

FORMULATION AND EVALUATION OF SIMVASTATIN GASTRORETENTIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Objective: The aim of this study was to formulate and evaluate gastro retentive drug delivery system (GRRDS) using an effervescent approach for simvastatin.

Methods: Floating tablets were prepared using directly compressible polymers hydroxypropyl methylcellulose (HPMC) K100M, HPMC K4M and carboxymethylcellulose sodium (NaCMC). The prepared tablets were subjected to pre-formulation studies like Compressibility index, Hausner ratio and post compression parameters like buoyancy/floating test and *In vitro* dissolution study.

Results: Drug-excipient compatibility studies performed with the help of FTIR instrument indicated that there were no interactions. The DSC thermogram of the formulations revealed that crystalline form of simvastatin existed in the formulation which was confirmed by X-ray powder diffraction. Dissolution studies indicated that there was a decrease in the drug release with an increase in the polymer viscosity. The tablets prepared with low-viscosity grade HPMC K4M exhibited short Buoyancy Lag Time and floated for a longer duration as compared with formulations containing high viscosity grade HPMC K100M. The 'n' value for dissolution studies for all the formulations was found to be in the range of 0.647 to 0.975 indicating non-Fickian or anomalous drug transport.

Conclusion: The drug release rate and floating duration of tablets depended on the nature of the polymer and other added excipients. The release rate of the drug can be optimized by using different ratios of polymers and other excipients. The formulation F8 achieved the optimized batch and complied with all the properties of the tablets.

Keywords: GRRDS, Simvastatin, Polymers, Drug release

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INTRODUCTION

Atherosclerosis is a general term describing any hardening (loss of elasticity) of the medium of large arteries (in Greek, "Arterio" meaning artery and "sclerosis" meaning hardening), is a condition in which fatty material collects along the walls of arteries. This fatty material thickens, hardens, and eventually blocks the arteries [1]. Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β -hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol. Also, it has been reported [2, 3] that simvastatin is more efficiently extracted by the liver than its corresponding hydroxy acid with subsequent minimization of systemic burden [4]. This suggests that compared to a conventional dosage form, a sustained/controlled release dosage form of simvastatin might provide similar or better efficacy [5].

One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive drug delivery system (GRRDS). GRRDS extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals but also increase patient compliance beyond the level of existing controlled release dosage form [6]. A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts such as Floating Systems [7], Bio/Mucoadhesive Systems [8], and Swelling and expanding systems [9], High-Density Systems [10], Incorporation of passage delaying food agents [11], Ion exchange resins [12], and Osmotic regulated systems [13].

Matrix tablets based on hydroxyl propyl methylcellulose (HPMC K4M) have been developed [14]. Upon contact with gastric fluid, the system takes up water and swell. As the increase in volume is

greater than the increase in mass during swelling, the densities of these devices decrease and the system starts to float after a short lag time. The influence of different processing and formulation parameters on the floating properties of matrix tablets has been studied [15, 16]. Reduced floating lag times could be achieved by reducing the compression forces (thus, increasing tablet porosities), increasing polymer molecular weights and increasing the particle sizes of the matrix-forming polymer [17].

The objective of this study was to develop and optimize GRRDS containing simvastatin as a gastric floating dosage form having a bulk density lower than that of gastric fluids so that it remains buoyant on the stomach contents. To achieve the objective, independent formulation variables such as a drug to total polymer ratio, the polymer to polymer ratio and different viscosity grades of HPMC (K4M, K100M), Carbopol and NaCMC were examined. The dependent variables such as floating time, release profile, hardness and the kinetics and mechanism of drug release for the formulations were studied.

MATERIALS AND METHODS

Materials

Simvastatin USP was received as a gift sample from Krebs biochemicals and industries Ltd, Visakhapatnam, India. Carbopol 71G, HPMC K100M and K4M, Citric Acid Anhydrous was received as a gift sample from Colorcon Asia Pvt. Ltd. Sodium CMC was purchased from SD Fine-chem Ltd., Mumbai. Avicel PH 102, DCP anhydrous, Aerosil 200, Sodium Bicarbonate, Magnesium stearate and Talc were purchased from Signet Chemical Corp.

Preparation of gastro retentive tablets

The composition of different formulations of simvastatin floating tablets is shown in table 1. Gastro retentive tablets containing simvastatin were prepared by direct compression technique using

variable concentrations of polymers like HPMC K100M, HPMC K4M, carbopol 71G and NaCMC. The respective ingredients (drug, polymer, and additives) were passed through a sieve no. 60 (250 μ m) and blended with a turbula mixer (Analytical Technology,

Bangalore, India). All the batches were compressed on a 10-station tablet machine (Cadmach, Ahmedabad, India) with 7-mm flat round punches. Three batches were prepared for each formulation (table 1).

Table 1: Composition of gastro retentive tablets of simvastatin

Ingredients	Sieve no	Quantity/tablet in mg								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
Simvastatin	#40	60	60	60	60	60	60	60	60	60
HPMC K100M	#60	80	80	--	--	--	--	--	--	--
Carbopol 71G	#40	20	--	--	--	--	--	--	--	--
Sodium CMC	#60	--	20	--	--	--	--	80	20	20
HPMC K4M	#60	--	--	30	60	60	80	--	80	100
Avicel PH 102	#40	42.8	42.8	36	54	--	62.8	62.8	42.8	22.8
DCP Anhydrous	#40	--	--	--	--	54	--	--	--	--
NaHCO ₃	#40	50	50	50	50	50	50	50	50	50
Citric acid anhydrous	#40	16	16	16	16	16	16	16	16	16
Aerosil 200	#40	5.6	5.6	4	5	5	5.6	5.6	5.6	5.6
Talc	#40	2.8	2.8	2	2.5	2.5	2.8	2.8	2.8	2.8
Magnesium stearate	#40	2.8	2.8	2	2.5	2.5	2.8	2.8	2.8	2.8
Total(mg)	--	280	280	200	250	250	280	280	280	280
Punch Size (mm)	--	9	9	7	8	8	9	9	9	9

Infrared spectroscopy

The infrared spectra of simvastatin and formulation were recorded on FTIR (JASCO-FTIR 5300). The samples were prepared on KBr press (Spectra Lab, Mumbai, India).

Flow properties of granules

The flow properties of granules were characterized in terms of angle of repose, Carr's consolidation index and Hausner ratio.

DSC (Differential scanning calorimetry)

The instrument used was Perkin-Elmer DSC-7. Samples were sealed hermetically in a flat bottom aluminum cells. These samples were then heated over a temperature range of 320 °K-520 °K in an atmosphere of nitrogen (20 mm/min) at a constant rate of 5 °C/min with alumina being reference standard.

X-ray diffraction

The physical state of simvastatin in the various preparations was evaluated by X-ray diffraction. Powder X-ray diffraction patterns of all samples were determined using Phillips PW 3710 scanner, IW 1830 generator with a CuK α anode at 40 kV and 30 mA and at a scan rate of 1 ° min⁻¹ from 2 θ range from 5 ° to 40 °.

Buoyancy/floating test

The time between introduction of the dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for the dosage form to emerge on the surface of the medium is called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time for which dosage form remain buoyant is called Total Floating Time (TFT) [18].

Effect of hardness on buoyancy lag time (BLT) or floating lag time (FLT)

Formulation F8 was selected to study the effect of hardness on buoyancy lag time. The tablets of batch F8 were compressed at three different compression pressures to get the hardness of 4 kg/cm², 5 kg/cm², 7 kg/cm² and 8 kg/cm². And were evaluated for Buoyancy Lag Time by following the method as done for Buoyancy test [19, 20].

In vitro dissolution study

Drug release profile was evaluated *in-vitro* by using a dissolution test apparatus (Electro Lab, TDT-08L, Mumbai, India). The USP XXIII Type II (paddle-type) method was selected to perform the dissolution profile of simvastatin. The dissolution for all the formulations was carried out in 900 ml 0.1 N HCl containing 0.5 % SLS. The temperature was maintained at 37 \pm 0.5 °C and a constant

paddle rotation speed of 50 rpm. Samples (10 ml) were withdrawn at regular intervals and filtered through a membrane filter (pore size 0.22 μ m). Each sample was analyzed at 239.1 nm using UV-visible spectrophotometer against reagent blank [21].

RESULTS AND DISCUSSION

In the present study the floating tablets of simvastatin were prepared by direct compression technique with HPMC K4M, HPMC K100M, NaCMC, Carbopol as matrix polymers, sodium bicarbonate and citric acid anhydrous were used as a gas generating agent, MCC and DCP were used as a diluents, magnesium stearate and talc as a lubricant and glidant respectively.

Drug-polymer interaction study

Drug-polymer interaction studies were performed using FTIR spectrophotometer. Characteristics peaks obtained for the pure drug correlated well with that of the formulation peaks. This indicated that the drug was compatible with the formulation components. The FTIR spectra's for the formulation and pure drug is shown in fig. 1. The FTIR spectra's of all samples are shown in fig. 1. The spectrum of pure drug and formulation F-8 presented characteristic peaks at 3553 cm⁻¹ (alcohol O-H stretching vibration), 3011 cm⁻¹ (olefinic C-H stretching vibration), 2957 and 2878 cm⁻¹ (methyl and methylene C-H asymmetric and symmetric stretching vibration), 1719 cm⁻¹ and 1701 cm⁻¹ (Lactone C=O and ester C=O stretch), 1453, 1406, and 1383 cm⁻¹ (methyl and methylene bending vibration), 1267, 1222, 1178, and 1080 cm⁻¹ (lactone and ester C-O-C bending vibration), 1060 cm⁻¹ (secondary alcohol C-O stretching vibration), and 879 cm⁻¹ (trisubstituted olefinic C-H wag), respectively.

Differential scanning calorimetry (DSC)

To understand the physical state of the drug, DSC was performed on pure drug and formulation F-8 (fig. 2). The DSC thermogram of the formulations revealed that an endothermic peak of melting of simvastatin at about 134.76 °C was shifted to about 133.97 °C. This suggested that a crystalline form of simvastatin existed in the formulation.

X-ray diffraction

Powder X-ray diffractograms of pure simvastatin and formulation F-8 are shown in fig. 3. The presence of numerous distinct peaks in the x-ray diffraction spectrum indicated that simvastatin was present as a crystalline material with major characteristic diffraction peaks appearing at a diffraction angle of 2 θ at 7.72, 8.22, 10.81, 14.82, 15.47, 16.39, 17.12, 17.57, 18.69, 19.28, 21.93, 22.52, 25.80, 28.24 and 31.91. Formulation F-8 showed similar major characteristic diffraction peaks indicating the existence of simvastatin in crystalline form in the formulation F-8.

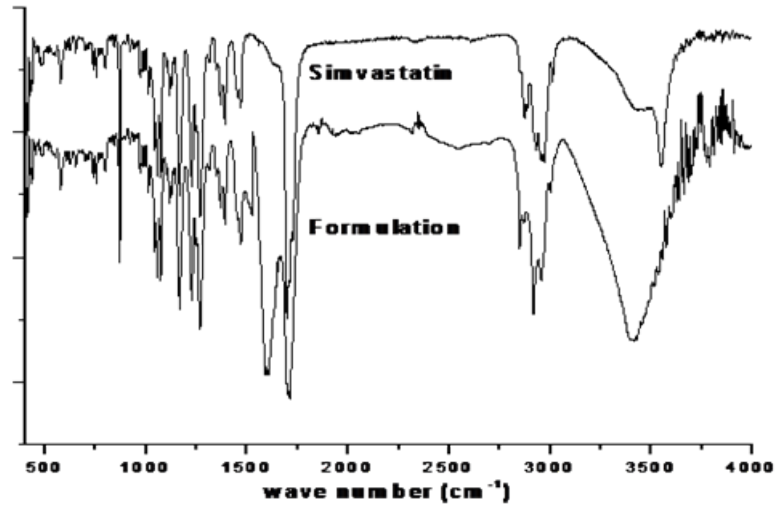


Fig. 1: Comparison of characteristic absorption peaks of simvastatin and formulation-F8

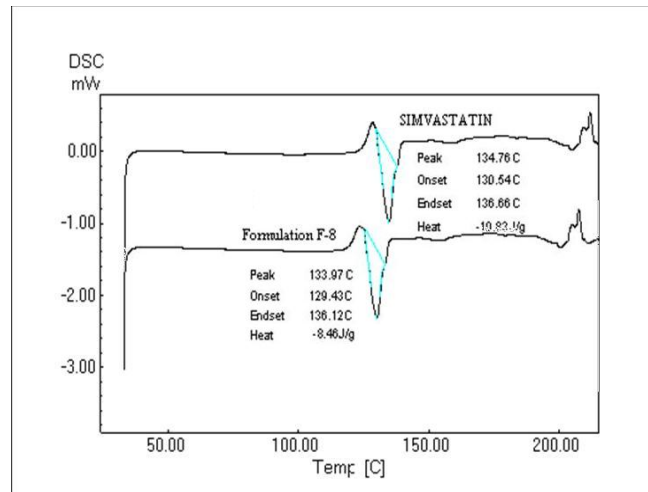


Fig. 2: DSC thermograms of pure drug simvastatin and formulation F8

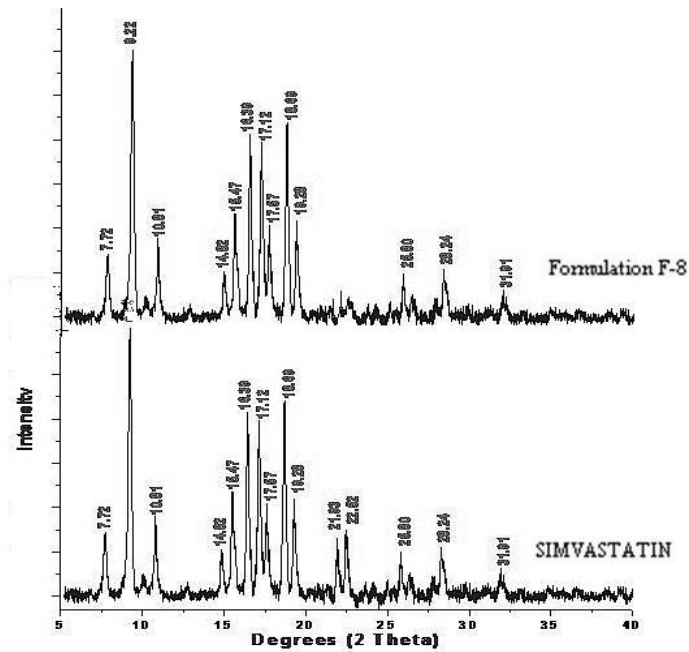


Fig. 3: XRD patterns of pure drug simvastatin and formulation F8

Flow properties of granules

The granules prepared for compression of floating tablets were evaluated for their flow properties (table 2). The angle of repose was in the range of 26.61 to 28.86 ° with granules containing HPMC K100M and 24.31 to 32.60 ° with HPMC K4M. Bulk density ranged between 0.462 to 0.503 gm/cm³ with granules containing HPMC

K100M and 0.408 to 0.536 gm/cm³ with HPMC K4M. Tapped density ranged between 0.552 to 0.563 gm/cm³ with granules containing HPMC K100M and 0.478 to 0.677 gm/cm³ with HPMC K4M. Carr consolidation index was found to be 6.02 to 13.59 and Hausner ratio ranged from 0.84 to 1.33 for granules of different formulations. These values indicated that the prepared granules exhibited good flow properties.

Table 2: Flow properties of granules

Code	Bulk density (g/cm ³)	Tapped density (g/cm ³)	Angle of repose (θ)*	Carr's consolidation index	Hausner ratio
F1	0.462	0.552	26.61±0.252 °	11.83	1.17
F2	0.503	0.563	28.86±0.352 °	9.90	1.11
F3	0.455	0.535	24.31±0.482 °	13.59	1.15
F4	0.486	0.531	26.77±0.285 °	9.51	1.11
F5	0.408	0.482	26.56±0.317 °	9.96	0.84
F6	0.433	0.478	26.85±0.159 °	10.96	0.84
F7	0.512	0.662	32.60±0.269 °	13.2	1.33
F8	0.536	0.677	29.86±0.421 °	6.02	1.26
F9	0.451	0.516	28.66±0.376 °	9.10	0.90

*n=3, Data presented as mean±SD. Rest of the values are given as mean of triplicate.

Buoyancy/floating test

On immersion in 0.1N HCl solution (pH 1.2), 0.5% SLS at 37 °C, the tablets floated and remained buoyant without disintegration. Table 3 shows the results of Buoyancy study. From the results, it was concluded that the batch F1 and F2 showed good Total floating time (TFT). Formulation F4 and F5 showed good BLT while the formulation F3 and F7 showed less TFT. And the formulation F8 and F9 showed good BLT as well as good TFT. All the batches of tablets

were found to exhibit short BLT due to the presence of sodium bicarbonate and citric acid. The tablets with low-viscosity grade HPMC K4M exhibited short BLT and floated for a longer duration as compared with formulations containing high viscosity grade HPMC K100M. Increasing the concentration of HPMC K4M level in the formulations F3, F4, F5, F6, F8, and F9 prolonged the BLT and the total floating time. Thus a combination of sodium bicarbonate (50 mg) and citric acid (16 mg) with HPMC K4M and HPMC K100M was found to achieve the optimum *in vitro* buoyancy and float ability.

Table 3: Buoyancy lag time and total floating time

Formulations	Buoyancy lag time (Sec)*	Total floating time (h)*
F1	82±2.32	11.32±0.02
F2	92±1.85	11.45±0.05
F3	28±2.15	6.15±0.1
F4	36±2.68	8.52±0.08
F5	40±1.92	8.33±0.05
F6	58±3.18	9.15±0.04
F7	126±2.65	5.27±0.06
F8	72±2.54	9.16±0.05
F9	80±1.69	10.21±0.07

*n=3, Data presented as mean±SD

Effect of hardness on buoyancy lag time (BLT) or floating lag time (FLT)

The effect of hardness on buoyancy lag time for batch F8 was studied. The results of floating lag time of tablets with hardness of 4 kg/cm², 5 kg/cm², 7 kg/cm² and 8 kg/cm² were 73, 89, 118 and 167 sec respectively. It can be concluded that as the hardness increases, the buoyancy lag time also increases linearly. The optimum hardness for the GRRDS was found to be 4-5 kg/cm².

In vitro dissolution study

The release data obtained for all the formulations is shown in fig. 4. The release of drug from the formulations containing HPMC K100M (F1 and F2) showed very slow drug release whereas tablets containing only HPMC K4M showed complete drug release within 10 h. A formulation containing only NaCMC (F7) showed good release rates at the initial hour but failed to maintain matrix integrity and disintegrated rapidly. Formulations containing both HPMC K4M and NaCMC polymers were found to be more sustained (F8 and F9). These findings are in agreement with the earlier report [22]. It was found that a combination of anionic NaCMC with nonionic HPMC produced a synergistic increase in viscosity. This was attributed to the stronger hydrogen bonding between the

carboxyl groups of NaCMC and hydroxyl groups of the HPMC, leading to stronger cross-linking between two gums. To confirm the exact mechanism of drug release from these tablets, the data were fitted according to the equation of Korsmeyer and Peppas, given as $M_t/M_\infty = Kt^n$ where M_t/M_∞ is the fractional release of drug in time t , K is a constant incorporating structural and geometric characteristics of the controlled-release device, and n is the diffusional release exponent indicative of mechanism of release. The value of n is 0.5 for Fickian transport, more than 0.5 and less than 1 for non-Fickian transport, and 1 for case II transport (zero order); when the value of n approaches 1, it may be concluded that the release is approaching zero order. The dissolution data were fit to the above equation by drawing a log-log plot of the fraction released versus time. The 'n' value was between 0.647 to 0.975, which indicated that the release followed non-Fickian diffusion mechanism or anomalous transport and suggesting that both diffusions of the drug in the hydrated matrix and chains relaxation process affect the drug release process (table 4). The initial burst effect is probably due to the fact that the gel layer, which controls the release of the drug, needs some time to become effective. The mixture of the two polymers, used as release modulator agents, enables the system to reach a nearly zero-order release kinetic (n for F8 is 0.975).

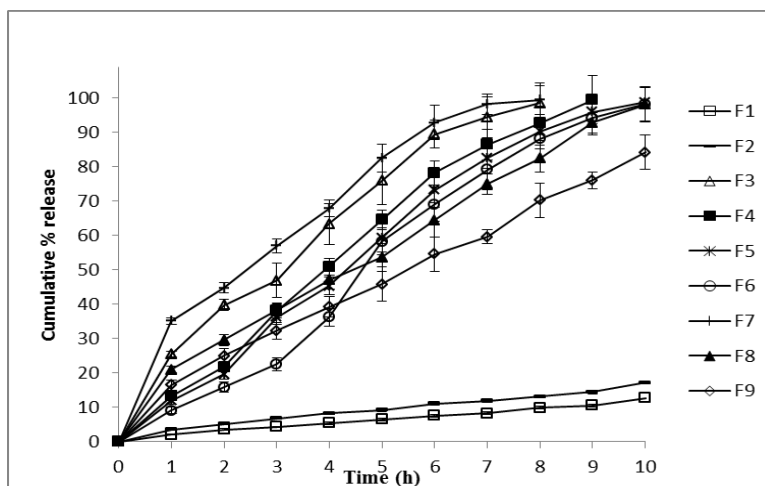


Fig. 4: Dissolution behaviour of the formulations n=3, Data presented as mean \pm SD

Table 4: Regression values for zero order and first order of all the formulations

Formulation	Zero order		First order		Higuchi model	Peppas model	
	r ²	K value	r	K value	r ²	n value	r ²
F1	0.991	1.103	0.989	0.011	0.986	0.767	0.990
F2	0.990	1.420	0.988	0.013	0.988	0.679	0.991
F3	0.990	11.31	0.975	0.276	0.987	0.627	0.981
F4	0.994	6.482	0.954	0.122	0.986	0.648	0.995
F5	0.995	6.238	0.965	0.112	0.983	0.743	0.994
F6	0.996	5.491	0.975	0.087	0.980	0.804	0.995
F7	0.997	11.79	0.905	0.421	0.997	0.432	0.977
F8	0.998	7.768	0.877	0.244	0.993	0.593	0.999
F9	0.998	7.438	0.943	0.172	0.992	0.664	0.996

*n=3, Average of three determinations

CONCLUSION

The concept of formulating GDDS containing simvastatin offers a suitable, practical approach to achieving a prolonged therapeutic effect by continuously releasing the medication over an extended period of time (10 h). This study discusses the preparation of GDDS of simvastatin; the effervescent based floating drug delivery system was a promising approach to achieve *in vitro* buoyancy. The drug release rate and floating duration of tablets depend upon the nature of the polymer and other added excipients. Thus, the release rate of the drug can be optimised by using different ratios of polymers and other excipients. The formulation F8 achieved the optimized batch and complied with all the properties of the tablets.

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CONFLICTS OF INTERESTS

Declare none

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