Original Article

Development and Evaluation of Regioselective Bilayer Floating Tablets of Atenolol and Lovastatin for Biphasic Release Profile

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Abstract

This study was performed to design bilayer regioselective floating tablets of atenolol and lovastatin to give immediate release of lovastatin and sustained release of atenolol. Bilayer floating tablets comprised two layers, i.e immediate release and controlled release layers. The immediate release layer comprised sodium starch glycollate as a super disintegrant and the sustained release layer comprised HPMC K100M and xanthan gum as the release retarding polymers. Sodium bicarbonate was used as a gas generating agent. Direct compression method was used for formulation of the bilayer tablets. Accelerated stability studies were carried out on the prepared tablets inaccordance with ICH guidelines. Roentgenography was carried out to study the in vivo buoyancy of the optimized formulation. All formulations floated for more than 12 h. More than 90% of lovastatin was released within 30 min. HPMC K100M and xanthan gum sustained retarded the release of atenolol from the controlled release layer for 12 h. After stability tests, degradation of both drugs were found but the drugs, contents were found to be within the range. Diffusion exponents (n) were determined for all the formulations (0.53-0.59). The release of atenolol was found to follow a mixed pattern of Korsmeyer-Peppas, Hixson-Crowell and zero order release models. The optimized formulation was found to be buoyant for 8 h in stomach. Therefore, biphasic drug release pattern was successfully achieved through the formulation of floating bilayer tablets inthis study.

Keywords: Lovastatin; Atenolol; Floating; Regioselective; Bilayer tablets.

Introduction

Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract. Controlled/sustained release preparations using alternating routes have also been formulated but oral route still remains preferable (1). In recent years, peroral dosage forms for gastric retention have attracted more and more attention for their theoretical advantage in gaining control over the time and the site of drug release. This would be particularly valuable for drugs that exhibit an absorption window in the upper part of the small intestine. Various approaches have been used to prepare dosage forms for gastric retention (2). These systems mainly consist of swelling and expanding systems (3-5), floating capsules (6, 7), floating pellets (8) and floating granules (9). Gastric retention of the drugs provides such advantages as better delivery of the drugs with narrow absorption windows in the small intestinal region, and longer residence time in the stomach, which could be advantageous for local

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Table 1. Formulation of immediate release layer.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lovastatin	50	50	50	50	50	50	50	50	50
Tablettose 80	41	41	41	41	41	41	41	41	41
SSG	08	08	08	08	08	08	08	08	08
Magnesium stearate	1	1	1	1	1	1	1	1	1
Total	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

All the amounts are shown as milligrams.

action in the upper part of small intestine (10). The current investigation aims at development of regioselective floating bilayer tablets different release patterns of lovastatin and atenolol by using a gas generating agent. Atenolol is a cardios selective beta-1 adrenoceptor blocker devoid of intrinsic sympathomimetic and membrane stabilizing activity. It is poorly absorbed from the lower GIT, and the oral bioavailability has been reported to be 50% (11). The human jejunal permeability to atenolol and the extent of absorption is low (12). Thus, it seems that an increase in gastric retention time may increase the extent of absorption and bioavailability of the drug. Lovastatin, a HMG Co-A reductase inhibitor, is used for treatment of hyperlipidemia. The drug has a very short half life of 1.1-1.7 h with a very low bioavailability (13, 14). Hypertension and hypercholesterolemia frequently coexist and may require concomitant drug treatment. Safety and efficacy profile of lovastatin given in presence of antihypertensive medication has been evaluated by various researchers (15-18). In the present study, we have attempted to formulate a bilayer floating system of lovastatin and atenolol. The optimized formulation was then considered for in vivo buoyancy studies.

Experimental

Materials

Atenolol was obtained from CIPLA Ltd., (Mumbai, India). Lovastatin was a generous gift from Panacea Biotech (Chandigarh, India). HPMC K100M and xanthan gum (XG) were obtained as gift samples from Panacea Biotech (Chandigarh, India). Sodium starch glycollate (SSG), was obtained from Okasa Pharma Ltd., (Satara, India). Spray dried lactose (Tablettose 80) was received as a gift sample from Wockhardt Ltd., (Aurangabad, India). Other materials were purchased from commercial sources: magnesium stearate (Loba chemicals, Mumbai, India), di-calcium phosphate (S.D. Fine chemicals, Mumbai, India) and Sodium bicarbonate (Research lab, Mumbai, India).

Methods
Preparation of bilayer floating tablets

Bilayer floating tablets were prepared by direct compression using sodium starch glycolate as a superdisintegrant, and HPMC K100M and XG as the release controlling polymers, and sodium bicarbonate as a gas generating agent. The optimum concentrations of the above ingredients were determined under experimental conditions and on the basis of trial preparation of the tablets. Preparation of bilayer floating tablets had two steps:

1. Preparation of the controlled release layer: the ingredients (Table 2) were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min. to obtain uniform distribution of the drug in formulation. 300 mg of the powder mix was accurately weighed and fed into the die of single punch tablet press (Cadmach, Ahemedabad, India.) and compressed at 1.5 N compression force using 10-mm concave punches.

2. Preparation of immediate of release layer: the ingredients (Table 1) were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min to obtain uniform distribution of the drug in formulation. 100 mg of the powder mix was accurately weighed and manually fed into the die on controlled release layer and compressed at a compression pressure of 3 N using 10-mm

Table 2. Formulation of controlled release layer.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atenolol	50	50	50	50	50	50	50	50	50
Xanthan gum	60	90	120	---	---	---	15	30	45
HPMC K100M	---	---	---	60	90	120	30	30	30
Magnesium stearate	2	2	2	2	2	2	2	2	2
Sodium bicarbonate	15	15	15	15	15	15	15	15	15
Dicalcium phosphate	15	15	15	15	15	15	15	15	15
Tablettose 80	158	128	98	158	128	98	173	158	143
Total	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**

All the amounts are shown as milligrams.
Total weight of the single bilayer tablet= 400 mg

concave punches.

Floating characteristics

Floating characteristics of the prepared formulations were determined by using USP 23 paddle apparatus (20) (Electrolab TDT-06P, Mumbai, India) at a paddle speed of 50 rpm in 900 ml of a 0.1 N HCl solution (pH=1.2) at $37\pm0.2\,°C$ for 24 h. The time between the introduction of tablet and its buoyancy on the simulated gastric fluid (floating lag time) and the time during which the dosage form remain buoyant (floating duration) were measured. Also, the integrity of the tablets during the study was (matrix integrity) visually monitored.

Drug content

UV spectrophotometric method (21-23) was developed and validated for simultaneous estimation of atenolol and lovastatin from the prepared formulations as follows:

Atenolol

Twenty tablets were accurately weighed and the average weight was calculated. The tablets were then ground to a fine powder. An accurately weighed amount of the powder equivalent to 50 mg of atenolol was dissolved in methanol and volume was made to 100 ml. The solution was then filtered through a Whatmann filter paper No. 41. An aliquot of 1 ml was taken and diluted to 100 ml with methanol. For the assay of atenolol, the absorbance of the sample solution was recorded at 230 nm and 242 nm. The difference between the two values was taken as the final absorbance to quantify atenolol in the sample solution using a calibration curve. The calibration curve for atenolol was plotted using the absorbance values of 10 standard solutions of atenolol over a concentration range of 10-60 µg/ml.

Lovastatin

Twenty tablets were accurately weighed and the average weight was calculated. These tablets were then ground to a fine powder. An accurately weighed amount of the tablet powder equivalent to 50 mg of lovastatin was dissolved in methanol and volume was made to 100 ml. The solution was filtered through a Whatmann filter paper No. 41. An aliquot of 1 ml was taken and diluted to 100 ml with methanol. For the assay of lovastatin, a difference spectrophotometric method was developed and validated to eliminate the interference of atenolol absorbance in sample solutions. The calibration curve for estimation of lovastatin was obtained by plotting the difference of absorbance values at 237 nm and 276 nm for 10 mixed standard solutions containing 10-60 µg/ml of lovastatin against their concentrations.

Drug release

The release of atenolol and lovastatin from different formulations were determined using USP 23 paddle apparatus 2 (Electrolab TDT-06P, Mumbai, India) under sink conditions. The dissolution medium was 900 ml of a 0.1 N HCl solution (pH=1.2), at $37\pm0.2\,°C$ and the stirring speed was 50 rpm. For each formulation, the experiments were carried out in triplicate. The release data were analyzed to study the release

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Table 3. Evaluation of physicochemical parameters.

Formulation code	Drug content %±s.d.				Hardness (kg/cm²) n=10		Floating characteristics					
	Atenolol n=3		Lovastatin n=3				Lag time (min)		Floating duration (h)		Matrix integrity	
	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
F1	98.14±5.26	97.32±50.19	98.52±1.89	97.3±1	4±0.11	4.4±0.15	11	13	17	14	+	+
F2	101.96±5.1	97.32±5.19	99.75±3.82	99.14±3.81	3.9±0.15	4.3±0.12	9	11	19	18	+	+
F3	99.51±1.63	94.05±5.44	99.14±4.2	97.91±2.12	3.7±0.04	4.1±0.12	4	5	24	24	+	+
F4	98.96±3.09	97.87±2.45	97.91±3.8	96.07±1.06	3.8±0.11	4.2±0.14	15	16	15	15	+	+
F5	96.51±5	95.96±4.11	99.75±2.1	97.91±2.12	3.8±0.11	4. 3±0.15	11	13	16	14	+	+
F6	100.87±0.94	97.32±6.16	100.36±.67	98.52±1.8	3.9±0.12	4. 6±0.05	6	8	24	24	+	+
F7	99.78±0.94	96.78±4.79	100.9±2.8	100.98±1.06	3.7±0.08	4.6±0.15	14	15	14	13	+	+
F8	98.42±3.69	95.69±6.14	100.36±3.18	99.14±2.8	4±0.18	4.4±0.14	11	14	24	24	+	+
F9	98.69±2.83	96.78±10.1	99.75±4.6	97.3±4.61	4±0.10	4.5±0.02	5	8	24	24	+	+

a. before stability studies

b. after stability studies

+. very good

kinetics using zero order, Korsmeyer-Peppas and Hixson Crowell equations (24, 25).

Hardness

Hardness values of the prepared formulations were determined using Monsanto hardness tester (26). (n=10)

Stability

Stability studies were carried out according to ICH guidelines. All formulations were sealed in aluminium packaging coated inside with polyethylene, and samples were kept in humidity chamber at 40°C and 75% RH for 3 months. At the end of the period, samples were analyzed for drug content, floating characteristics, hardness values, and in vitro dissolution studies.

DSC studies

Thermal analysis was carried out using Mettler Toledo 821^e DSC (Switzerland). The tablet was ground to powder and a 1-2 mg sample was hermetically sealed in an aluminum pan and heated at a constant rate of 10°C/min, over a temperature range of 50-200°C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 20 ml/min.

Assessment of similarity factor

The similarity factor (f_2 factor) was used to compare dissolution profiles of atenolol before and after the stability studies. The in vitro release profiles of the formulations before the stability studies were considered as reference and the profiles after the stability studies were considered as test. The similarity factors were calculated using PCP Disso software. The f_2 factor is a logarithmic reciprocal square root transformation of the sum of squared error. The f_2 factor was used to quantitate the agreement between two dissolution profiles. Dissolution tests were conducted under the same conditions. The values of f_2 between 50 to 100 show similarity in in vitro release profiles (27).

$$f_2 = 50 \times \log\left\{ \left[1 + (1/n)\sum_{j=1}^{n}|R_j - T_j|^2 \right]^{-0.5} \times 100 \right\}$$

In vivo determination of buoyancy of the floating tablet using roentgenography

The optimized formulation F5 was studied with regard to buoyancy, using Roentgenography. Atenolol in formulation, was replaced with 50 mg barium sulfate (BaSo4) and the tablets were prepared as previously mentioned. The prepared tablets were taken to ten healthy human volunteers aged 30 to 33, after an overnight fasting and along with 100 ml of lemon juice. Roentgenograms were obtained at 30 min, 2 h, 4 h and 8 h after the administration. During

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Table 4. In vitro release profile.

Formulation code	% Atenolol released at 12 h		% Lovastatin released at 30 min		Similarity factor f_2
	%±S.D^a.	%±S.D^b.	%±S.D^a.	%± S. D^b.	
F1	107.58±1.56	104.36±3.2	99.48±1.05	98.87±3.14	69.77
F2	95.23±3.45	86.61±0.8	97.66±2.77	96.45±1.05	65.15
F3	85.56±0.78	79.4±1.22	97.06±1.82	95.24±1.82	53.86
F4	108.18±2.77	106.78±2.12	98.27±2.1	95.85±2.77	67.59
F5	97.89±1.68	94.56±3.49	98.87±3.14	96.45±2.77	69.86
F6	86.63±2.36	82.06±0.92	99.48±4.19	97.66±2.77	49.63
F7	110.5±2.11	108.14±1.22	98.27±2.77	97.06±3.14	64.07
F8	98.46±2.36	95.65±0.46	97.06±1.82	97.06±3.14	66.73
F9	88.49±2.4	82.88±0.86	100.08±2.77	99.48±2.77	55.1

a. before stability studies

b. after stability studies

+. very good

this, the volunteers were allowed to have normal movements. This study was carried out with the approval of the Institutional Ethical Committee.

Results

Floating characteristics

All formulations floated more than 12 h with a lag time of up to 15 min. During floating duration, formulations maintained matrix integrity (Table 3). Swelling of the tablets was observed, which gave floating ability to formulations. A 5% concentration of sodium bicarbonate was found to be optimum for obtaining low lag time and prolonged floating duration. Floating duration and lag time were found to be dependent

to the amounts of polymers incorporated in formulations

Drug content

Atenolol (96.51%-101.96%) and lovastatin (97.91%-100.98%) contents were found to be within the accept able range. Additives in formulations did not have any effect on drug content (Table 3).
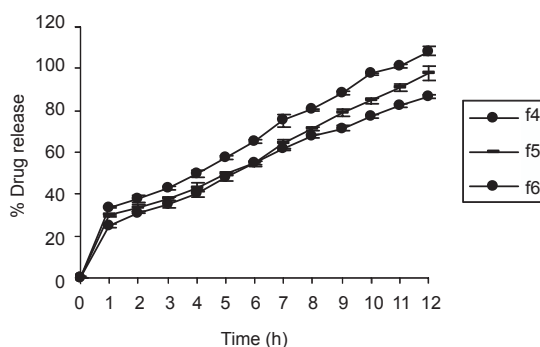
In vitro drug release
Atenolol

The release of atenolol was found to be a function of the polymer concentration. All formulations retarded the release of drug for 12 h (Table 4). The effect of xanthan gum at different
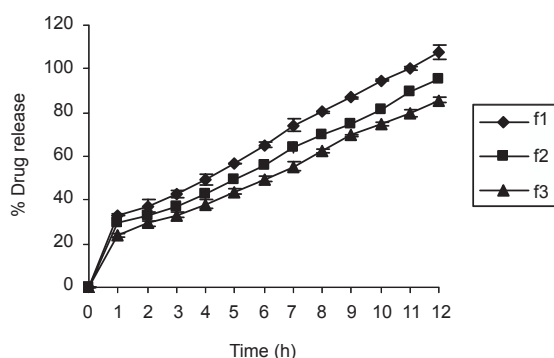
Figure 1. In vitro release profile of atenolol from formulations F1, F2 and F3 (with 20%, 30% & 40% of xanthan gum respectively).

Figure 2. In vitro release profile of atenolol from formulations F4, F5 and F6 (with 20%, 30% & 40% of HPMC K100M, respectively).

Table 5. Model fitting for atenolol.

Formulation code	Matrix		Zero order		Korsmeyer-Peppas			Hixson-Crowell		Best fit
	R	k	R	k	R	k	n	R	k	
F1	0.9614	23.5	0.9711	8.18	0.9673	18.99	0.59	0.9576	-0.04	Zero order
F2	0.9738	22.6	0.9592	7.83	0.9734	19.47	0.56	0.9803	-0.03	Hixson-Crowell
F3	0.9792	22.0	0.9493	7.71	0.9735	20.23	0.54	0.9854	-0.03	Hixson-Crowell
F4	0.9601	23.9	0.9711	8.2	0.9661	19.3	0.58	0.9417	-0.04	Zero order
F5	0.9694	23.10	0.9618	7.99	0.9704	19.77	0.56	0.9726	-0.04	Hixson-Crowell
F6	0.9884	23.5	0.9349	8.0	0.9832	21.53	0.53	0.9899	-0.03	Hixson-Crowell
F7	0.9791	24.7	0.9464	8.5	0.9804	22.47	0.53	0.9334	-0.04	Korsmeyer-Peppas
F8	0.9898	23.91	0.9333	8.2	0.9924	21.63	0.54	0.9852	-0.04	Korsmeyer-Peppas
F9	0.9912	23.6	0.9357	8.1	0.9947	20.82	0.55	0.9881	-0.04	Korsmeyer-Peppas

concentrations (ranging from 20% to 40%) on the release of atenolol from tablet matrices was studied. Figure 1 and Figure 2 show the drug release profile of drug from xanthan gum and HPMC K100M matrices, respectively (at different concentrations of polymer (20% to 40%). Figure 3 show the drug release profile from combined xanthan gum and HPMC K100M matrices (HPMC K100M: xanthan gum ratios 1:0.5, 1:1, and 1:1.5). It was also observed that xanthan gum retarded the drug release more than HPMC K100M. The diffusion exponent 'n' values (0.53-0.59) indicated that the release mechanism is non-fickian or anomalous transport. The release data were fitted to different kinetic models and based on correlation coefficients (R), the best fitted models were determined (Table 5). Formulations F1 and F4 followed zero order model while other formulations followed either

Korsmeyer-Peppas model or Hixson-Crowell model.

Lovastatin

The immediate release layer of the bilayer floating tablets disintegrated, and liberated lovastatin. All formulations liberated more than 90% of lovastatin content within 30 min (Table 4). A concentration of 8% of sodium starch glycollate was found to be optimum. Disintegration of the immediate release layer did not have any effect on characteristics of the controlled release layer.

Hardness

Hardness for all formulations was found to be between 3.7 to 4 kg/cm^2 and did not affect the floating characteristics and the drug release (Table 3).
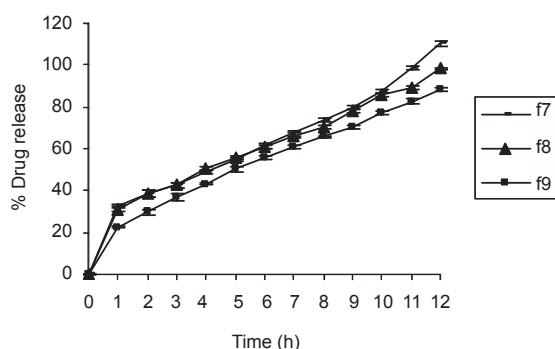
Figure 3. In vitro release profile of atenolol from formulations F7, F8 and F9 (with xanthan gum and HPMC K100M combinations in rations of 1:0.5, 1:1 & 1:1.5, respectively).
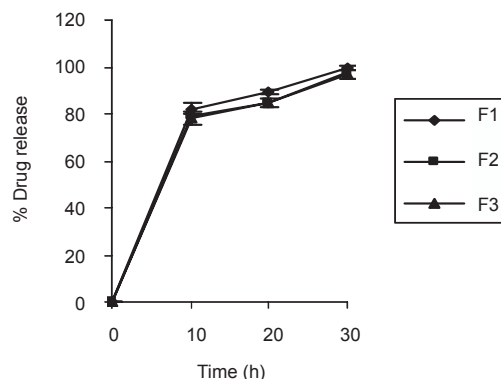
Figure 4. In vitro release profile of lovastatin from formulations F1, F2 and F3.

DSC studies

DSC curves showed that there was no any incompatibility between atenolol and lovastatin. In the combination DSC, one peak was obtained at 171°C for lovastatin and another at 154°C for atenolol. In the individual DSC studies of the drugs, lovastatin peak was obtained at 168°C and atenolol peak at 155°C. These peaks match the peaks reported in the literature for pure drugs (28, 29) (Figure 7).

Stability studies
Floating characteristics

The tablets under the stability studies showed increased lag time. All formulations floated for more than 12 h and showed good matrix integrity (Table 3).

Drug content

Atenolol (94.05%-97.87%) and lovastatin (96.07%-100.98%) contents of all formulations were found to be decreased compared to the original contents. Loss of atenolol and lovastatin was found to be upto 4%. This may be due to the drug degradation during the stability studies (Table 3).

Drug release
Atenolol

Decreased percent drug release was observed from all formulations compared to the original in vitro drug release data. However, no significant difference was observed between the release

pattern of bilayer tablets before and after the stability studies (Table 4).

Lovastatin

There was no significant effect on immediate release of lovastatin from the immediate release layer. The amounts of drug release from all formulations were found to be more than 90% within 30 min (Table 4).

Hardness

Hardness values of the bilayer tablets had been increased to 4.1 to 4.6 kg/cm^2. This may be due to the absorption of trace quantity of moisture during the accelerated stability studies. This increased hardness did not have any significant effect on drug release (Table 3).

Similarity factor

Similarity factors (f_2) for all formulations are shown in Table 4. All formulations except f_6 showed (f_2) value between 50 to 100 indicating similar release profiles of the formulations before and after stability studies. F6 showed a similarity value below 50, indicating dissimilar release profiles before and after the stability studies (Table 4).

In vivo determination of buoyancy of the floating tablet using roentgenography

Figure 8 shows the roentgenogram of a volunteer who was administered the buoyant tablet. After 8 h, the tablet was on the surface of the gastric juice (Figure 8).
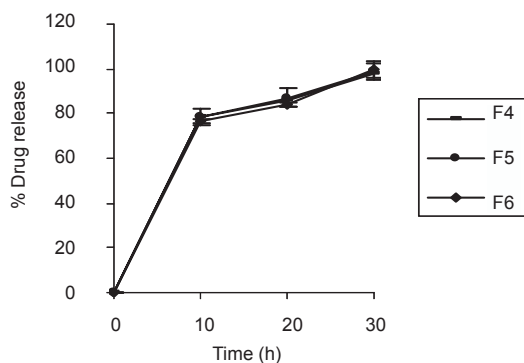
Figure 5. In vitro release profile of lovastatin from formulations F4, F5 and F6.
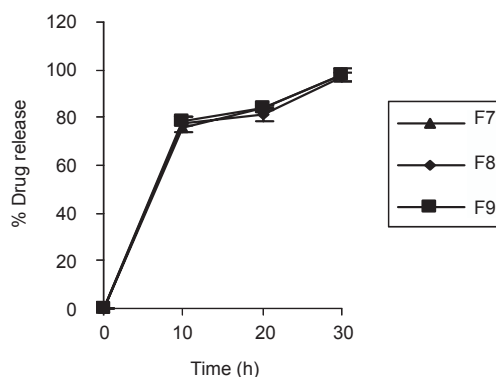
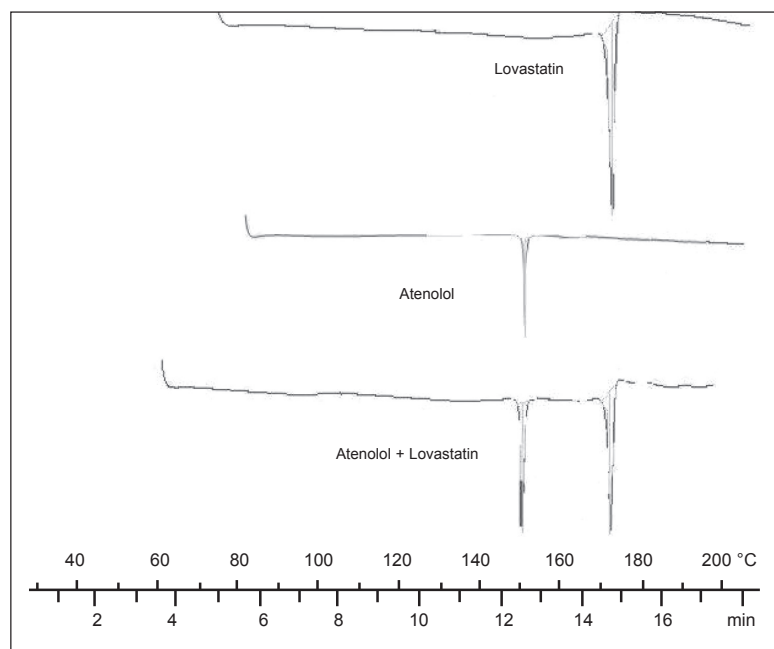**Figure 6.** In vitro release profile of lovastatin from formulations F7, F8 and F9.

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Figure 7. DSC combined thermogram of atenolol and lovastatin.

Discussion

On contact with 0.1 N HCl medium, the hydrochloric acid in medium reacted with the sodium bicarbonate in controlled release layer of the bilayer tablet, inducing CO_2 formation. The generated gas bubbles were trapped in the polymer matrix and were well protected by the gel formed by hydration of the polymers. A 5% concentration of sodium bicarbonate was found to be optimum to impart floating characteristics to the system. It was observed that sodium bicarbonate concentrations of sodium bicarbonate more than 5% led to fast reaction, and dispersion of the tablets. Hardness value upto 4 kg/cm² were found optimum for the system. The gel formed by polymers, alone or in combination, was effective for protection of the gas bubbles. Further more, an increase in bulk volume and the presence of internal voids in the dry center of tablet, i.e the porosity, made the tablet float on the test medium for more than 12 h. During floating, all formulations showed good matrix integrity, which may be due to the compactness of system. This is necessary to prevent the sweep of the tablet in lower parts of gastrointestinal tract during interdigestive myloelectric cycle (Phase I-Phase IV).

Uniform content of the drugs in formulations indicated the presence of labeled amounts of drugs. Additives in formulations did not have any effect on the active ingredients. Also, there was no incompatibility between the two drugs. This was further supported by DSC studies.

On immersion of bilayer tablets in the medium, the immediate release layer disintegrated liberating lovastatin with fine dispersion. The superdisintegrant, sodium starch glycollate, swelled by absorbing the liquid medium leading to disintegration of this layer without affecting the controlled release layer. 8% concentration, of sodium starch glycollate was found to be optimum; 10% concentration, disintegrated the layer but with formation of flakes rather than fine dispersion, which is undesirable for rapidly disintegrating tablets.

Formulations F1, F2 and F3 containing different concentrations of xanthan gum retarded the drug release as a function of polymer concentration (Figure 1). Xanthan gum, a hydrophilic polymer, upon contact with aqueous fluid is able to form quite viscous

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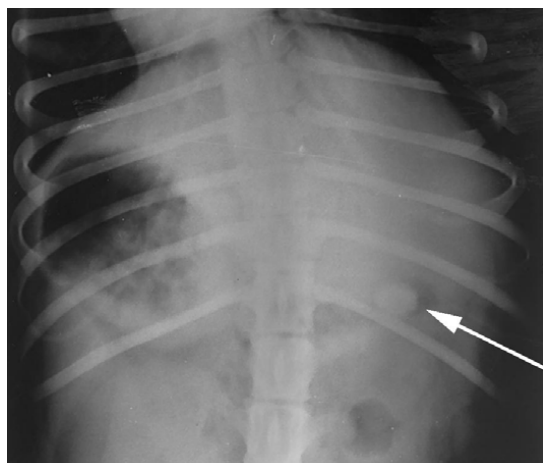
Figure 8. X ray photograph of a healthy volunteer after 8 h following administration of buoyant tablet (F5) containing BaSo$_4$.

gel, and hence retard the drug release from hydrophilic matrix. Formulations F4, F5 and F6 containing HPMC K100M as the polymer could retard the drug release for 12 h by formation of a viscous gel (Figure 2). Xanthan gum showed a stronger retardation of the drug release compared to HPMC K100M under identical experimental conditions. The release of the drug from xanthan gum matrices followed an almost time-independent kinetics while the release from HPMC K100M matrices followed time dependent kinetics (30-32). Under identical experimental conditions, the drug diffusivity in HPMC K100M gel is higher than in xanthan gum gel. This difference in hindered transport of drug molecules within the two polymers brings out the real cause for the reported higher release retarding ability of xanthan gum compared to a HPMC K100M. Formulations F7, F8 and F9 containing combinations of polymers did not show any synergistic retarding effect when compared to the individual polymer matrices (Figure 3). As concentration of xanthan gum was increased, keeping concentration of HPMC K100M constant (F8), more drug retardation was achieved. Further increase in xanthan gum concentration caused further increase in drug release retardation. With all formulations, a burst effect was observed, which could be due to the fact that the gel layer, which controls the release of the drug, needs some time to become effective (33) and also due to the dissolution of

atenolol from the surface of the tablets (34, 35). Yet, this effect was least with HPMC-containing formulations. This finding could be explained by the hydrophilic nature of HPMC. When the tablets are exposed to dissolution medium, the solvent penetrates into free spaces between the macromolecular chains of the polymer. After solvation of the polymer chain, the dimensions of the polymer molecule increase due to polymer relaxation by the stress of the penetrated solvent. This phenomenon is defined as swelling and is characterized by formation of a gel-like network surrounding the tablet. This swelling and hydration property of HPMC causes an immediate formation of a surface barrier around the matrix tablet, which reduces the burst release (24). Diffusion exponent 'n' value obtained (0.53-0.59) for all formulations indicate that the release mechanism was non fickian or anomalous transport of drug (coupled diffusion/polymer relaxation) (24). This can be explained by the fact that atenolol is a hydrophilic drug in a hydrophilic polymer matrix. The drug release from hydrophilic matrix is governed sequentially by the following processes: 1. hydration and swelling of the polymer which results in formation of a gel; 2. dissolution of drug in hydrated matrix/gel; 3. diffusion of drug molecule through that hydrated matrix; and finally 4. surface erosion and/or dissolution of that formed gel-matrix. Diffusion of drug was the main mechanism of drug release from hydrated matrix.

In stability studies, the increased lag time indicates the possibility of reaction of sodium bicarbonate with moisture during the study period. But, there was very little effect on the floating duration and matrix integrity of the tablets. Some drug degradation was found, but it was not statistically significant. Decreased drug release was found from all formulations, but drug release complied the official standard of release, since more than 80% of the drug was released. Statistical analysis of dissolution data before and after stability studies was carried out. Student's t-test was used to assess the results. No significant change was observed in percent drug release before and after stability studies for three months. Based on the release data and similarity factor f_2 values, formulation F5 was

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found to be the optimized formulation. The buoyancy of the tablet was almost the same as that observed in the in vitro test using acidic test medium, except that the duration of buoyancy vitro (more than 12 h) was longer than in vivo (8 h). This may be due to the escape of carbon dioxide gas from the tablet caused by peristalsis of the stomach.

Conclusion

Bilayer floating tablets having different release profiles for different drugs can be formulated using HPMC K100M and xanthan gum (alone and in combination) to give controlled release of atenolol, and sodium starch glycollate to give immediate release of lovastatin. Hence, this dosage form should be further evaluated for delivery of two drugs from, a single dosage form. which could improve patient compliance and give better disease management.

Acknowledgement

References

(1) Rahman Z, Ali M and Khar RK. Design and evaluation of bilayer floating tablets of captopril. *Acta Pharm.* (2006) 56: 49-57

(2) Wei Z, Yu Z and Bi D. Design and evaluation of a two layer floating tablets for gastric retention using cisapride as a model drug. *Drug Dev. Ind. Pharm.* (2001) 27: 469-474

(3) Patel VF and Patel NM. Intragastric floating drug delivery system of cefuroxime axetil: *in vitro* evaluation. *AAPS Pharm. Sci. Tech.* (2006) 7: E1-E7

(4) Nur AO and Zhang JS. Captopril floating and/or bioadhesive tablets: design and release kinetics. *Drug Dev. Ind. Pharm.* (2000) 26: 965-969

(5) Patel VF and Patel NM. Statistical evaluation of influence of xanthan gum and guar gum blends on dipyridamole release from floating matrix tablets. *Drug Dev. Ind. Pharm.* (2007) 33: 327-334

(6) Li S, Lin S, Daggy BP, Mirchandani HL and Chien YW. Effect of HPMC and carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. *Int. J. Pharm.* (2003) 253: 13-22

(7) Rouge N, Alleman E, Gex-Fabry M, Balant L, Cole ET, Buri P and Doelker E. Comparative pharmacokinetic

(8) Sungthongjeen S, Paeratakul O, Limmatvapirat S and Puttipipatkhachorn S. Preparation and *in vivo* evaluation of a multiple-unit floating drug delivery system based on gas formation technique. *Int. J. Pharm.* (2006) 324: 136-143

(9) Patel DM, Patel NM, Patel VF and Bhatt DA. Floating granules of ranitidine hydrochloride-gelucire 43/01: formulation optimization using factorial design. *AAPS Pharm. Sci. Tech.* (2007) 8: E1-E7

(10) Rocca J, Omidian H and Shah K. Progress in gastroretentive drug delivery systems. *Pharmatech.* (1998) 152-156

(11) Melander A, Stenberg P, Liedholm H, Schersten B and Wahlin- Boll E. Food induced reduction in bioavailability of atenolol. *Eur. J. Clin. Pharm.* (1979) 16: 327-330

(12) Amidon GL, Lennernas H, Shah VP and Crison JR. A theoretical basis for a biopharmacutics drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability. *Pharm. Res.* (1995) 12: 413-420

(13) Dollery C. *Therapeutic Drugs.* Churchill Livingstone, Edinburgh (1999) L105-L109

(14) Tripathi KD. *Essentials of Medical Pharmacology.* Jaypee Brothers Medical Publications, New Delhi (2003) 145

(15) Dollery C. *Therapeutic Drugs.* Churchill Livingstone, Edinburgh (1999) D139-D143

(16) Pool JL, Shear CL, Downton M, Schnaper H, Stinnett S, Dujovne C, Bradford RH and Chremos AN. Lovastatin and coadministered antihypertensive/cardiovascular agents. *Hypertension* (1992) 19: 242-248

(17) Rubin R, Silbiger S, Sablay L and Neugarten J. Combined antihypertensive and lipid-lowering therapy in experimental glomerulonephritis. *Hyper. Aha. J.* (2007) 92-95

(18) Faggiotto A and Paoletti R. Statins and blockers of the renin-angiotensin system. *Hypertension* (1999) 34: 987-996

(19) *Stability Testing Guidelines. Stability Testing of New Drug Substances and Products.* (2003)

(20) *United States Pharmacopoeia.* 23rd ed. US Pharmacopoeial Convention, Rockville (1993) 951

(21) Dyade GK and Sharma AK. Simultaneous spectrophotometric estimation of spironolactone and hydroflumethiazide in tablet formulations. *Ind. Drugs* (2001) 38: 75-78

(22) Khan MR and Jain D. Simultaneous spectrophotometric determination of atorvastatin calcium and amlodipine besylate in tablets. *Ind. J. Pharm. Sci.* (2006) 68: 546-548

(23) Sachan A and Trivedi P. Simultaneous spectrophotometric estimation of tripprolidine hydrochloride and phenylpropanalamine hydrochloride. *East-Pharm.* (1999) XLII: 107-110

(24) Siepmann J and Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). *Adv. Drug. Deli. Rev.* (2001) 48: 139-157

(25) Costa P and Lobo JMS. Modeling and comparison of dissolution profiles. *Eur. J. Pharm. Sci.* (2001) 13: 123-133

(26) Banker GS and Anderson NR. Tablets. In: Lachman L, Lieberman H and Kanig JL. (eds.) *The Theory and Practice of Industrial Pharmacy.* Varghese Publishing House, Bombay (1998) 298-301

(27) Shahrzad M and Reza F. Release characterization of dimenhydrinate from an eroding and swelling index: selection of appropriate dissolution apparatus. *Int. J. Pharm.* (2005) 293: 35-42

(28) Nagel A and Blazevic N. Atenolol. In: Brittain HG. (ed.) *Analytical Profiles of Drug Substances.* Academic Press Inc., California (2005) 1-25

(29) Brenner GS, Ellison DK and Kaufman MJ. Lovastatin. In: Brittain HG (ed.) *Analytical Profiles of Drug Substances.* Academic Press Inc., California (2005) 277-305

(30) Talukdar MM and Kinget R. Swelling and drug release behaviour of xanthan gum matrix tablets. *Int. J. Pharm.* (1995) 120: 63-72

(31) Talukdar MM and Kinget R. Comparative study on xanthan gum and hydroxypropylmethyl cellulose for controlled-release drug delivery. II. Drug diffusion in hydrated matrices. *Int. J. Pharm.* (1997) 151: 99-107

(32) Conti S, Maggi L, Segale L, Machiste EO, Conte U, Grenier P and Vergnault G. Matrices containing NaCMC and HPMC. 1. Dissolution Performance and characteristics. *Int. J. Pharm.* (2007) 333: 136-142

(33) Mehrgan H and Mortazavi SA. The release behavior and kinetic evaluation of atenolol from various hydrophilic and plastic based matrices. *Iranian J. Pharm. Res.* (2005) 3: 137-146

(34) Tiwari SB, Murthy TK, Pai MR, Mehta PR and Chowdary PB. Controlled release formulation of tramadol hydrochloride using hydrophilic and hydrophobic matrix system. *AAPS Pharm. Sci. Tech.* (2003) 4: 31

(35) Reza MS, Quadir MA and Haider SS. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. *J. Pharm. Pharmaceut. Sci.* (2003) 6: 282-291

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