Appendix-I
The purpose of the study is to design bilayer floating tablets of diltiazem HCl and lovastatin to give
controlled release ofLovastatin and controlled release of diltiazem HCl and to study the influence of presence of one
drug on the release pattern of other drug. The bilayer tablets consist of sodium starch glycolate as superdisintegrant
ovastatin in the immediate release layer and hydroxypropyl methylcellulose (HPMC) K4M and Xanthan gum as
rate-retarding agents for diltiazem HCl in the controlled release layer. Sodium bicarbonate was used as the gas
ating agent. Dicalcium phosphate was used as the channeling agent. The direct compression method was
ployed for preparation of the bilayer tablets. Various physicochemical parameters were evaluated for the prepared
The physicochemical parameters were found to be within range. There was significant difference in drug
asc and floating lag time ($P < 0.05$). All the formulations showed good matrix integrity. All the formulations
ved lovastatin within 30 min. The diffusion exponent for diltiazem HCl was found to be independent of polymer
The release pattern of diltiazem HCl was fitted to different models based on coefficient of correlation
$R^2$ All the formulations followed the Higuchi model, except F1 which followed the Peppas model. HPMC K4M and
than gum retarded the release of diltiazem HCl for 12 h. The release of one drug remained unaffected in presence
of other drug. In conclusion, such kind of combined dosage forms can effectively be formulated to deliver more
one drug so as to have improved patient compliance and better disease management.

**WORDS:** Bilayer tablets. Floating, Lovastatin, Diltiazem HCl.

The current investigation employs development of a floating bilayer tablet for different release patterns of
lovastatin and diltiazem hydrochloride using a gas-generating agent.

Diltiazem hydrochloride, a calcium channel blocker, has been used widely for the treatment of angina
pectoris and hypertension. The drug is water-soluble and has half-life of 3.4 h. The drug has low bioavailability (12).
Therefore it is a suitable model candidate for a gastro-retentive formulation. Lovastatin, a HMG
Co-A reductase inhibitor, is used for the treatment of hyperlipidemia. The drug has very short half life of
1.1-1.7 h with low bioavailability (13, 14). Hypertension and hypercholesterolemia frequently coexist and
may require concomitant drug treatment. The safety and efficacy profile of lovastatin given in the presence
of antihypertensive medication has been evaluated by various researchers (12, 15-17).

In the present study, an attempt is made to formulate and evaluate a bilayer floating system of lovastatin and
diltiazem hydrochloride. The bilayer tablet is comprised of an immediate-release layer of lovastatin and a controlled-release layer of diltiazem hydrochloride. Sodium starch glycolate is used as a superdisintegrant to release lovastatin. Hydroxypropyl methylcellulose (HPMC) K4M and Xanthan gum are employed to control release of diltiazem hydrochloride. Sodium bicarbonate is used as the gas-generating agent, and di-calcium phosphate is employed as the channeling agent. The release kinetics of diltiazem hydrochloride are analyzed using different mathematical models.

Materials and Methods

Materials

Diltiazem HCl was procured from CIPLA Ltd (Mumbai, India). Lovastatin was a generous gift from Panacea Biotech (Chandigarh, India). HPMC K4M and Xanthan gum were obtained as gift samples from Panacea Biotech (Chandigarh, India). Sodium starch glycolate was procured from Okasa Pharma Ltd. (Sathara, India). 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, India), sodium bicarbonate (Research Lab, India).

Methods

Preparation of Bilayer Floating Tablets

Bilayer floating tablets were prepared by the compression method employing sodium starch glycolate as a superdisintegrant, HPMC K100M and Xanthan gum as rate-controlling polymers, sodium bicarbonate as the gas-generating agent. The optimum conditions of the above ingredients were developed on the basis of trialed formulation conditions and on the basis of trination of the tablets. Preparation of bilayer tablets had two steps:

1. Preparation of controlled release layer. The ingredients (Table I) were accurately weighed and added into the blender in ascending order, and blended for 20 min so as to achieve uniform distribution of drug in the form of a powder. Three hundred milligrams of the powder was weighed accurately and fed into the die of the punch machinery (Cadmach, Ahmedabad).
compressed at a 1.5-N compression force using 10-mm concave punches.

Separation of immediate release layer. The ingredients (Table I) were accurately weighed and were added into the blender in ascending order. The powder mix was blended for 20 min so as to have uniform distribution of drug in the formulation. An hundred milligrams of the powder mix was weighed accurately and fed onto the controlled release layer and compressed at 3-N compression using 10-mm concave punches.

Drug Characteristics

Characteristics of the prepared formulation, determined by using USP 23 paddle apparatus (Electrolab TDT-06P, Mumbai, India) at paddle speed 1 rpm in 900 mL 0.1 N HCl (pH 1.2) at 37 ± °C for 24 h. The time between introduction of the table into the medium and its buoyancy on the simulated gastric fluid was recorded (floating duration) and the time during which the tablet remained buoyant (floating duration) measured. Also, the integrity of the tablet during dissolution was observed visually (matrix integrity).

Hardness

Hardness of the prepared formulations was determined using Monsanto hardness tester (n = 10) (25).

Differential Scanning Calorimetry (DSC) Studies

Thermal analysis was carried out using Mettler Toledo 821° DSC (Switzerland). The tablet was ground to a 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 50-500 °C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 20 mL/min.

Statistical Analysis

Analysis of variance (ANOVA) was performed to find out significant difference in drug released at 12 h, floating lag time, and drug content from all formulations.
Evaluation of Physicochemical Parameters

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Drug content % ± SD (n=3)</th>
<th>Hardness (kg/cm²) n = 10</th>
<th>Floating characteristics</th>
</tr>
</thead>
</table>
|                  | Diltiazem HCl | Lovastatin | Lag Time (min) | Floating Duration (h) | M
| F1               | 102.03 ± 2.45 | 99.75 ± 1.33 | 4.1 ± 0.36 | 11 | 14 | Very |
| F2               | 100.74 ± 2.89 | 99.46 ± 1.33 | 4.2 ± 0.25 | 7  | 20 | Very |
| F3               | 99.89 ± 0.92  | 100.04 ± 1.74 | 4.5 ± 0.5  | 4  | 24 | Very |
| F4               | 98.28 ± 2.45  | 98.87 ± 1.81  | 4.3 ± 0.32 | 9  | 13 | Very |
| F5               | 100.42 ± 0.92 | 99.16 ± 2.3   | 4.5 ± 0.3  | 5  | 17 | Very |
| F6               | 99.35 ± 3.2   | 100.91 ± 3.79 | 4.8 ± 0.28 | 3  | 24 | Very |

**Results and Discussion**

**Floating Characteristics**

On contact with dissolution medium, hydrochloric acid in the test medium reacted with the sodium bicarbonate in the controlled release layer of the bilayer tablet, inducing CO₂ formation. The generated gas bubble was trapped in the matrix of the polymer and was well protected by gel formed by hydration of polymers. Significant difference (P < 0.05) in lag time was observed because of the difference in amount of polymers incorporated and gel formation. (Table II). A 5% concentration of sodium bicarbonate was found to be optimum to impart floating characteristics to the system. It was observed that concentration of sodium bicarbonate more than 5% led to fast reaction with hydrochloric acid and formation of dispersion of the tablet. Hardness 4–4.8 kg/cm² was found optimum to impart compactness to the system. Swelling of the tablets was observed, which added to the floating ability of the formulations. Gel formed by polymers was effective for the protection of the gas bubble. As concentration of polymer was increased from 10 to 20% (F1 and F4), the floating lag time was found to be reduced. Further increase in concentration of polymers (F3 and F6) to 30% again led to a decrease in floating lag time (Table II). This may be because of the fact that at lower concentrations the polymers have less ability to form gel (26). Further, an increase in bulk volume, and presence of internal voids in the dry center of tablet (porosity), made the tablet float on the test medium for 24 h. During floating all the formulations showed good matrix integrity, which may be because of the compactness of the system, which is necessary to prevent the sweep of the tablet into the lower part of gastrointestinal tract during the interdigestive myoelectric cycle (Phase I–Phase II).

**Drug Content**

Diltiazem hydrochloride and lovastatin content found within the specifications (90 ± 110%). Additives in the formulations did not have any

**In Vitro Drug Release**

**Lovastatin**

On immersion of the bilayer tablet in the medium, immediate release layer disintegrated, liberating statin with fine dispersion. The superdisintegrant starch glycolate, swelled by absorbing medium, which led to disintegration of the layer, thus affecting the controlled-release layer. A percent concentration of sodium starch glycolate found to be optimum. A 10% concentration of starch glycolate disintegrated the layer, but with formation of flakes rather than a fine dispersion; this is undesirable for rapidly disintegrating tablets. All the formulations released more than 90% statin within 30 min.

**Diltiazem HCl**

All the formulations showed controlled release of drug for 12 h and exhibited an initial burst effect a decreased final release. Burst effect observed can be attributed to dissolution of water-soluble diltiazem HCl from the surface of the tablets (29). Yet this effect was lowest with HPMC-containing formulations. This finding could be explained by the hydrophilic nature of HPMC. When exposed to dissolution medium, solvent penetrates into the free spaces between molecular chains of the polymer. After solvation the polymer chain, the dimensions of the polyn molecule increase due to polymer relaxation caused the stress of the penetrated solvent. This phenomenon...
release profile of diltiazem HCl from formulations F1, F2, and F3 containing 10%, 20%, and 30%, respectively, retarded the drug release for 12 h as a function of concentration of polymer (Figure 1). Formulations F4, F5, F6, containing Xanthan gum 10%, 20%, and 30%, respectively, released the drug in a controlled manner (Figure 2). Xanthan gum, a hydrophilic polymer, retarded the drug release and provided time-independent release kinetics (30, 31). The drug release is controlled by formation of gel layer around the tablet-mass. Xanthan gum retarded drug release more than did HPMC K4M. This is because, under identical experimental conditions, the drug diffusivity in HPMC gel was higher than in Xanthan gum gel. This difference in hindered transport of the drug molecules within the two polymeric systems brings out the real cause for the higher retarding ability of drug release.
DSC combined thermogram of diltiazem HCl and lovastatin.

from a Xanthan gum matrix tablet than from an HPMC matrix tablet.

The release of diltiazem hydrochloride from all the formulations fitted to different release kinetic models. The diffusional exponent “n” value obtained (0.51–0.55) for all formulations indicated that that release mechanism was diffusion and that it was independent of polymer concentration (32). 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 gel; (2) dissolution of drug in hydrated matrix/gel; (3) diffusion of drug through that hydrated matrix; and (4) surface erosion and/or dissolution of that formed matrix. Diffusion of drug was the main mechanism of release of drug from hydrated matrix. The release profiles of all formulations were fitted best-fit model based on coefficient of correlation (33). All formulations followed the Higuchi except for formulation F1, which followed the mayer-Peppas model. Formulations did not follow zero-order release kinetics. Percent dissolution efficiency was found to be uniform for all the formulations.

TABLE III

In Vitro Release Profile

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Percent drug release ± SD (diltiazem HCl) at 12 h</th>
<th>Percent Dissolution Efficiency</th>
<th>Mean Dissolution Time</th>
<th>Percent drug release ± SD (lovastatin) at 3 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>109.3 ± 0.55</td>
<td>52.86</td>
<td>5.18</td>
<td>97.38 ± 1.31</td>
</tr>
<tr>
<td>F2</td>
<td>85 ± 1.1</td>
<td>54.02</td>
<td>4.81</td>
<td>99.6 ± 0.86</td>
</tr>
<tr>
<td>F3</td>
<td>81.1 ± 0.55</td>
<td>55.97</td>
<td>4.33</td>
<td>98.82 ± 0.86</td>
</tr>
<tr>
<td>F4</td>
<td>106.89 ± 0.96</td>
<td>58.22</td>
<td>4.83</td>
<td>101.5 ± 1.31</td>
</tr>
<tr>
<td>F5</td>
<td>83.4 ± 0.96</td>
<td>57.46</td>
<td>4.56</td>
<td>101.5 ± 0.5</td>
</tr>
<tr>
<td>F6</td>
<td>80.12 ± 0.55</td>
<td>55.14</td>
<td>4.5</td>
<td>104.5 ± 0.86</td>
</tr>
</tbody>
</table>

n = 3
### In Vitro Release Data of Diltiazem Hydrochloride

<table>
<thead>
<tr>
<th>formulation code</th>
<th>Zero-order</th>
<th>Matrix</th>
<th>Pappas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>K</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>0.9462</td>
<td>8.1</td>
<td>0.9794</td>
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<tr>
<td></td>
<td>0.9491</td>
<td>8.2</td>
<td>0.9829</td>
</tr>
<tr>
<td></td>
<td>0.9184</td>
<td>8.3</td>
<td>0.9952</td>
</tr>
<tr>
<td></td>
<td>0.9294</td>
<td>8.8</td>
<td>0.9884</td>
</tr>
<tr>
<td></td>
<td>0.9254</td>
<td>8.6</td>
<td>0.9925</td>
</tr>
<tr>
<td></td>
<td>0.9130</td>
<td>8.4</td>
<td>0.9965</td>
</tr>
</tbody>
</table>

greater than time for 90% dissolution of the drug. However, further clinical studies are needed to assess the utility of this system for patients suffering from hypertension concomitantly with hypercholesterolemia with improved patient compliance and better disease management.

### References


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