International Journal of Drug Delivery 4 (2012) 175-183

http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

Development and evaluation of gastro retentive floating tablets of anti-hyperlipidemic drug

Gowda DV[1*], Raghunandan V[1], VasanthKumar Pai[2], CRS Lakshmi[3], Mohammed S Khan[1], Shivaprasd Bhat[3],

*Corresponding author:

Gowda D.V

[1*]Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Sri Shivarathreeshwara Nagar, Mysore-570015, Karnataka, India.
[2]Department of Industrial Chemistry, Kuvempu University, Shankara Ghatta, BR Project, Shiomoga-577201, Karnataka, India.
[3]Department of Pharmaceutics, Naragund College of Pharmacy, Bangalore -570085, Karnataka, India.

Abstract

The aim of the present study was to develop Gastro retentive effervescent floating tablets (GREFT) containing 20 mg of simvastatin were developed by direct compression method using HPMC K4M, HPMC K15M, HPMC K100M with different drug to polymer ratio. Tablets were evaluated for their physical characteristics, *viz.*, hardness, friability, drug content and floating properties. Further, tablets were studied for *in vitro* drug release characteristics for 12 h. The tablets exhibited controlled and prolonged drug release, with optimum hardness, consistent uniformity in weight and low friability. The formulation with F2 (HPMC K100M 1:3 ratio) showed 85.83 % drug release at the end of 12 h and exhibited optimum floating lag time. A decrease in release rate of the drug was observed on increasing polymer ratio and also by increasing viscosity grades of the polymer (HPMC). Drug release from effervescent floating matrix tablets was sustained over 12 h with buoyant properties. DSC study revealed that there is no drug excipient interaction. Based on the release kinetics, all formulations best fitted the Higuchi, first-order model and non-Fickian as the mechanism of drug release. Optimized formulation (F9) was selected based on the similarity factor (*f*2) (71.32) and *invitro* dissolution was used in radiographic studies by incorporating BaSO4. *In vivo* X-ray studies in human volunteers showed that the mean gastric residence time was 5.4 ± 0.32 h.

Keywords: Simvastatin, Direct compression, HPMC K4M, HPMC K15M,HPMC K100M.

Introduction

Effervescent floating drug delivery systems generate gas (CO_2), thus reduce the density of the system and remain buoyant in the stomach for a prolonged period of time and released the drug slowly at a desired rate [1]. The gastro retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability [2]. Controlled release (CR) dosage forms have been extensively used to improve therapy with several important drugs. However, the development processes are faced with several physiological difficulties such as the inability to restrain and localize the system within the desired region of the gastrointestinal tract and the highly variable nature of the gastric emptying process. This variability may lead to unpredictable bioavailability and time to achieve peak plasma level. On the other hand, incorporation of the drug in controlled release gastro retentive forms (CR-GRDF) which can remain in the gastric region for several hours would significantly prolong the gastric residence time of drugs and improve bioavailability, reduce drug waste, and enhance the solubility of drugs that are less soluble in high pH environment. Gastro retention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastro retention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients [3]. Simvastatin is anti hyper lipidemic Simvastatin belong to the category of statin which inhibits the enzyme HMG-CoA reductase. HMG-CoA reductase catalyses the conversion of HMG-CoA to mevalonate, the rate limiting step in de novo cholesterol synthesis. Competitive inhibition of this enzyme by Simvastatin decreases hepatocyte cholesterol synthesis. The associated reduction in intracellular cholesterol concentration induces LDL-receptor expression on the hepatocyte cell surface. Which results in increased extraction of LDL-C from the blood and decreased circulating LDL-C concentration? Simvastatin also have beneficial effects on other lipid parameters including increase in high-density lipoprotein cholesterol (HDL-C) concentration and decreases in triglyceride concentration. Secondary mechanism by which simvastatin may reduce levels of atherogenic lipoproteins include inhibition of hepatic synthesis of apolipoprotein B100 and a reduction in the synthesis and secreation of triglyceride-rich lipoproteins. In addition, simvastatin may excert beneficial

cardiovascular effects independent of their lipid-modifying properties. These pleiotropic properties may be explained by inhibition of synthesis of nonsteroidal isoprenoid compounds, which are also produced from mevalonic acid and include improvement of endothelial cell function, modification of inflammatory responses and reduction of smooth muscle cell proliferation and cholesterol accumulation [4]. Side effects produced by the drug are abdominal pain, diarrhea, indigestion, and a general feeling of weakness. Rare side effect include joint pain, memory loss, and muscle cramp. Cholestatic hepatitis, hepatic cirrhosis, rhabdomyolysis and myosistis have been reported in patients receiving the drug chronically. Grapefruit juice inhibit intestinal CYP3A4 enzyme. This in turn slows metabolization of simvastatin and resulting in higher plasma levels of drug. Due to risk of toxicity patients taking simvastatin should avoid intake of grapefruit and grapefruit containing products [5]. Simvastatin has absorption window in upper G.I. tract, and as result display low bioavailability [6]. Simvastatin is difficult to formulate in to sustained release dosage forms because on arrival to colon (or even before) its absorption is diminished or nonexistent, In the present investigation efforts were made to increase the residence time of simvastatin at or above the absorption window through preparation of gastro retentive tablet considering the fact that it is stable under gastric condition [7].

The purpose of this research is to prepare gastro retentive effervescent floating tablet consisting of polymers HPMC K4M, HPMC K15M, HPMC K100M and Simvastatin drug, by direct compression method and to evaluate their gastro-retentive and controlled-release properties. The effect of various formulations and process variables on the in- *vitro* floating behavior, and *in- vitro* drug release was studied.

Materials and Methods

Materials

Simvastatin was a generous gift from Biocon India, Bangalore, India, HPMC K4M, HPMC K15M, HPMC K100M were obtained from Colorcon Asia Private Limited (India) and Acetonitrile (AR) was obtained from Merck India Ltd. Mumbai, India. All excipients were of USP/NF grades and all other chemicals used were of analytical grades.

Method

Preformulation studies

The angle of repose of powder blend was determined by the funnel method. Both loose bulk density and tapped bulk density were determined. Tapping was continued until no further change in volume was noted. Total porosity was determined by measuring the volume occupied by a selected weight of a powder and the true volume of the powder blend. Hausner ratio indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density. Compressibility index is an important measure that can be obtained from the bulk and tapped densities[8].

Fourier transform- infrared spectroscopic analysis (FT-IR)

FTIR spectra of pure drug and formulation with drug were obtained using KBr pellet method (applying pressure of 6000 kg/cm^2). Spectral measurements were obtained by powder diffuse reflectance on a FTIR spectrophotometer (Shimadzu, Model 8400S, Japan) in the wave number region of 400-4000 cm^{-1} to study drug excipient interactions if any[9].

Differential scanning calorimetry (DSC)

DSC studies (Du Pont thermal analyzer with 2010 DSC module) were carried out to study the thermal behaviors of pure drug and formulation with drug. Calorimetric measurements were made with the help of an empty cell (high purity alpha alumina disc) as the reference. The instrument was calibrated using high purity indium metal as standard. The DSC scans of the samples were recorded in nitrogen atmosphere at a heating rate of 10 °C/min [10].

HPLC10: Chromatographic conditions

Column : Supelcosil C_{18} 33mmX4.6mm, 3µm or equivalent Detection : UV-VIS Wavelength : 238nm,Flow rate: 3.0mL/min, Injection volume: 5µL, Run time: 15.0 min.Filtered and degassed mixture of acetonitrile and dilute phosphoric acid (50:50) was prepared. The solution was filtered through 0.45µm membrane and degassed before using.5µL of standard preparation was injected in replicate (6 injections) and the chromatograms were recorded. 5µL of the test preparation was injected in duplicate and the chromatograms were recorded. The sensitivity of the system was adjusted so that the height of the principle peak in chromatogram obtained is at least 20% of the full scale of the recorder.

Preparation of effervescent tablets

Effervescent Floating tablets containing simvastatin were prepared by direct compression technique using varying concentrations of different grades of polymers with Sodium bicarbonate and citric acid. All the ingredients were accurately weighed and passed through different mesh sieves (#40) accordingly. Then, all other ingredients were blended uniformly in glass mortar. After sufficient mixing of drug as well as other components, tablets were compressed using rotary tablet machine (Rimek mini press -1, 10 stations 8 mm concave punches, Karnavati Engineering Ltd, Mehsana, Gujarat). The weights of the tablets were kept constant for all formulation

Evaluation of effervescent floating tablet formulations

Hardness, Friability & Weight variation

Hardness of the tablets was tested using a Monosanto hardness tester. Friability of tablets was determined in Roche friabilator. Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. The results are given in table no. 2.

X-ray diffractometery (XRD)

X-ray diffraction patterns of pure simvastatin and drug loaded tablet (F9) were recorded using (Phillips PW 1710, Tokyo, Japan) X-ray diffractometer with a copper target, voltage 40 Kv, current 30 MA at a scanning speed of 0.30 °C/min.

In vitro buoyancy

The *in vitro* buoyancy was determined by floating lag time, per the method described by Rosa *et al* [11]. The tablets were placed in a 100 ml beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface of time the dosage form constantly remained on the surface of medium was determined as the total floating time.

Drug content

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to average weight was added in 100ml of 0.1N hydrochloric acid, followed by stirring for 30 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured HPLC.

Determination of swelling index

Floating matrix tablet was introduced into basket type dissolution apparatus containing 900mL of 0.1N HCl (pH 1.2 at 37^{0}C) at 100rpm. The tablets were removed at definite time intervals and swollen weight of each tablet was determined . Swelling (%) (%) was calculated [12].

Stability studies

Stability studies were conducted for the optimized formulation F9. To assess their stability with respect to drug content after storing at 40°C/75% RH for 3 months was seen.

In vitro drug release

The release rate of Simvastatin from floating tablets was determined using *United States Pharmacopeia* (USP) Dissolution Testing Apparatus 2 (paddle method; Veego Scientific, Mumbai, India). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at regular intervals and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitably, resultant solution was measured HPLC. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Drug release kinetics

The rate and mechanism of drug release was analyzed by fitting the dissolution data into several mathematical models [13,14]. Dissolution profiles were compared with the similarity factor using the theoretical release profile as a reference[15]. Similarity factor (*f2*) is a logarithmic, reciprocal square root transformation to the sum of squared errors. If *f2* value is between 50 and 100, the two dissolution profiles are considered to be similar.

In vivo X-ray studies

The *in vivo* X-ray studies were approved by the Institutional Human Ethical Committee of Nargund College of Pharmacy, Bangalore, India. The study was performed on 3 healthy male human volunteers, weighing between 50 and 63 kg and in an age group of 22 ± 2 years. Before participation in these studies, a written consent was obtained from the volunteers and an expert radiologist and a physician supervised these studies. F9 was modified by adding 20 mg of X-ray grade barium sulfate (20 mg of lactose was replaced). After overnight fasting, the volunteers were fed low calorie food and the tablet was given to every subject with 200 mL water. After one hour of tablet ingestion, a glass of water was given to the subject. Gastric radiography was done after 1, 2, 4 and 6 h. The mean gastric residence time was calculated.

Results and Discussion

Pre formulation parameters data were presented in Table 2 and all the obtained values are well within the limit.

FTIR Studies

From the FTIR studies (Fig.1), the characteristic bands for important functional group of pure drug simvastatin and simvastatin containing formulation (F9) was identified. It was observed that 3546 cm-1 due to Free O-H stretching, 2924 cm-1 due to Methylene C-H asymmetric stretching, 1697 cm-1 due to Ester C=O stretching, 1268 cm-1 due to Lactone – C-O-C bend stretching, 1164 cm-1 due to Ester –C-O-C- bending and 1072 cm-1 due to secondary alcohol c-o stretching. FTIR spectra showed that the characteristics bands of simvastatin were not altered after successful encapsulation without any change in their position, indicating no chemical interactions between the drug and carriers used. A comparison and interpretation of this region in our spectra agrees with their conclusions [9].

DSC Studies

DSC studies were performed on pure drug and simvastatin containing formulation (F9) mixture exhibits a sharp endothermic peak at 143.74°C presented in Fig. 2. It was observed that presence of a endothermic peak of the drug at 143.01°C in the drug

simvastatin containing formulation (F9) indicates, that the drug is uniformly distributed in the mixture. The peak intensity corresponding to the melting of simvastatin decreased in the thermograms of simvastatin containing formulation (F9) mixture [9].
The effervescent floating tablets of simvastatin were formulated in ten different batches F1 to F9 by using hydrophilic polymers HPMC K4M,HPMC K15M, HPMC K100M along with effervescing agent sodium bicarbonate and citric acid. All the formulations were prepared by direct compression method. The prepared tablets of all the formulations were evaluated for physical characters like tablet hardness, friability, weight variation buoyancy lag time, total floating time, drug content, *in-vitro* drug release. The main aim was to optimize the formulation for 24 h *in-vitro* release and total floating time to more than 24 h.
The measured hardness of tablets of each formulation ranged between 4.2 to 4.4 kg/cm^2 presented in table 2. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ± 5% of the weight. The content uniformity of the tablets were well within the Pharmacopoeial limits.

X-ray diffraction studies

X-ray diffraction patterns revealed the crystalline nature of pure simvastatin. The X-ray diffractogram of simvastatin showed number of sharp and intense peaks presented in Fig.3. The diffractogram of simvastatin loaded matrix tablet (F9) showed broad peaks with low intensity. This may be attributed to the incorporation of simvastatin between parts of the lattice of the HPMC K100M , leading to a change in the degree of crystallinity of the simvastatin. Increase in peak width was observed in XRD pattern of simvastatin loaded matrix tablets (F9).
8 h, F4 BLT of 120sec and TFT of < 8h, F5 BLT of 119 sec and TFT of <10 h, F6 BLT of 116 sec and TFT of <10 h, F7 BLT of 114 sec and TFT of >12 h, F8 BLT of 112 sec and TFT of >12 h, F9 BLT of 110 sec and TFT of >12 h. Formulation F9 containing HPMC K100M showed good BLT of 110 sec and TFT of more than 12 h, presented in Fig 4. In this study, penetration of water into tablets with high viscosity HPMC K4M was slow, causing increasing the gel formation and subsequent increasing in the floating lag time and decreased total floating duration (>24 hrs) compared to the tablets prepared with K4M and K15M. With the exception of formulations F1 to F4, all the formulated tablets were buoyant less than 8h. Different grades of HPMC (K4M, K10M & K100M) were used as swellable polymers. HPMC was chosen because it is widely used as low-density hydrocolloid system, upon contact with water, a hydrogel layer would be formed to act as a gel boundary for the delivery system [16]. Various grades of HPMC were reported to have a duration of buoyancy of more than 12 h in the simulated meal medium, as well as in distilled water [17]. Our focus was on the floatability of the dosage form, so the HPMC concentration was increased throughout the experimental design. As stated above, different viscosity grades of HPMC show good floatability

Drug Content

USP specifies that Simvastatin tablets contain not less than 90.0 percent and not more than 110.0 percent of labeled amount of Simvastatin presented in Table 2. All the formulations complied with the USP specification.

Stability studies

Optimized formulation F9, after storing at 40±2°C /75±5% RH for 3 months showed no changes in the drug content.

In vitro drug release

Formulation F1, F4, F5 & F8 showed first hour release of 75.0478%, 80.308%, 71.420%, 77.313% respectively. These

Table 1: Formulations for simvastatin floating tablets

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Simvastatin	20	20	20	20	20	20	20	20	20
HPMC K4M	40	60	80		-	-	-	-	-
HPMC K15M	-	-	-	40	50	60	80	-	-
HPMC K100M	-	-	-	-	-	-	-	40	60
Sodium bicarbonate	20	20	20	20	20	20	20	20	20
Citric acid	5	5	5	5	5	5	5	5	5
Dicalcium phosphate	15	15	15	15	15	15	15	15	15
Lactose	100	80	60	100	90	80	60	100	80
Total weight	200	200	200	200	200	200	200	200	200

*All the quantities are in mg

Table 2: Pre formulation parameters

Formulation	Bulk density (g/cm^3)	Tap density (g/cm^3)	% Carr's Index	Hausner's ratio	Angle of repose (θ)
F_1	0.634	0.740	14.28	1.16	25.19
F_2	0.597	0.727	17.91	1.218	23.89
F_3	0.625	0.727	14.06	1.163	26.68
F_4	0.689	0.869	20.68	1.260	26.53
F_5	0.701	0.851	17.54	1.212	21.20
F_6	0.677	0.851	20.33	1.255	23.77
F_7	0.714	0.833	14.28	1.166	25.62
F_8	0.714	0.888	19.64	1.244	24.943
F_9	0.689	0.869	20.68	1.260	25.61

n=3

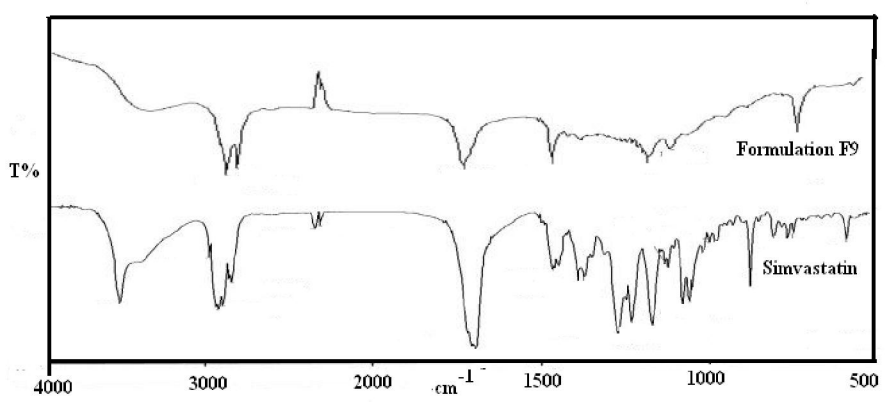

Figure 1. FTIR spectra of simvastatin and formulation F9

Table 3: Hardness, Friability, Weight variation of tablets of different formulation F1 to F9

Formulation	Hardness (Kg/cm^2)	Friability (%)	Weight Variation (mg)	Drug content (%)
F1	4.2 ± 0.21	0.82	204 ± 4%	98.89 ± 1.4 %
F2	4.3 ± 0.22	0.79	199 ± 3%	99.12 ± 3.2 %
F3	4.3 ± 0.31	0.82	202 ± 4%	97.99 ± 2.4 %
F4	4.4 ± 0.43	0.83	200 ± 5%	99.56 ± 3.5%
F5	4.2 ± 0.31	0.86	203 ± 4%	98.99 ± 1.4 %
F6	4.3 ± 0.33	0.76	203 ± 4%	99.32 ± 3.1%
F7	4.2 ± 0.25	0.80	202 ± 5%	98.88 ± 2.1%
F8	4.3 ± 0.15	0.74	202 ± 3%	99.23 ± 2.6%
F9	4.2 ± 0.11	0.88	203 ± 4%	98.35 ± 1.4 %

*Values are mean ± S.D

Table 4: Buoyancy Lag Time, Total Floating Time of formulations (F1toF9)

Formulation	Buoyancy LagTime (Sec)	Total Floating Time (h)	Similarity factor (f2)	Swelling Index (%)
F1	128	< 8	50.14	71.32
F2	126	< 8	56.13	97.98
F3	124	< 8	54.98	105.23
F4	120	<10	56.87	115.12
F5	119	<10	53.51	123.51
F6	116	<10	66.56	136.56
F7	114	>12	65.33	139.33
F8	112	>12	68.23	145.23
F9	110	>12	71.32	156.01

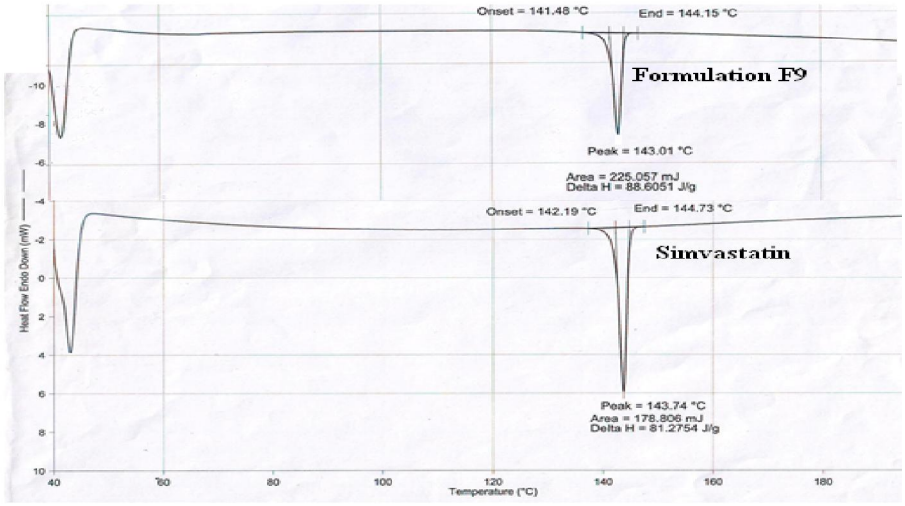

Figure 2. DSC thermograms of simvastatin and formulation F9

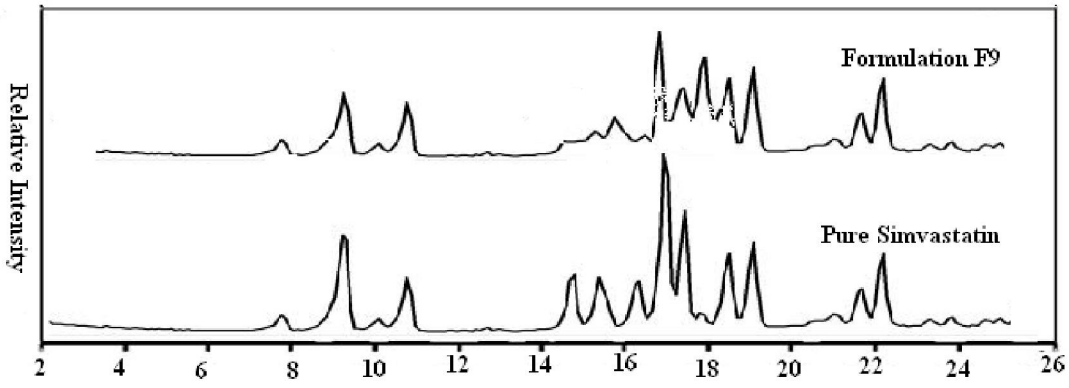

Figure 3. X-ray powder diffraction patterns of Pure simvastatin and formulation F9

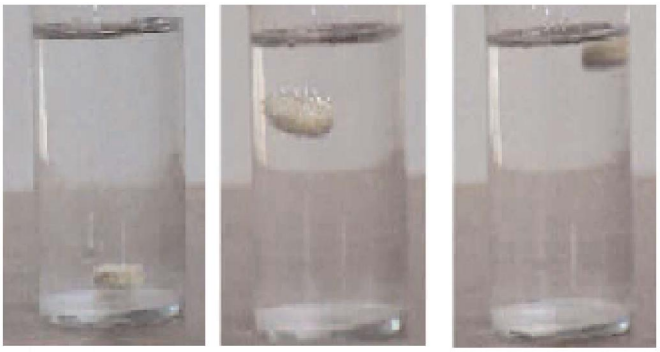

Figure 4: Floating behavior of Formulation F9

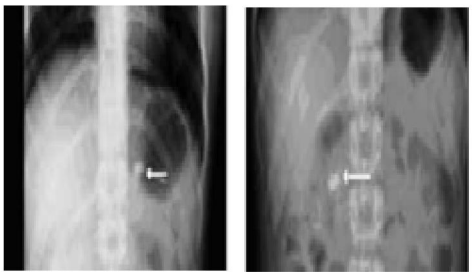

Figure 5. Radiographic photo images showing the presence of a BaSO4-loaded floating tablet (F9) in the stomach at different time periods. The tablet altered its position in the stomach.

In vitro buoyancy

Buoyancy lag time (BLT) and total floating time (TFT) of different formulation were noted, where F1 BLT of 128 sec and TFT of < 8 h, F2 BLT of 126 sec and TFT of < 8h, F3 of 124 sec and TFT of < formulations failed to maintain integrity. As soon as the tablet gets disintegrated, it forms a layer of polymer on the surface. So, this might be the reason for the high drug release in the first h. At the end of 5^{th} h, F1 formulation showed 92.31% release, F4 formulation showed 91.81% release at the end of 6^{th} h, F5 formulation showed release of 96.96 % at the end of 8^{th} h and F_8 shows 92.92 % at the end of 7^{th} h. This sustained release of drug from these formulations after a high drug release in the first hour might be due to the slow release of drug from the polymer matrix which was floating as a layer [18].

The reason for disintegration of tablet might be due to low amount of polymer and high amount of water soluble diluent lactose. Hence the tablet was not able to withstand the pressure generated by the release of CO_2 from the effervescent mixture. So, the formulations F_1, F_4, F_5, and F_8 failed as gastro-retentive dosage forms. Formulations F2, F3, F6, F7 & F8 showed first h release of 6.46 %, 7.012%, 8.920%, 5.917%, 12.18% respectively and maintained the integrity. The F9 formulation showed 12.18 % release in first h. This might be due to the pores formed due to release of carbondioxide, and also due to erosion. The release may also be due to the drug which was stuck to the surface of the tablet. This can be justified by swelling index and erosion index. The erosion index of F9 formulation at 2h is 20%. From 2^{nd} h to 12^{th} h, the release is sustained. This can be justified by swelling index which reaches maximum of 156% at 12^{th} h.

At the end of 12 h, F_2 formulation showed 62.76 % drug release, F_3 formulation showed 57.835% release, F_6 formulation showed 73.18 % release, F_7 formulation showed 45.653% release and F_9 formulation showed 85.76 % release. Though the F9 formulation

showed 12.18 % release in the 1st h, it is an advantage. Since the mechanism of absorption of Simvastatin is by passive diffusion, concentration gradient is very important. The drug release of 12.18 % will provide the concentration gradient and it is maintained by the sustained release of drug. Since the formulation F9 showed the best release of 85.76 % at the end of 12 h, it was selected as the optimized formulation. Release of the drug was faster with lower viscosity grades of HPMC K4M due to lower gel strength, less entanglement and smaller diffusion path length compared to higher viscosity grades of HPMCs. In all the formulations, polymer concentration greatly affected the release of the drug. The drug release rate was inversely proportional to the polymer concentration present in the matrix.

The first phase of the drug release profile depended on the concentration of the drug in the upper layer as an immediate dose and hence followed first-order release kinetics. In the second phase of the release (2-12 h), the diffusion coefficient was found to be 0.29 to 0.38. Based on the n value, the mechanism of Metaprolol Tartrate release from the floating layer followed Fickian transport. The optimized formulation was selected based on the similarity factor (*f2*) (14) value, The similarity factor (*f2*) of F9, when compared with the theoretical release profile, was found to be 71.32 (Table3), which was higher than for other formulations.

In vivo X-ray studies

After ingestion of the floating tablets developed by using barium sulfate, the duration of the tablet in the stomach was monitored by radiograms presented in Fig.5. Tablet was more or less at the same position in stomach for the first 2 h and moved slightly downwards and remained within the stomach till the end of 12h. The change in the location of the tablet at different time points suggested that the tablet did not adhere to the gastric mucosa. The mean gastric retention time was 5.4 ± 0.32 h.

Conclusion

The present study was conducted to develop an effervescent floating drug delivery system using three grades of HPMC polymer, in different concentrations. Optimized formulation F9 showed an excellent buoyant ability and a suitable drug release pattern. This could be advantageous in terms of increased bioavailability of Metaprolol Tartrate. The developed gastroretentive drug delivery system provides advantages of ease of preparation and sustained drug release for 12

Conflict of Interest

There is no conflict of interest

References

[1]. Talukder R, Fassihi R. Gastroretentive Delivery Systems: A Mini Review. Drug Dev Ind Pharm.2004; 30(10): 1019-28.

[2]. Garg R, Gupta GD. Progress in Controlled Gastroretentive Delivery Systems. Trop J Pharm Res. 2008 Sep; 7(3): 1055-66.

[3]. Patil JM, Hirlekar RS, Gide PS, Kadam VJ. Trends in floating drug delivery systems. J Sci Ind Res. 2006 Jan; 65: 11-21.

[4]. Corsini A, Bellosta S, Baetta R, Fumagalli R, Paoletti R, Bernini F. New insights into the pharmacodynamic and pharmacokinetic properties of statins. Pharmacology and Therapeutics.1999 Dec; 84(3): 413-428.

[5]. Schachter M. Chemical, Pharmacokinetic and Pharmcodynamic Properties of Statins: an update. Fundamental and Clinical Pharmacology. 2004 Nov; 19(1): 117-25

[6]. Prueksaritanot T, Ma B, Yu N. The human hepatic metabolism of simvastatin hydroxyl acid is mediated primarily by CYP3A and not CYP2D6. Br J Clin Pharmacol. 2003 July; 56(1): 120- 124.

[7]. Grozdanis MT, Hilfinger JM, Amidon GL, Kim S, Kijek P et al. Pharmacokinetics of the CYP3A substrate Simvastatin following administration of Delayed Versus Immediate release oral dosage forms. Pharmaceutical research. 25(7): 1591-1600.

[8]. Brittain H. Physical Characterization of pharmaceutical solids. Marcel Dekker .Inc. 1995.

[9]. Gambhire MS, Bhalekar MR, Gambhire VM. Simvastatin loaded Solid lipid nanoparticles: Formulation optimization using Box Behnken design, characterization and in vitro evaluation Cur Pharma Res 2011;1: 157 – 164.

[10]. Lucie Novakeva, Dalibor Satinsky, Petr Solich. HPLC method for the determination of simvastatin and atorva statin. Trends Anal Chem 2008 ; 27: 352 – 367.

[11]. Rosa M, Zia H, Rhodes T. Dosing and testing in-vitro of a bioadhesive and floating drug delivery system for oral application, Int. J. Pharm.1994; 105: 65–70.

[12]. Kendre PN. Oral Sustained Delivery of theophylline floating matrix tablets: Formulation and in-vitro evaluation. Int J PharmTech Res. 2010 Jan; 2(1): 130-9

[13]. Higuchi T. Rate of release of medicaments from ointment bases containing drugs in suspensions, Pharm. Sci. 1961;50: 874–875.

[14]. Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas N. A., Mechanisms of solute release from

porous hydrophilic polymers, Int. J. Pharm 1983;15: 25–35.

[15]. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers, Pharm. Acta Helv. 1985;60: 110–111.

[16]. Xu G, Sunada H. Influence of formulation change on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. Chem Pharm Bull (Tokyo). 1995;43:483 -487.

[17]. Ingani HM, Timmermans J, Moes AJ. Conception and *in vivo* investigation of peroral sustained release floating dosage forms with enhanced gastrointestinal transit. Int J Pharm. 1987;35:157 -164.

[18]. Moore JW, Flanner HH. Mathematical comparison of dissolution profiles, Pharm. Tech.1996; 20: 64–74.