratio was estimated as :Hausner ratio=Tapped density /Bulk density.

In vitro wash off test for mucoadhesion

A 4-cm by 4-cm piece of sheep intestine mucosa was tied onto a glass slide using the thread. The microspheres were spread (∞ 100) onto the wet, rinsed, tissue specimen and the prepared slide was hung on to one of the groves of a USP tablet disintegrating test apparatus[5,9]. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movements in the beakers containing the simulated gastric fluid USP (pH 1.2), and the pH 7.0 phosphate buffer. At the end of 30 minutes, 1 hour, and at hourly intervals up to 8 hours, the number of microspheres still adhering on to the tissue was counted. The graphical representation of results of the In vitro wash-off test of batches F1 to F15 are shown in Fig.4 and 5.

$$\text{Mucoadhesive Property} = \frac{\text{No. of Mucoadhesive adhered}}{\text{No. of Microspheres applied}} \times 100$$

***In-vitro* drug release studies**

Drug release study was carried out in USP paddle type dissolution test apparatus (Electro lab TDT-06L). A quantity of microspheres equivalent to 20 mg of Simvastatin was used for the test. The dissolution medium pH 7.0 phosphate buffer containing 0.5% sodium lauryl sulphate was used. The volume of the dissolution medium was 900ml, and the bath temperature was maintained at 37°C ± 0.5°C. The microspheres were placed in the dissolution vessel and the vessel was covered, the apparatus was operated for 8hrs at 50 rpm. At definite time intervals the 5 ml of the dissolution fluid was withdrawn, filtered and again 5ml blank sample was replaced.The samples were analyzed spectrophotometrically at λmax 239 nm using a UV- spectrophotometer (Lab. India). All the studies were conducted in triplicate (n = 3).

Kinetics of drug release

The analysis of the drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of mucoadhesive controlled release systems. As a model-dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, Higuchi and the Korsemeyer-Peppas equations. The order of drug release from the mucoadhesive microspheres was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the mucoadhesive controlled release systems was studied by using the Higuchi equation and the Korsemeyer - Peppas equation. The results are given in Table 3.

Zero Order Release Kinetics

It defines a linear relationship between the fraction of drug released versus time.

$\mathbf{Q = k_o t}$ .Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant.A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is: $\mathbf{\ln (1-Q) = - K_1 t}$. Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant. Thus, a plot of the logarithm of the fraction of drug undissolved against the time will be linear if the release obeys the first order release kinetics.

Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time. $\mathbf{Q = K_2 t^{½}}$. Where, K_2 is the release rate constant.A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation.[10] This equation describes drug release as a diffusion and erosion process based on the Fick's law, square root time dependant.

Power Law

In order to define a model, which would represent a better fit for the formulation,dissolution data was further analyzed by Peppa's and Korsemeyer equation (Power Law). $\mathbf{M_t/M = K t^n}$. Where, M_t is the amount of drug released at time t and M is the amount released at time , thus the M_t/M is the fraction of drug released at time t,k is the kinetic constant and n is the diffusion exponent. To characterize the mechanism for both the solvent penetration and the drug release, the value of n can be used as abstracted in table 1a. A plot between log of M_t/M and log of time will be linear if the release obeys Peppa's and Korsemeyer equation and the slope of this plot represents "n" value.[11]

Table 1a: Diffusion exponent and the solute release mechanism

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

Fourier Transform Infrared Spectroscopy (FTIR)

There is always a possibility of drug - polymer interaction in any formulation due to their intimate contact. The technique employed in the present study for this purpose is FTIR spectroscopy. The FTIR spectra of Simvastatin, sodium alginate, methyl cellulose and F-10 formulation were obtained by the potassium bromide pellet method employing Bruker FTIR (ALPHA-T series). The scanning range used was 4400 to 500 cm^{-1} at a scan speed of 1 min (Fig . 6).

Scanning Electron Microscopy(SEM)

The external surface morphology was evaluated under a scanning electron microscope (SEM-JEOL,JSM-840A, Japan). The microspheres were mounted directly on the SEM sample stub using the double sided sticking tape and coated with gold film (thickness 200nm) under the reduced pressure (0.001 mm of Hg). The voltage 5KV was used (Fig. 7).

Differential Scanning Calorimetry (DSC)

The samples: pure drug alone (sample A),drug:sodium alginate:methyl cellulose(1:2:1)physical mixture (sample B),optimized batch of microspheres,drug:sodium alginate:methyl cellulose(1:2:1)(sample C) were analyzed on DSC.The samples were heated from 40°C-280°C at a heating rate of 10°C/minute,under the argon atmosphere (Fig.8).

RESULTS AND DISCUSSION

Drug Content and Flow Properties

All the prepared microspheres were found to be spherical, discrete and free flowing with white in color.The microspheres of Simvastatin with a coat consisting of sodium alginate and different mucoadhesive polymers - Sodium

Table 1b: Composition of different formulations

Batch	Coat Composition	Ratio
F1	Drug:Sod. Alginate	1:1
F2	Drug:Sod. Alginate:Carbopol (940)	1:0.9:0.1
F3	Drug:Sod. Alginate:HPMC (K100M)	1:0.9:0.1
F4	Drug:Sod. Alginate:Sod.CMC	1:0.9:0.1
F5	Drug:Sod. Alginate:Ethyl cellulose	1:0.9:0.1
F6	Drug:Sod. Alginate	1:2
F7	Drug:Sod. Alginate:Carbopol (940)	1:2:1
F8	Drug:Sod. Alginate:PMC (K100M)	1:2:1
F9	Drug:Sod. Alginate:Guar gum	1:2:1
F10	Drug:Sod. Alginate:Methyl cellulose	1:2:1
F11	Drug:Sod. Alginate:Xanthan gum	1:2:1
F12	Drug:Sod. Alginate:Guar gum	1:3:1
F13	Drug:Sod. Alginate:Xanthan gum	1:3:1
F14	Drug:Sod. Alginate:Xanthan gum	1:3:0.5
F15	Drug:Sod. Alginate:Xa.gum: Guar gum	1:3:1:1

Table 2: Quality Control Parameters of Mucoadhesive Microspheres of Simvastatin

Batch	Percent Drug Content		Encapsulation efficiency(%)
	Theoretical(%)	Practical(%)	
F1	50	39.70	79.40±0.025
F2	50	42.02	84.05±0.027
F3	50	39.03	78.07±0.027
F4	50	48.33	96.67±0.02
F5	50	28.73	57.47±0.012
F6	33.33	26.24	78.73±0.013
F7	25	19.14	76.57±0.032
F8	25	17.47	69.91±0.013
F9	25	18.60	74.40±0.017
F10	25	19.37	77.51±0.025
F11	25	18.10	69.64±0.019
F12	20	14	70.0±0.014
F13	20	13.62	65.75±0.017
F14	22.22	16.49	71.46±0.015
F15	16.66	10.59	61.18±0.012

CMC, Methyl cellulose, Carbopol 940P, HPMC K100M, Ethyl cellulose, in 1:1, with HPMC K100M, Carbopol 940P, Guar gum, Xanthan gum, Methyl cellulose in 1:2, with Guar gum ,and Xanthan gum in 1:3 were prepared by the orifice-ionic gelation process.The diameter of the microspheres was found to be in the range of 900 – 1200 µm.The values of % drug content and the encapsulation efficiency of all the formulations are represented in table 2. All the prepared microsphere formulations showed uniformity of drug content.The encapsulation efficiency was in the range of 57% to 96%, it was highest for F4 and lowest for the F15 batch (Table 2). The prepared batches of microspheres were evaluated for micromeritic study such as tapped density, bulk density, Carr's index, Hausner ratio and angle of repose (Table 4).The tapped density of the different formulations ranged from 0.552-0.869g/ml.The bulk density of the formulations ranged from 0.297-0.817g/ml.Compressibility index values of the different batches of microspheres ranged from 4.02-17.75%.The angle of repose of all the formulations ranged from11-19^{o} (Table 4).Based on the above micromeritic properties all the batches of microspheres demonstrated excellent flow properties.

Mucoadhesive property

The microspheres with a coat consisting of sodium alginate and a mucoadhesive polymer exhibited good mucoadhesive properties in the in vitro wash-off test. (Fig.4 and 5). The wash off test was faster at intestinal pH than at the gastric pH. It was observed that the pH of the medium was critical for the degree of hydration, solubility and mucoadhesion of the polymers. The rapid wash off observed at gastric pH is due to ionization of ester group and other functional groups in the polymer , which increase their solubility and reduces the mucoadhesive property. The formulations:F9,F13,F15 showed the mucoadhesive time for 6hr in pH 1.2,where as the formulations :F1,F3 exhibited the mucoadhesive time for

Table 3: Kinetic evaluation of drug release data for mucoadhesive microspheres of Simvastatin

Formulation	Kinetic Models							
	Zero Order		First Order		Higuchi's Model		Korsemeyer Peppa's Model	
	R^2	k_0	R^2	k_1	R^2	k_H	R^2	n
F1	0.939	8.64	0.943	0.557	0.984	56.22	0.961	0.629
F2	0.904	5	0.964	0.610	0.978	49.44	0.940	0.591
F3	0.980	15.71	0.820	0.400	0.927	68.56	0.969	1.141
F4	0.936	4.16	0.822	0.950	0.976	60.08	0.944	0.882
F5	0.872	2.93	0.929	0.090	0.957	23.36	0.945	0.610
F6	0.926	4.68	0.965	0.835	0.967	65.64	0.957	0.558
F7	0.937	12.06	0.933	0.414	0.976	50.41	0.977	0.538
F8	0.951	11.2	0.918	0.780	0.985	56.92	0.992	0.668
F9	0.950	9.56	0.976	0.550	0.996	56.71	0.985	0.684
F10	0.953	10.86	0.913	0.13	0.980	50.78	0.926	0.861
F11	0.944	4.14	0.986	0.117	0.989	24.71	0.987	0.553
F12	0.987	8.92	0.946	0.310	0.954	51.56	0.961	0.730
F13	0.878	4.85	0.968	0.105	0.967	22.16	0.969	0.380
F14	0.998	7.46	0.996	0.09	0.966	26.51	0.996	0.370
F15	0.965	4.83	0.994	0.101	0.981	22.56	0.980	0.593

Table 4: Flow Properties of Different Formulations

Formulation	Angle of Repose(Ø)	Bulk density (g/ml)	Tapped density (g/ml)	Hausner ratio	Compressibility index(%)
F1	12	0.816	0.866	1.06	5.77
F2	14	0.672	0.717	1.06	6.2
F3	11	0.556	0.602	1.08	7.6
F4	12	0.692	0.721	1.04	4.02
F5	15	0.297	0.371	1.24	9.2
F6	13	0.656	0.772	1.17	7.8
F7	16	0.454	0.552	1.21	17.75
F8	19	0.772	0.821	1.06	5.96
F9	14	0.659	0.721	1.09	8.59*
F10	19	0.604	0.679	1.12	11.04
F11	18	0.721	0.869	1.20	17.03
F12	16	0.526	0.619	1.17	15.02
F13	17	0.618	0.721	1.16	14.28
F14	15	0.536	0.590	1.10	9.1
F15	19	0.817	0.871	1.06	5.4

only 1 hr in pH 1.2(Fig.4).The batches : F10,F13,F14,F15 showed the mucoadhesive time for 7 hr in pH 7 phosphate buffer,where as the batches:F1,F4,F7 exhibited the mucoadhesive time for only 1 hr in the phosphate buffer pH 7(Fig.5).The results of the *in vitro* wash-off test indicates that the formulation F10, F13, F14, and F15 are having considerable mucoadhesive property (Fig. 4 and 5).

In vitro Drug Release Study

Simvastatin release from the microspheres was studied in phosphate buffer (pH 7.0) for 8 hours. The drug release[12-15] from the microspheres was slow and depended on the composition of the coat. Based on $T_{50\%}$(hr) values,(time taken for 50% of drug release),the order of drug release from the different formulations can be indicated as : F14<F15<F10<F13<F11<F5<F12<F3<F1<F4<F2<F7<F8< F9<F6.Similarly,based on $T_{75\%}$(hr)values(time taken for 75% of drug release),the order of drug release from the different formulations can be arranged as F10 <F12< F7< F4 <F3andF9<F2<F1<F8<F6.The batches:F5,F11,F13,F14,F15 did not attain the $T_{75\%}$ values,even after the 8 hr of the dissolution study.Based on the $T_{90\%}$(hr)values(time taken for 90% of drug release),the order of the drug release can be arranged as:F10 <F12< F7< F2 <F4 <F1< F9< F3< F6 <F8.The batches:F5,F11,F13-F15 did not attain the values of $T_{90\%}$ after the 8 hr of the dissolution study.Among all the batches, the F10 (Drug: Sod. Alginate : Methyl cellulose = 1:2:1) batch is considered to be the optimized formulation ($T_{50\%}$ = 5.3 h ,$T_{75\%}$ = 6.8 h , $T_{90\%}$ = 7.5 h), because among all the batches it shows better extent of drug release 97.11% (8hrs) , good entrapment efficiency (78%), and the *in vitro* wash-off test showed good mucoadhesive property. Simvastatin release from alginate – Methyl cellulose (F10) microspheres was slow and extended over a period of 8 hrs and these microspheres were found suitable for the oral controlled release formulation(Fig.1,2,3).In case of microspheres containing the higher concentration of the mucoadhesive polymer, the hydrophilic property of the polymer may bind better with water to form viscous gel structure,which may block the pores on the microsphere surfaces and prolong the drug release.As the polymer concentration of the prepared microspheres was increased,the release rate was decreased.An inverse relationship was observed between the polymer concentration and the drug release from the prepared microspheres.

The release of drug was considered to occur mostly by diffusion but could be accelerated by the weight loss of the mucoadhesive polymers[16]. The microsphere structure changed significantly over time,indicating that there was substantial hydration and swelling of the mucoadhesive polymeric matrix. The alginate-mucoadhesive polymeric gel might have acted as a barrier to the penetration of the dissolution medium ,there by suppressing the diffusion of the drug from the swollen alginate-mucoadhesive polymeric matrix. The release of the drug was modulated by the diffusion of the drug through the swollen polymeric matrix[17].

Kinetics of Release

The regression coefficient (R^2) values and the release rate constants,K,(for the zero order,first order,higuchi equation and the peppas equation) for the different formulations are indicated in table 3.Based on the values of R^2 ,the drug release from the formulations :F3,F4,F7,F8,F10,F12,F14

Fig. 1: Dissolution profile of mucoadhesive microspheres of Simvastatin (F1, F2, F3, F4, and F5) formulations.

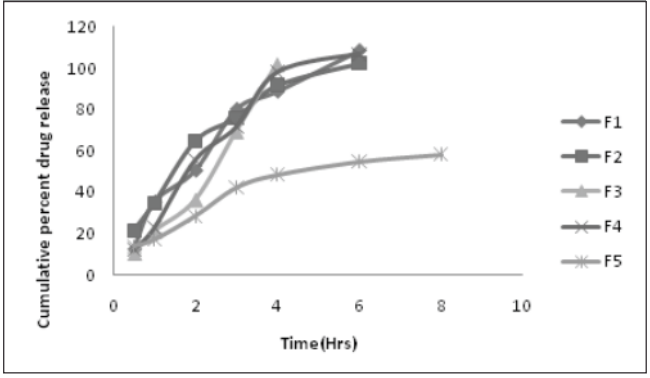


Fig. 2: Dissolution profile of mucoadhesive microspheres of Simvastatin (F6, F7, F8, F9, and F10) formulations.

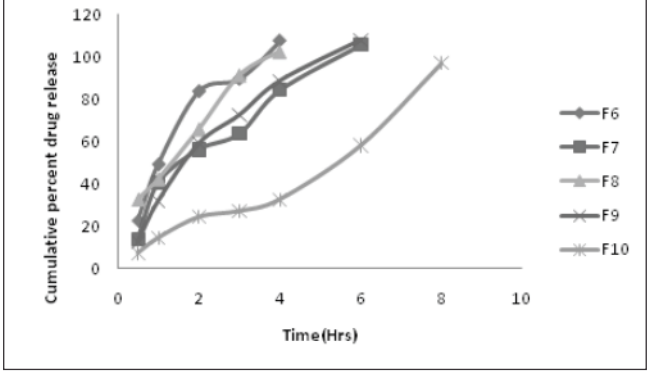


Fig. 3: Dissolution profile of mucoadhesive microspheres of Simvastatin (F11, F12, F13, F14 and F15) formulations.

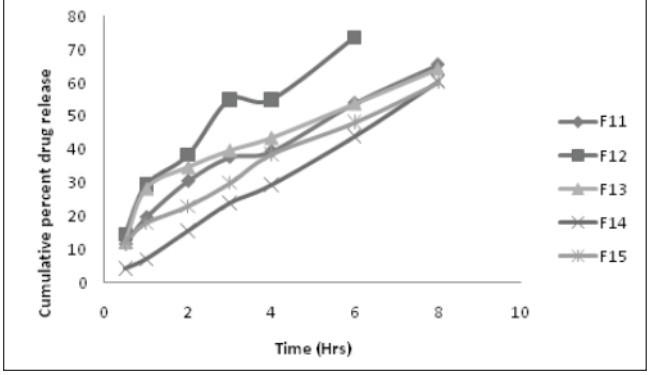


Fig. 4: Mucoadhesive Property of different formulations in pH 1.2 HCl buffer

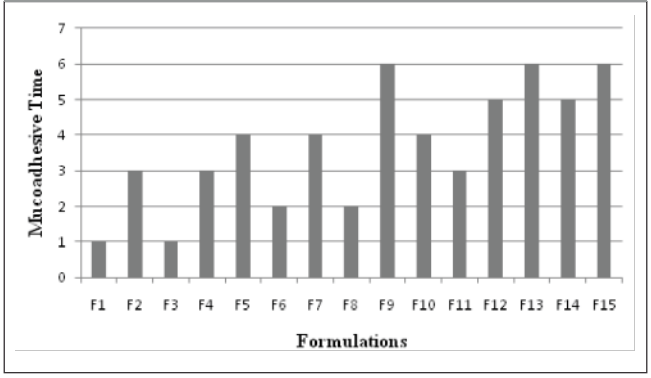
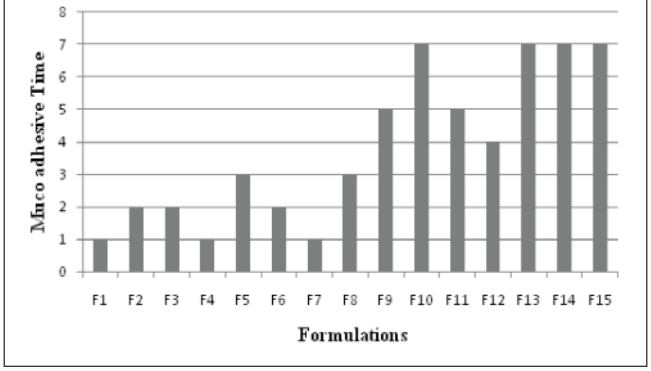


Fig. 5: Mucoadhesive Property of different formulations in pH 7.0 Phosphate buffer



demonstrated zero order kinetics,where as the drug release from the batches:F1,F2,F5,F6,F9,F11,F13,F15 exhibited first order kinetics.All the formulations obeyed Higuchi equation(R^2> 0.9),indicating that the drug release mainly depends on diffusion and erosion.The values of n(diffusion exponent) for all the formulations ranged from 0.37(batch F14)to 1.141(batch F3).Based on the n values ,the drug release from the formulation F14 followed fickian diffusion(n<0.45),where as the drug release from the batches:F1,F2,F4-F12,F15 exhibited non-fickian diffusion(n > 0.45),the drug release from the formulation F3 demonstrated super case-II transport(n > 0.89) mechanism controlled by swelling and relaxation of the polymeric matrix. The drug release for the optimized formulation F10 followed zero-order kinetics (R^2 = 0.953).The Higuchi plot showed an "R^2" value of 0.980 for the optimized formulation (F10) suggesting that the diffusion and erosion plays an important role in the drug release. The data was fitted to Korsemeyer - Peppas equation and the value of diffusion exponent 'n' (0.86) indicated that the drug release from the formulation,F10, shows non-fickian diffusion.

Fourier Transform Infrared Spectroscopy(FTIR)

The FTIR spectrum of the pure drug,sodium alginate(polymer),drug:sodium alginate:methyl cellulose(1:2:1)physical mixture and the optimized formulation (F10)are depicted in Fig.6.The drug-polymer interactions were ruled out by the FTIR spectroscopic studies for the optimized formulation (F10).The FTIR spectrum of the pure drug shows the characteristic peaks at 3550 cm^{-1} and 1011 cm^{-1} due to alcoholic and C=O stretching of the ester group . The FTIR spectrum of the F10 formulation exhibited peaks at 3429.27 cm^{-1} and 1055 cm^{-1}. As all the peaks of the drug are

Fig. 6: FTIR spectra of Simvastatin (A), Sodium alginate (B), Methyl cellulose (C) and Optimized formulation F10 (D).

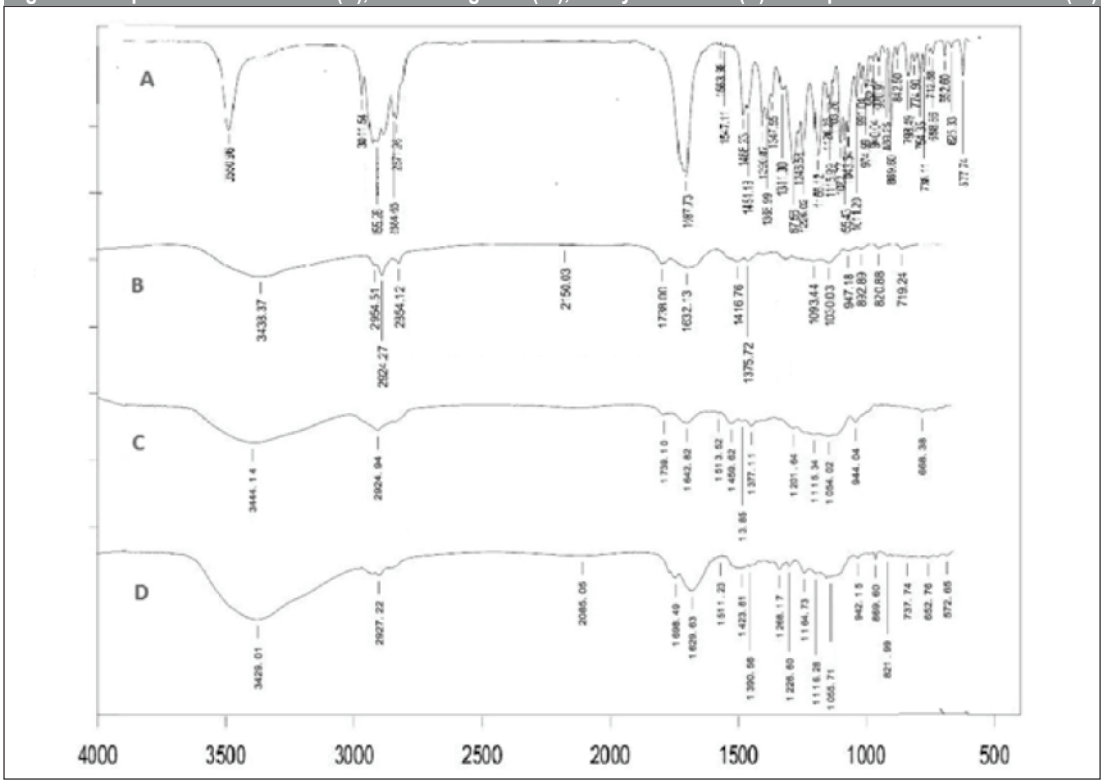


Fig. 7: SEM images of Optimized formulation F10

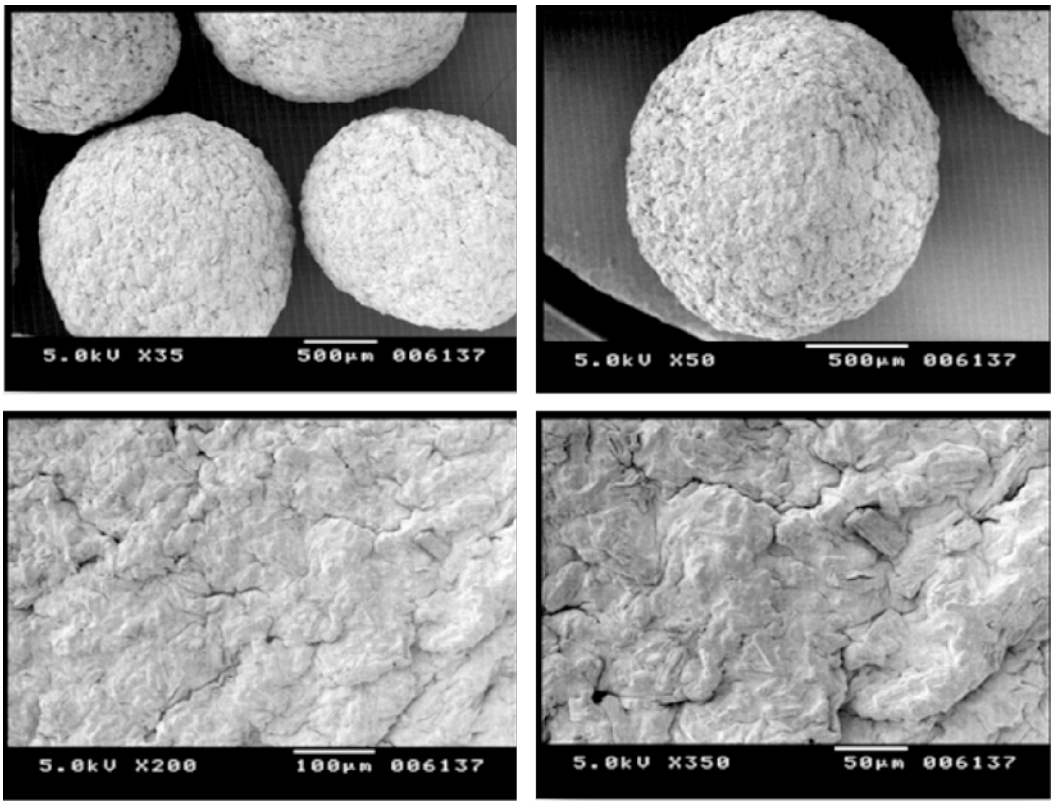
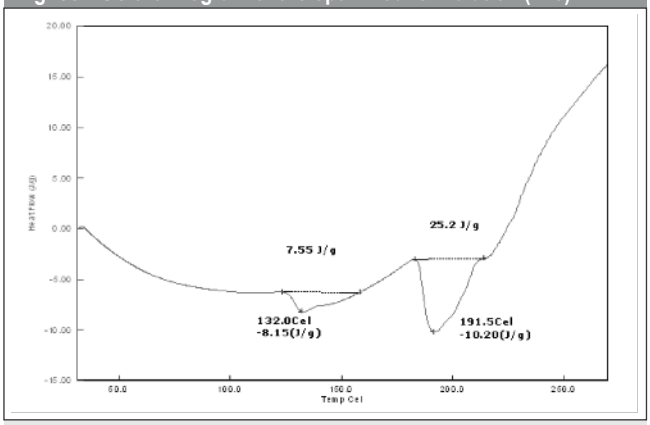
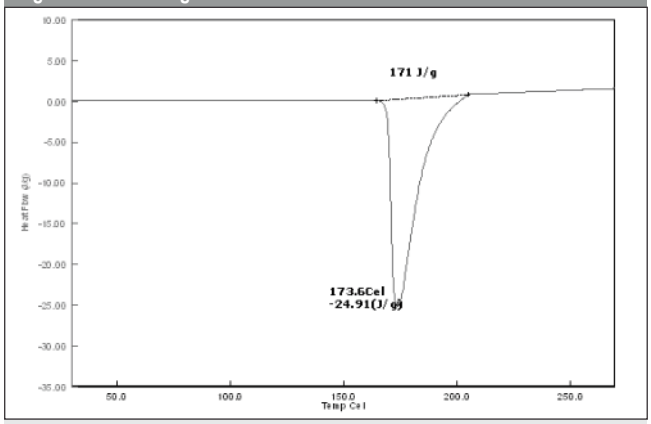


Fig.:8c:DSC thermogram of the optimized formulation (F10)



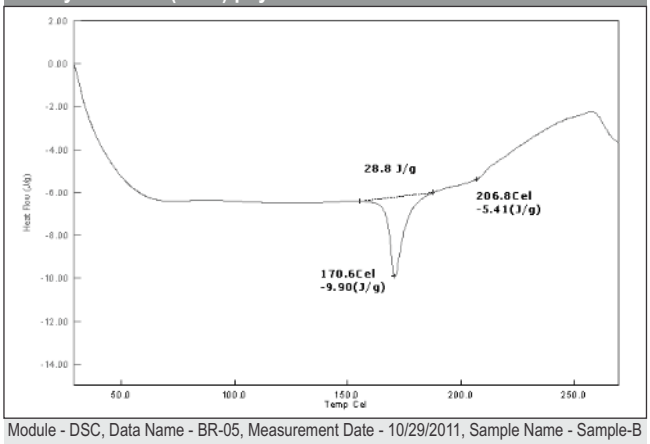
Module - DSC, Data Name - BR-01, Measurement Date - 10/29/2011, Sample Name - Sample-C Sample Weight - 12.963 mg, Reference Name - Alumnium pan, Reference Weight - 0.000 mg

Fig. 8a:DSC thermogram of Simvastatin



Module - DSC, Data Name - BR-04, Measurement Date - 10/29/2011, Sample Name - Sample-A Sample Weight - 5.316 mg, Reference Name - Alumnium pan, Reference Weight - 0.000 mg

Fig: 8b:DSC thermogram of drug:sodium alginate: methyl cellulose(1:2:1) physical mixture



Module - DSC, Data Name - BR-05, Measurement Date - 10/29/2011, Sample Name - Sample-B Sample Weight - 2.720 mg, Reference Name - Alumnium pan, Reference Weight - 0.000 mg

observed in the optimized formulation(F10),the drug-polymer interaction is absent.This confirms the undisturbed structure of the drug in the formulation(Fig.6).

Scanning Electron Microscopy(SEM)

The SEM studies revealed that the optimized formulation (F10) of the mucoadhesive microspheres were spherical and completely covered with the coat polymer (Fig.7). At higher magnification,cracks and crevices were observed,which can influence the rate of drug release from the microspheres.

Differential Scanning Calorimetry(DSC)

The DSC thermograms for the pure drug(sample A),physical mixture(sample B) and the optimized batch of microspheres(sample C)are exhibited in the Fig. 8 .The pure drug (sample A) showed the endotherm(melting point) at 173.6°C.The endotherm of the drug was evident in the physical mixture(sample B) and also in the optimized batch (F10) of microspheres(sample C).The presence of the endotherm clearly indicated the absence of drug-polymer interaction in the microspheres.The shift in the melting endotherm in the sample (C)may be due to the physical and chemical changes taking place in the microspheres after the entrapment of the drug.

CONCLUSION

The microspheres of simvastatin(optimized formulation, drug-sodium alginate-methyl cellulose, 1:2:1 ratio)demonstrated oral controlled release of the drug for 8 hours and exhibited good mucoadhesive property.The FTIR and DSC studies revealed the absence of drug-polymer interaction.The SEM studies indicated the spherical shape of the microspheres.The formulated novel mucoadhesive multiparticulate drug delivery system of simvastatin can control the drug release, it has good mucoadhesive property and can improve the bioavailability of simvastatin.

ACKNOWLEDGEMENT

We are grateful to the chairman sir, the director,the principal and the management of shri vishnu college of pharmacy for providing the necessary facilities to carry out this work.

REFERENCES

1. Chowdary KPR, Srinivas L. Mucoadhesive Drug Delivery System. A Review of Current Status. Indian Drugs. 2000; 37 : 400-5.
2. Cheng H, Sutton SC,Pipikin JD,Zentner GM. Evaluation of sustained/controlled-release dosage forms of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor in dogs and humans. Pharm. Res. 1993;10 : 683–1687.
3. Hiremath JG,Sarfaraz MD, Hiremath D, Sarudkar SA.Preparation and Physicochemical Characterization of Simvastatin Loaded Mucoadhesive Bilayered Tablet. Indian Journal of Novel Drug Delivery2009; 1:18-24.
4. Martindale:The Complete Drug reference,34th ed.,edited by S.C. Sweetman, Pharmaceutical Press, U.K.,2005, 997.

5. Kalyankar TM, Nalanda T. Formulation and Evaluation of Mucoadhesive Pioglitazone HCl Microspheres. International Journal of Pharma World Research. 2010;1:1-14.
6. Chowdary KPR ,Srinivas Rao Y. Design and in-vitro and in-vivo evaluation of glipizide mucoadhesive microspheres for oral controlled release. AAPS Pharm. SciTech. 2003; 4:39.
7. Swamy PV, Amit H, Shirsanad SB. Preparation and In Vitro Evaluation of Mucoadhesive Microcapsules of Atenolol. Ind. J.Pharm.Edu.Res. 2007; 41: 358-64.
8. Chowdary KPR ,Srinivas Rao Y. Preparation and Evaluation of Mucoadhesive microspheres of Indomethacin. Indian J. Pharm. Sci. 2003; 65:49-52.
9. Jayvadan K,Patel R,Patel P. Formulation and Evaluation of Mucoadhesive Glipizide Microspheres. AAPS PharmSciTech.2005; 6 : 21-6.
10. Higuchi T. Mechanism of Sustained-action medication. Theoretical Analysis of rate of release of solid drugs dispersed in solid matrices, J. Pharm, Sci., 1963;51: 1145-9.
11. Peppas NA. Analysis of Fickian and Non-Fickian drug release from polymers. Pharm.Acta.Helv, 1985; 60:110-1.
12. Patil PBL, Gawali VU. Preparation and Evaluation of Mucoadhesive Microspheres of Atenolol and Propranolol. International Journal of PharmTech Research.2009; 3: 639-43.
13. Yadav S, Jain S. Formulation and *In Vitro* and *In Vivo* Characterization of Acyclovir Loaded Mucoadhesive Microspheres. Int.J Pharm. Sci. and Nanotech. 2011; 3 : 441-7.
14. Xingna Zhao, Guofei Li, Lili Zhang. Preparation and evaluation of nicotinic acid sustained-release pellets combined with immediate release simvastatin. Int. J. Pharm. 2010;400:42-48.
15. Monica Rao, Yogesh Mandage. Dissolution Improvement of Simvastatin by Surface Solid Dispersion Technology. Dissolution Technologies. 2010; 61:27-34.
16. Arica B, Calis S, Atilla P, Durlu NT, Cakar N, Kas HS, Hincal AA. In vitro and *In vivo* studies of ibuprofen loaded biodegradable alginate beads. Journal of microencapsulation.2005;22:153-65.
17. Gallardo A,Eguiburu JL,Berridi MJFRoman JS.Preparation and *In vitro* release studies of ibuprofen loaded films and microspheres made from graft copolymers of poly(L-lactic acid) on acrylic back bones.J Control. Rel.1998; 55:171- 9.
18. Prajapati SK,Tripathi P, Ubaidullah U,Anand V.Design and development of gliclazide mucoadhesive microcapsules:In vitro and in vivo evaluation. AAPS Pharm SciTech.2008;9 :224-30.
19. Varshosaz J,Tavakali N,Minayian M,Rahdari N.Applying theTaguchi design for optimized formulation of sustained release gliclazide chitosan beads:an in vitro/in vivo study.AAPS Pharm Sci Tech 2009;10 :158-65.
20. Pal DK,Nayak AK. Development ,optimization and antidiabetic activity of gliclazide loaded alginate –methyl cellulose mucoadhesive microcapsules.AAPS Pharm Sci Tech.2011; 12 :1431-41.