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Development and evaluation of gastroretentive tablets of Simvastatin

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ABSTRACT

Simvastatin is a lipid lowering agent that is derived synthetically from the fermentation of Aspergillus terreus. It is a potent competitive inhibitor of 3-hydroxy-3-methyl glutaryl coenzyme A reductase. It is used to lower cholesterol and triglycerides (types of fats) in the blood. It is also used to lower the risk of stroke, heart attack and other heart complications in people with diabetes and coronary heart disease. Common side effects of simvastatin may include headache, constipation, nausea and stomach pain. The GFDDS of simvastatin were developed in the form tablets comprising of an effervescent agent. The GFDDS of simvastatin prepared from HPMC remained intact and the compactness of the tablets was not affected during the invitro dissolution test.

INTRODUCTION

Historically, oral drug administration has been the predominant route for drug delivery [1]. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient. Controlled drug delivery results in optimum therapy, [2] and not only reduces the frequency of dosing, but may also reduce the severity and frequency of side effects [3]. The de novo design of oral controlled drug delivery systems should primarily be aimed at achieving more predictable and increased bioavailability of drugs. However [4], the developmental process is precluded by several physiological difficulties [5], such as inability to restrain and locate the controlled drug delivery systems within desired regions of gastrointestinal tract due to the variable gastric emptying and motility. An important factor [6], which may adversely affect the performance of oral controlled drug delivery systems [7], is the gastrointestinal transit in humans, estimated to be 8-10 hr from mouth to colon, is relatively brief with considerable fluctuation [8].

Gastric Retention System is a device, which resides in the confines of the stomach over a prolonged period of time (prolonging the residence time) for the purpose of providing a platform for controlled release of biologically active agents [9]. The system releases the active agent to be absorbed or released from the stomach to be absorbed in the upper parts of the small intestine [10]. In particular it allows for less frequent dosing of the active agent than with immediate release formulations or sustained release formulations that are not gastric retention dosage forms [11]. In other applications the frequency of dosing may be the same, but the gastric retention dosage forms will beneficially alter the absorption profile of the active agent from that available with immediate release formulations. This may result in increased bioavailability of the active agent with reduced side effects [12].

MATERIALS AND METHODS

All the chemicals obtained and used are of pharmaceutical grade. Simvastatin is obtained from Natco pharma ltd and the other materials have been obtained from SD fine chemicals, hyd.

Table: 1. Materials used for the formulation development

S. No.	Ingredients
1	Simvastatin
2	HPMC 100 cps
3	Xanthan gum
4	Guar gum
5	Ethyl cellulose
6	Sodium bicarbonate
7	Citric acid
8	Lactose
9	Starch
10	Magnesium stearate
11	Talc

Table 2: Composition of Formulation table for Simvastatin

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Simvastatin	20	20	20	20	20	20	20	20	20	20	20	20
Xanthan gum	15	20	25	30	--	--	--	--	--	--	--	--
Guar gum	--	--	--	--	15	20	25	30	--	--	--	--
HPMC 100 cps					--	--	--	--	15	20	25	30
$NaHCO_3$	10	10	10	10	10	10	10	10	10	10	10	10
Citric acid	5	5	5	5	5	5	5	5	5	5	5	5
MCC	96	91	86	81	96	91	86	81	96	91	86	81
Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	150	150	150	150	150	150	150	150	150	150	150	150

Analytical method development

Preparation of standard solution for standard graph

100 mg of Simvastatin was dissolved in methanol in a 100 ml volumetric flask and the solution was made up to the mark with methanol [13].

Procedure

The standard solution of Simvastatin was subsequently diluted with 0.1 N Hydrochloric acid to obtain a series of dilutions containing 2, 4, 6, 8 and 10µg of Simvastatin in 1 ml solution and the absorbance of these solutions was measured at 238nm in spectrophotometer (UV spectrophotometer) against corresponding blank [14].

The calibration curve for the estimation of Simvastatin was constructed by plotting linear best fit between the concentration of Simvastatin and the corresponding mean absorbance values [15].

Evaluation of tablets

Weight variation test

To study weight variation twenty tablets of the formulation were weighed using a electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

Drug content

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1 N HCl with 0.5% w/v SLS, the drug content was determined measuring the absorbance at 285 nm after suitable dilution using a Systronics UV/Vis double beam spectrophotometer.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Thickness

The thickness of the tablets was determined by using vernier calipers. Five tablets were used, and average values were calculated.

Friability Test

The friability of tablets were determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The % friability was then calculated by **$\%F = 100 (1-W_0/W)$**

% Friability of tablets less than 1% are considered acceptable [16].

In vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag time method described by Dave B.S.The tablets were placed in 900 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

In Vitro dissolution studies

The release rate of Simvastatin from floating tablets was determined using United States Pharmacoapoeia (USP) XXIV dissolution testing apparatus II (paddle method). The samples diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 238 nm using a Systronics UV/Vis double beam spectrophotometer [17].

Compatibility studies

Drug- excipient compatability studies by IR spectroscopsy

The FTIR spectroscopic studies were carried out between drug and polymer physical mixtures. The FTIR was carried out for Simvastatinand HPMC K100M, xanthan gum and guar gum, pure drug, tablet

formulation. The results obtained by the physical mixtures compared with the standard [18].

RESULTS AND DISCUSSION

The effect of various formulation factors such as concentrations of cellulose polymers, different gums and effervescent agent on floating properties and drug release kinetics were studied to optimize the formulation. The floating lag time mainly depends up on the concentration of effervescent agent present in the matrix. In the present study sodium bicarbonate was used as effervescent agent, as it is cheap and safe.

Table: 3. Calibration curve for the estimation of Simvastatin in 0.1N HCl

Concentration (µg/ml)	Absorbance at 238 nm
0	0
5	0.124
10	0.242
15	0.323
20	0.402
25	0.539
30	0.654

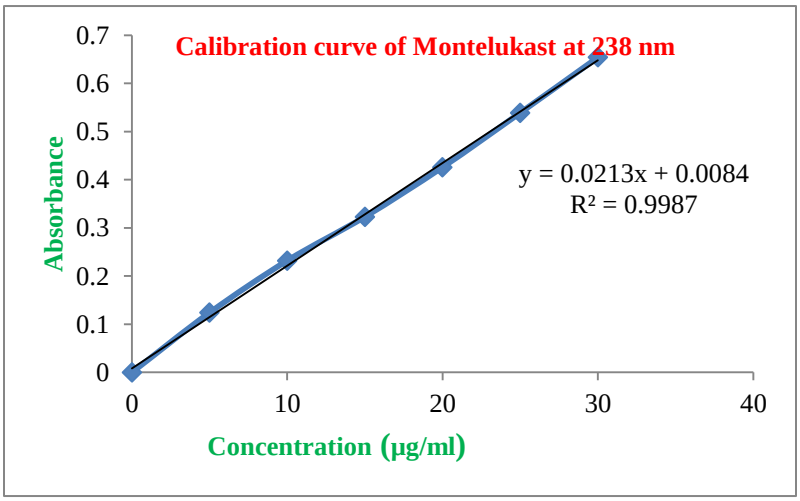

Fig: 1.Standard plot of Simvastatin at 238 nm

Table: 4: Physical parameters of the prepared formulations

Formulation	Compressibility Index	Angle of repose	Hausner ratio
F1	13.25±0.34	22.25±0.12	1.18±0.82
F2	18.59±0.12	21.16±0.31	1.38±0.54
F3	15.52±0.14	36.52±0.93	1.24±0.78
F4	17.86±0.25	28.56±0.34	1.18±0.56
F5	14.29±0.32	22.85±0.67	1.23±0.38
F6	17.84±0.54	21.43±0.89	1.16±0.32
F7	19.58±0.43	23.45±0.41	1.32±0.93
F8	15.56±0.61	22.47±0.62	1.16±0.26

F9	14.78±0.28	26.89±0.64	1.15±0.46
F10	17.42±0.32	27.45±0.15	1.27±0.62
F11	18.56±0.36	22.51±0.41	1.35±0.39
F12	14.28±0.53	21.85±0.62	1.26±0.20

Table: 5. Evaluation of post compression parameters

Batch No.	Average weight (mg)	Hardness (kg/cm^2)	Friability (%)	D.T (min)	Drug content (%)
F1	148.23±0.72	4.23±0.271	0.20	1.7	99.1
F2	149.62±0.56	4.61±0.268	0.12	1.5	99.7
F3	150.71±0.76	4.52±0.36	0.18	1.2	98.23
F4	149.25±1.42	4.73±0.361	0.16	1.5	99.62
F5	151.43.±0.96	4.76±0.213	0.13	2.4	97.27
F6	150.70±0.37	5.85±0.301	0.23	1.10	99.5
F7	148.52±0.18	4.88±0.310	0.20	1.4	101.4
F8	149.96±1.21	4.52±0.213	0.19	1.5	97.9
F9	150.95±1.32	4.36±0.403	0.20	1.3	98.8
F10	149.91±1.44	4.95±0.415	0.18	2.8	99.97
F11	151.84±1.51	4.11±0.353	0.18	1.4	99.2
F12	148.77±1.67	5.17±0.347	0.17	1.5	101.2

Table 6: Cumulative % release of formulations F1-F4

Time (hrs.)	F1±SD	F2 ±SD	F3±SD	F4±SD
0.25	38.93±0.51	24.96±0.65	19.87±1.23	6.76±0.54
0.50	45.34±0.45	32.32±.84	24.05±1.98	18.86±0.84
0.75	55.87±0.95	40.02±0.94	38.45±0.98	24.67±0.38
1	65.08±0.45	54.98±0.97	42.99±0.76	39.97±0.32
2	81.90±0.62	65.04±0.76	59.94±0.46	52.45±0.39
4	98.56±0.72	85.43±0.49	62.54±0.59	60.66±0.76
6	---	97.67±0.39	78.09±0.93	77.76±0.49
8	---	---	99.86±0.49	86.12±0.96
10	---	---	---	98.34±0.67
12	---	---	---	---

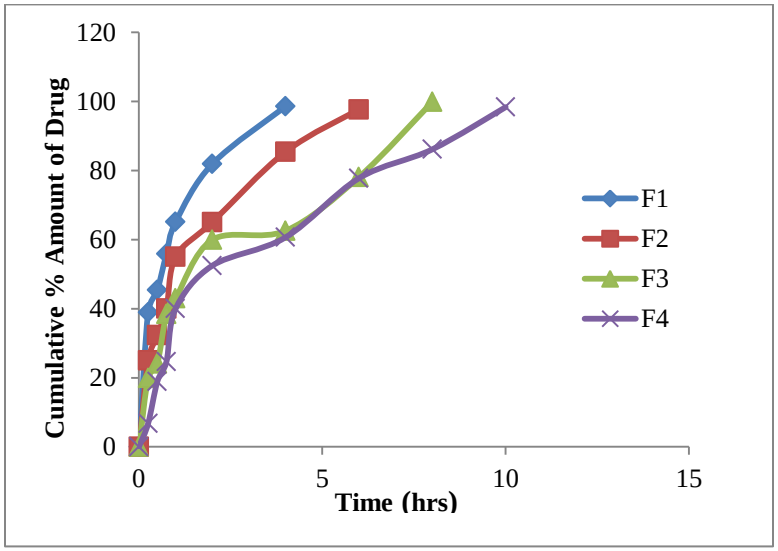

Fig 2: Comparative dissolution profiles of F1-F4

Table 7: Cumulative % release of formulations F5-F8

Time (hrs)	F5±SD	F6 ±SD	F7±SD	F8±SD
0.25	35.92±0.31	26.26±0.18	15.82±1.13	9.27±0.88
0.50	9.74±0.73	30.52±0.52	20.05±1.98	12.26±0.18
0.75	55.14±0.35	49.20±0.25	26.24±0.98	29.47±0.52
1	69.10±0.25	63.18±0.24	39.18±0.76	35.92±0.32
2	72.70±0.23	70.04±0.76	58.84±0.24	47.25±0.49
4	97.15±0.45	89.29±0.19	68.52±0.62	52.33±0.54
6	---	96.77±0.32	89.10±0.45	70.25±0.60
8	---	---	97.82±0.29	78.69±0.72
10	---	---	---	88.24±0.56
12	---	---	---	97.23±0.66

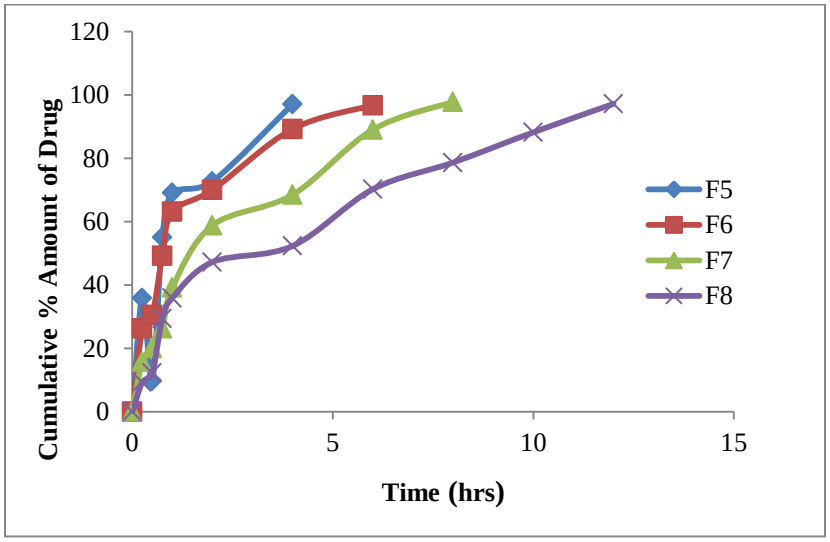

Fig 3: Comparative dissolution profiles of F5-F8

Table: 8. Cumulative % release of formulations F9-F12

Time (hrs)	F9±SD	F10 ±SD	F11±SD	F12±SD
0.25	13.47±0.47	10.96±0.65	5.87±1.52	3.76±0.32
0.50	20.34±0.45	19.32±0.84	15.25±1.92	9.86±0.58
0.75	36.87±0.95	32.02±0.94	28.45±0.48	20.67±0.88
1	40.08±0.45	39.98±0.97	36.99±0.82	29.97±0.93
2	63.90±0.62	58.04±0.76	45.94±0.46	32.45±0.48
4	78.56±0.72	69.43±0.49	58.54±0.59	39.66±0.77
6	84.96±0.23	79.67±0.39	69.09±0.93	49.76±0.29
8	96.29±0.54	85.0±0.59	76.86±0.49	59.12±0.71
10	---	97.03±0.98	89.02±0.58	67.34±0.52
12	---	---	99.32±0.69	75.56± 0.95

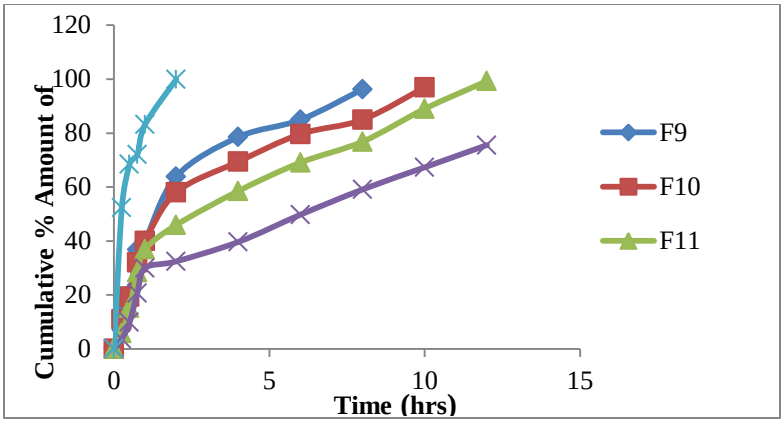

Fig.4. Comparative dissolution profiles of F9-F12 & Pure Drug

Drug release kinetics

The drug release profiles of different GFDDS were fitted to various curve fitting approaches of model dependent methods like Zero Order Model, First Order Model, Higuchi Model, Erosion Model and Pappas equation. The values of correlation coefficients (r) obtained by fitting the data to four popular release models are tabulated.

Table: 9. Drug release kinetics of prepared floating formulations (dependent model method)

	Correlation Co-efficient (r) value				Korsemeyer - Peppas	
Formulation	**Zero order**	**First order**	**Higuchi's**	**Erosion**	**r value**	**n value**
F1	0.744	0.983	0.596	0.733	0.984	0.353
F2	0.835	0.97	0.613	0.826	0.853	0.345
F3	0.863	0.936	0.615	0.855	0.954	0.441
F4	0.891	0.894	0.709	0.886	0.911	0.630
F5	0.703	0.946	0.638	0.698	0.441	0.558
F6	0.759	0.949	0.590	0.826	0.921	0.427
F7	0.899	0.952	0.694	0.893	0.973	0.549
F8	0.903	0.924	0.703	0.898	0.925	0.569
F9	0.840	0.967	0.671	0.834	0.943	0.556
F10	0.850	0.935	0.667	0.844	0.935	0.547
F11	**0.981**	**0.873**	**0.735**	**0.896**	**0.900**	**0.615**
F12	0.912	0.971	0.734	0.906	0.883	0.646
Pure Drug	0.84	0.730	0.700	0.921	0.986	0.311

Drug-polymer compatibility studies

IR spectroscopic studies

Simvastatin pure drug and simvastatinand polymer physical mixture, optimized tablet formulation were subjected to IR spectroscopic studies to check the compatability among them.

No prominent difference was observed in the IR peaks of Simvastatin+ HPMC 100 K physical mixtures and optimized formulations upon comparison with the peaks of drug and polymer alone, which may considered that Simvastatinand HPMC K100M are compatible enough without any interactions.

SUMMARY AND CONCLUSION

Retention of drug delivery systems in the stomach prolongs overall G.I. transit time, resulting in improved oral bioavailability of the drugs. Various approaches have been developed to retain the dosage form in the stomach. Gastric floating drug delivery systems offer numerous advantages over other gastric retention systems. There are no reports on the formulation of gastric floating drug delivery systems of montelukast. Hence, in the present investigation, GFDDS of simvastatin were developed with

hydrophilic polymers like HPMC K100M, xanthan gum and guar gum to deliver simvastatin to the upper parts of the small intestine in **a** controlled manner to improve its bioavailability. The GFDDS of simvastatin were developed in the form of tablets comprising of an effervescent agent. The GFDDS of simvastatin prepared from all the polymers were found to be of good quality fulfilling all the official and other requirements of compressed tablets.

The GFDDS of simvastatin prepared from HPMC remained intact and the compactness of the tablet was not affected during the *in vitro* dissolution test. It was found that the drug release from the GFDDS of simvastatin mainly depended upon the concentration of polymer present in the GFDDS for all the twelve formulations. By increasing the concentration of the polymer, decreased dissolution rates were obtained for the all the polymers. The slow rate of polymer hydration and the presence of effervescent agent caused a burst release initially.

The dissolution data were fitted to four popular release models such as zero-order, first-order, diffusion and erosion equations to determine the release mechanism. The correlation coefficients and the slope values from Higuchi plots indicated that the release mechanism followed diffusion and erosion with zero order kinetics. The results of the present study thus clearly indicated that GFDDS for simvastatin were successfully formulated by using different grades of hydrophilic polymers such as HPMC K100, xanthan and guargum.

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