Development, *in vitro* Characterization and Stability Study for Matrix Tablets Containing Chlorpheniramine Maleate Prepared by Direct Compression

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**ABSTRACT**

The objectives of this study were to prepare matrix tablets of Chlorpheniramine Maleate (CPM) using a series of hydrophilic and hydrophobic polymers and determine the effect of the type and concentration of the polymer on the physical properties, *in vitro* drug release and stability of the matrix tablets. The CPM matrix tablets containing 10% w/w and 25% w/w of hydrophilic polymers (hypromellose and Carbopol 934) and hydrophobic polymers (Eudragit S100 and Compritol®) were prepared by direct compression technique. The flow properties of the powder mixtures as well as the physical properties and accelerated stability of the prepared tablets were determined. The CPM release profiles were investigated *in vitro* using commercially available Pheniram® IR tablets as a control group. The results showed that the type and polymer concentration did not have a significant effect on the flow properties of the powder mixture, the physical properties of the prepared tablets and their short-term stability. *In vitro* release data showed that matrix tablets containing 25% hypromellose exhibited a superior ability to control the release of CPM associated with complete release and minimum dose dumping, when compared to other formulae. Besides illustrating the effect of polymer type and concentration on the *in vitro* release of CPM from different matrix tablets, the study showed that hypromellose in concentration of 25% w/w could be a potential candidate to be used in formulating CPM matrix tablets.

**Key words:** Chlorpheniramine maleate, controlled release, hydrophilic polymers, hydrophobic polymers, matrix tablets

**INTRODUCTION**

Antihistamines act as reversible antagonists at the H1 receptor sites by competitively blocking those receptors leading to relaxation of smooth muscles of the respiratory and gastrointestinal systems (Fang *et al.*, 1998; Assanasen and Naclerio, 2002). They are more effective in preventing the actions of histamines rather than reversing those actions once they occurred. Reversal of pathophysiologic symptoms caused by histamine production is largely due to the anticholinergic characters associated with those drug molecules. This activity is responsible for the drying effect which reduces the problem of nasal, salivary and lacrimal gland hypersecretion (Fang *et al.*, 1998). Antihistamines can be generally classified into the older or first generation that is coupled with a sedating effect such as acrivastine, brompheniramine maleate and Chlorpheniramine Maleate (CPM) and the more recent non-sedating second generation, which include loratadine, coticizine and azelastine. Both classes are still used clinically to alleviate the symptoms of allergic disorders (Assanasen and Naclerio, 2002).
Chlorpheniramine Maleate or (4)-3-(4-chlorophenyl)-NN-dimethyl-3-(2-pyridyl) propylamine hydrogen maleate is a member of the first generation antihistamine agent that possesses a moderate degree of sedation and some antimuscarinic activity. It is frequently used alone for the symptomatic relief of several allergic conditions, such as urticaria, rhinitis, pruritis and other skin sensitivity disorders. It is also used in combination with antitussive oral therapy for the symptomatic treatment of cough and common cold and also intravenously as an adjunct agent in the emergency treatment of an anaphylactic reaction (Aaronson, 1991).

After oral administration, the absorption of CPM from the gastrointestinal tract is relatively slow with an onset of action of 3-6 h followed by a wide range of inter-individual variations in elimination profile and a short duration of action. Accordingly, CPM requires 4-6 h dosing frequency for optimum therapeutic efficacy (Vallner et al., 1982). This high dosing frequency increases the risk of gastrointestinal side effects, such as nausea, vomiting and diarrhea. Therefore, many modified-release formulae of CPM have been developed such as sustained release tablets and capsules as well as transdermal patches (Vallner et al., 1982; Kotzan et al., 1982; Khan, 2012). The use of such controlled release drug delivery systems has dramatically improved the compliance of the patients as the frequency of administration and side effects of the drug decreased (Lu et al., 2007).

The preparation of matrix tablets using hydrophilic or hydrophobic polymers is considered a suitable approach to control the release of many drug molecules for oral administration (Uhrich et al., 1999; Siepmann and Gopferich, 2001). The use of hydrophilic polymers, such as Xanthan gum, Carbopol 934, hydroxypropyl cellulose and hypromellose for the preparation of matrix tablets results in the formation of a viscous gel barrier at the tablet/liquid interface due to hydration and gelation of the polymer. Drug release from these polymeric matrices is controlled by polymer erosion and/or drug diffusion through the polymer matrix or pores in the matrix (Siepmann and Gopferich, 2001; Siepmann and Peppas, 2001). On the other hand, hydrophobic matrices prepared by addition polymers such as ethyl cellulose, cellulose acetate butyrate, Eudragit and Compotril results in gradual release due to slow diffusion of the drug out of the hydrophobic matrix (Siepmann and Peppas, 2001; Karolewicz, 2015). The contribution of each release mechanism to the overall drug release profile from matrix tablets is influenced by many factors such as the nature of the drug, the method of preparation, the hydration characteristics of the matrix polymer, its molecular mass and crystallinity, the copolymer ratio and the subsequent physical and mechanical properties of the gel layer that forms around the tablet (Miyajima et al., 1998; Siepmann and Peppas, 2001). The main limitation of matrix tablets is that many of the polymers used are not biodegradable. Hence, the remaining matrix scaffold must be removed after the drug has been released (Abd-Elbary et al., 2012).

The aim of this study was to prepare a series of matrix tablets to control the release of CPM using different hydrophilic polymers (hypromellose and carbopol 934) and hydrophobic polymers (Eudragit S100 and Compotril®) by direct compression. The effect of changing the type and concentration of polymer on the physical characteristics, in vitro drug release and short-term stability was determined.

**MATERIALS AND METHODS**

**Materials:** The CPM and Pheniram® IR 4 mg Tablets were obtained from MedPharma (Sharjah, U.A.E). Hypromellose and Eudragit S100 were provided by Colorcon Limited (Dartford Kent, U.K) and Evonik Industries AG (Essen, Germany). Carbopol 934P was purchased from Goodrich
Table 1: Composition of CPM matrix tablets

<table>
<thead>
<tr>
<th>Ingredient (mg/tablet)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypermellose</td>
<td>25</td>
<td>62.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carbopol 934 P</td>
<td>-</td>
<td>-</td>
<td>25</td>
<td>62.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eudragit</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25</td>
<td>62.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Compritol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25</td>
<td>62.5</td>
<td>-</td>
</tr>
<tr>
<td>CPM</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>215.25</td>
<td>177.75</td>
<td>215.25</td>
<td>177.75</td>
<td>215.25</td>
<td>177.75</td>
<td>215.25</td>
<td>177.75</td>
</tr>
</tbody>
</table>

Chemical Co. (Cleveland, OH) and Compritol® 888 ATO (glyceryl behenate) was acquired from Gattefosse Co. (St. priest, France). Magnesium Stearate was obtained from Alfa Chemicals (Kings Point, NY). Microcrystalline Cellulose were purchased Sigma (St Louis, MO). All other chemicals and solvents used in the in vitro drug release and stability studies were of analytical grades.

**Preparation of matrix tablet powder mixtures:** Tablet formulae containing drug, microcrystalline cellulose as a binding agent, magnesium stearate as lubricant and different amount of hydrophilic or hydrophobic polymers namely Hypermellose, Carbopol 934P, Eudragit and Compritol (Table 1) were prepared by direct mixing using a Double Cone Mixer (YC-DM-10/3, Yenchen, Taiwan). In all formulae, the drug concentration was held constant at 8 mg CPM per 250 mg of formulation and the lubricant concentration was kept constant at 0.7% w/w. Random samples of the blend were visually analyzed to determine the uniformity of mixing.

**Determination of flow properties of the matrix tablets powder mixtures:** The flow properties of the powder blends were determined using an Automated Powder Testing Machine (PTG-S3, Pharmatest, Germany). Powder samples were individually poured through the funnel till a cone was formed. Powder flow was then stopped and the average diameter (d) and height of the formed cone were determined. The angle of repose was then computed from the following equation

\[ \tan \theta = 2 \cdot \frac{d}{h} \]

(Antequera et al., 1994).

The bulk and tapped density were assessed in accordance with the USP requirements using a tapped volumeter apparatus (Erweka, SVM101, Heusenstamm, Germany). The volumeter was filled with 10 g of the drug alone or its blends and the occupied volume was recorded as initial bulk volume \( V_b \) and the initial bulk density \( D_b \) was calculated as \( D_b = \frac{\text{powder weight}}{V_b} \). The cylindrical graduated was tapped at a constant velocity till a constant volume is obtained, the final bulk volume \( V_f \) was then recorded and the final density \( D_f \) was calculated as powder \( D_f = \frac{\text{powder weight}}{V_f} \) [12]. The percentage compressibility, Carr's index, was then determined from the equation:

\[ \text{Carr's index} = 100 \times \left( \frac{V_f}{V_i} - 1 \right) \]

(Carr, 1964) and Hausner ratio was obtained by dividing \( V_i \) by \( V_f \) (Hausner, 1967).

**Preparation of CPM matrix tablets:** The CPM matrix tablets were prepared by direct compression using the same blends mentioned previously in section 2.2. The drug was mixed with the polymer and microcrystalline cellulose using a Double Cone Mixer (YC-DM-10/3, Yenchen, Taiwan), for 10 min at 15 rpm. Then, 0.7% magnesium stearate was added and the mixture was blended again using the same mixer and speed of mixing for 5 min. The resulting blends were
directly compressed using a tablet single punch press machine (model XP-1, Korsch, Berlin, Germany) into 250 mg tablets using 8 mm flat punch and die where the force of compression was kept constant at 22.1±0.5 kN.

**Physical characterization of prepared CPM matrix tablets:** The determination of physical properties of the prepared matrix tablets was performed 24 h after their preparation. Determination of weight variation was carried out according to the British Pharmacopeia, where 20 tablets from each formula were individually weighed using Sartorius Balance with Data Printer (model GC 2502, Sartorius, Germany). The mean weight of tablets was calculated and the weight variation was determined.

The thickness and diameter of ten compressed tablets from each formula were individually measured using an electronic micrometer (model G, Peacock, Japan) and the mean thickness and diameter were calculated.

The friability was determined by using a friabilator (Model FR 1000, Copley, U.K) using 20 tablets and rotating for 4 min at a speed of 25 rpm in accordance with the USP requirements. The tablets were then brushed and reweighed. The percentage of weight loss was calculated and taken as a measure of friability using the equation:

\[
\text{Weight loss (\%)} = 100 \left(1 - \frac{W^*}{W}\right)
\]

where, \((W^*)\) and \((W)\) represent the initial and final weights, respectively (Ruippi et al., 1998). Finally, the hardness of ten tablets was determined using hardness tester (model TBH-220-WTD, Erweka, Germany).

**High performance liquid chromatography assay for CPM content:** The uniformity of drug content of the prepared matrix tablets was determined by individually crushing ten tablets from each formula and dissolving the resulting fine particles in 50 mL of acetonitrile, sonicated for 5 min and then shaken for 10 min using a BMC ultrasonic cleaner bath (QC/EQ/065, Beijing, China). The stock solution was prepared containing equivalent amount (80 mg) of Chlorpheniramine Maleate by the same way. The solution was then filtered using a 0.45 μm filter and diluted by another 50 mL of acetonitrile. Equal volumes (about 10 μL) of the standard and assay preparations were separately injected into the chromatograph (HFL-12789-OPUY, Shimadzu, Japan). Separation was achieved on a Li Chrosorb RP-C18 column (5 μm, 15×4.6 mm), using a mobile phase of 0.05 M ammonium acetate and acetonitrile, (60%, v/v) at a flow rate of 1.0 mL min\(^{-1}\) and UV detection at 265 nm using a spectrophotometer (UV-14786387-LKJ, Shimadzu, Japan) (Al-Deeb et al., 1997). Each injection was repeated 6 times and the average retention times were recorded.

**In vitro drug release studies:** The dissolution and release studies were carried out using USP dissolution apparatus, type II (Model TBH-225-WFD, Erweka, Germany) equipped with paddles which were operated at the speed of 50 rpm. Studies were carried out at 37±0.5°C in 900 mL of 0.1 M HCl (pH 1.2) for a period of 2 h, then 0.1 M NaOH was added to raise the pH of the dissolution medium, followed by release in phosphate buffer (pH 7.4) for 10 h. The amount of drug released was measured at suitable time intervals (1, 2, 3, 4, 6, 8 and 12 h) and then determined.
spectrophotometrically (UV-14786387-LKJ, Shimadzu, Japan) at λ_{max} 265 nm using 0.1 M HCl (pH 1.2) as a blank for the first 2 h then phosphate buffer saline (pH 7.4) for the remaining samples. Each in vitro release study was repeated 6 times and compared to the release of CPM from the commercially available Pheniram® IR tablets.

**Stability testing:** An accelerated stability study was conducted in which the prepared matrix tablets were subjected to stressful conditions in an attempt to accelerate their degradation. Matrix tablets were inserted in transparent PVC-PVDC blisters and packed in a box along with a leaflet and placed in stability chambers (Sanyo, U.K) in which the temperature and relative humidity were set to be 40°C and 75%, respectively for 6 months. Tablets from each formula were divided to four groups for assay at 0, 1, 3 and 6 months using the same assay mentioned previously in section 2.6 to measure the percent content of CPM in the tablets. A comparison was made to unstressed product that was assayed in the same manner. The stressed sample recovery is expressed as percent of unstressed sample recovery, using the following equation (Haider, 2011):

\[
\text{API remaining (\%)} = \frac{\text{Peak area of test}}{\text{Peak area of standard}} \times 100
\]

**Statistical analysis:** All mean values were presented as Mean±SD. The Student’s t-test (two-tailed) was used to evaluate the statistical significance of any differences in mean values in the experimental groups. In addition, ANOVA test was used to assess the differences in means between treatments. The significance level was set at α = 0.05 for all statistical tests.

**RESULTS AND DISCUSSION**

**Characterization of the flow properties of the powder mixture:** The flow properties of the powder mixture directly affect the die filling process as well as the weight and content uniformity of tablets prepared by direct compression (Sinka et al., 2004). Constant uninterrupted flow and reproducible filling of dies are essential to reduce air entrapment which leads to capping and lamination and also to obtain more uniform tablets with consistent physicochemical properties. In addition, flow properties of the powder mixture may have a direct effect on other tablet manufacturing process steps such as sieving, mixing, micronization and granulation processes. Powder flow is mainly governed by physical rather than chemical properties of the particles, such as crystal form, shape, size and size distribution of the particles and their moisture content (Hegde et al., 1988; Guerin et al., 1999). In addition, the flow properties of the powder may be affected by mechanical factors, such as elastic and plastic deformations as well as environmental factors such as humidity and adsorbed impurities (Chowhan and Yang, 1981). Therefore, due to the complexity of the issue several parameters are frequently used to determine powder flow characteristics since no single type of measurement adequately assesses all the factors influencing them. In this study, the flow properties of the powder mixtures used in preparation of CPM matrix tablets were determined by measuring of the angle of repose θ and computing Carr’s index (compressibility index) and Hausner ratio.

The angle of repose (θ) is a measure for interparticle cohesion, friction, or resistance to movement between particles and hence used to determine powder flowability. Powders with angle of repose above 50° have unsatisfactory and difficult flow properties, those with angles from 25-40° have reasonable flow potential, whereas powders with angles close to 25° possess very good flow properties (Carr, 1964). The results of angle of repose (θ) measurements (Table 2) showed that the
Table 2: Flow properties powder mixtures used in preparation of CPM matrix tablets

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Angle of repose (θ)</th>
<th>Carr’s index (Ci)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>32.6±0.2°</td>
<td>19±0.68</td>
<td>1.28±0.05</td>
</tr>
<tr>
<td>F2</td>
<td>27.4±0.4°</td>
<td>17±0.52</td>
<td>1.19±0.04</td>
</tr>
<tr>
<td>F3</td>
<td>30.8±0.7°</td>
<td>20±0.77</td>
<td>1.30±0.06</td>
</tr>
<tr>
<td>F4</td>
<td>39.2±0.5°</td>
<td>19±0.81</td>
<td>1.26±0.02</td>
</tr>
<tr>
<td>F5</td>
<td>35.5±0.2°</td>
<td>21±0.54</td>
<td>1.31±0.05</td>
</tr>
<tr>
<td>F6</td>
<td>33.2±0.4°</td>
<td>20±0.72</td>
<td>1.24±0.07</td>
</tr>
<tr>
<td>F7</td>
<td>38.2±0.5°</td>
<td>29±0.33</td>
<td>1.32±0.05</td>
</tr>
<tr>
<td>F8</td>
<td>36.2±0.2°</td>
<td>19±0.45</td>
<td>1.27±0.04</td>
</tr>
</tbody>
</table>

All values are expressed as Mean±SD, n = 3

amount of polymer used in powder blends affected the flow properties, where formulae containing more hydrophilic or hydrophobic polymers had significantly lower angles of repose and better flow properties. However, this difference did not have an effect on the overall suitability of flow properties of the powder mixtures, which remained within acceptable limits as all formulae had an angle of repose between 25° and 40° indicating reasonable flow.

Carr’s index or compressibility index (Ci) is considered as an indirect method to assess bulk density, cohesiveness, moisture content and surface area of the powders. However, it should be noted that Ci is a one-point determination and hence, it does not reflect the ease or speed with which consolidation occurs therefore it is used in combination with angle of repose measurements to determine the flow properties of powders. Generally, Ci values above 21 indicates poor flow while those between 16 and 21 and below 16 indicate good and excellent flow properties, respectively (Wells, 1988; Abd-Elbary et al., 2012). Carr’s index determination (Table 2) showed that all formulae had Ci values between 17 and 21 indicating good flow for all powder blends except F7 containing 10% Compritol. The results correlate with those obtained from angle of repose measurements, where F7 also showed a significantly larger angles than the other. Compritol is a hydrophobic powder that is known to impart good flow properties to powder blends. However, it seems that Compritol can only improve flowability at concentration higher than 10% w/w as shown by the increase in flow properties, when 25% of the hydrophobic polymer was added to the powder blend F8.

Hausner’s ratio is a measure of interparticle friction, thus used to predict powder flow properties. Particles with low interparticle friction have ratios of approximately 1.2, whereas, more cohesive poor flowing powders have ratios greater than 1.6 (Wells, 1988; Abd-Elbary et al., 2012). The Hausner's ratio values for the tested powder blends (Table 2) showed that formulae had values between 1.2-1.6, indicating medium to low interparticle friction and acceptable flow which was in good correlation with the results obtained from angle of repose measurements and Carr’s index determination. The results also showed that Hausner’s ratio was significantly affected by the amount of polymer added to each formulae where those containing more hydrophilic or hydrophobic polymers had significantly lower ratios indicating less cohesion between particles and better flow properties which again supported the results obtained from angle of repose and Ci measurements.

Physical characterization of CPM matrix tablets: The physical properties of the prepared CPM matrix tablets were determined after a relaxation period of 24 h at room temperature. The results of average weight determination for 10 tablets are shown in Table 3. All the measured matrix tablets deviated from the average required weight (250 mg) by less than 5% showing an acceptable weight variation range from approximately 247.0-258.0 mg.
The determination of average thickness and diameter of CPM matrix tablets by an electronic micrometer showed that both dimensions were consistent among all parameters, which confirms the uniformity of tablet compression and excludes the effects of changes in tablet diameter or force of compression on drug release.

Average drug content measurements showed that all tested matrix tablets formulae are in compliance with the USP pharmacopoeial limits (Abd-Elbary et al., 2012). The results in Table 3 showed that the average drug content of all formulae were within the range of 85-115% of the label claim and the relative standard deviation was less than 6%. Those results are in correlation with the flow properties characterization and shows the uniformity of drug content in the prepared matrix tablets and the suitability of the method of preparation.

The friability values for all tested CPM matrix tablet formulae were less than 1% and correlates with hardness values for the formulae which were also suitable (Table 3). Those results confirm results obtained previously showing the excellent compactability properties of the used polymers and their suitability for direct compression conditions used to prepare the matrix tablets (Abd-Elbary et al., 2012).

**In vitro drug release:** Drug release from Immediate release Pheniram® IR 4 mg tablets was complete after 4 h showing that the study design and selection of media were suitable for studying the release of CPM from matrix tablets. The study was carried out for 12 h in order to confirm the complete dissolution of the drug in controlled release dosage form provided that not less than 75-80% of drug has been released (Sievert and Sievert, 2000) taking into consideration that the release of 20-50% of the drug within the first 3 h is an indication for dose dumping. The release profiles of CPM from matrix tablets (Fig. 1a, b) showed that the drug release was affected by both the type and amount of the used polymers.

The effect of the amount and type of hydrophilic polymer on CPM release from matrix tablets was studied using formula containing 10 and 25% of hydroxypropylmethylcellulose and Carbopol 934P, respectively. The results showed that the overall extent of drug release from matrix tablets containing hydrophilic polymers is inversely proportional to the polymer concentration, where a larger amount of the drug was released per time interval from matrix tablets containing 10% polymer concentration. Tablets containing Carbopol 934 P showed no dose dumping in the first 3 h. However, the overall amount of drug released was less than 60%, even in tablets containing only 10% of the polymer. Tablets containing 10% hydropolymer suffered from a fast release of the drug where 75% of the dose was released after 3 h, while those containing 25% showed an excellent controlled release profile with a complete release of the drug after 12 h and only 45% of the drug
Fig. 1(a-b): Effect of type and concentration of (a) Hydrophilic polymers, (b) Hydrophobic polymers on release of CPM from matrix tablets. Points represent the Mean±Standard deviation for n = 3 samples released after 3 h indicating the absence of dose dumping. The results of drug release from tablets prepared using hydrophilic polymers (F1-F4) correlate with those reported in previous studies on the effect of HPMC and Carbopol on drug release (Skoug et al., 1993; Khan and Jiabi, 1998; Abd-Elbary et al., 2012). Matrix tablets containing 10 and 25% Carbopol showed a significant swelling after 2 h which resulted in a significant decline in the amount of drug released. This swelling may be due to the ionization of the carboxylic acid group in Carbopol leading to ionic repulsion between the polymer chains at pH 7.4. The swelling may also be due hydration of the polymer chains at the same pH leading to an increase in the radius, volume and end-to-end distances of the polymer chains (Duchene et al., 1988). On the other hand, in aqueous media, hypermellose does not swell but only increase the viscosity. The dose dumping from low concentration of HPMC is due to the insufficient viscosity of the gel matrix to control the initial drug release leading to an increase in the diffusion coefficient of the drug (Gao et al., 1996;
Matharu et al., 2011). Upon increasing the concentration of hypromellose to 25% w/w, a more viscous gel barrier is formed at the tablet/liquid interface resulting in more control over the initial drug release rate.

The effect of the amount and type of hydrophobic polymer on CPM release from matrix tablets was studied using formula F5-F8, containing 10 and 25% of Eudragit and Compritol, respectively. In contrast with hydrophilic matrices, most of the tablets containing hydrophobic polymers suffered from fast release and dose dumping except for those containing 25% of Compritol, which showed a slow initial release followed by an incomplete release of the drug of the period of the study. Therefore, the hydrophobic polymers used were incapable of providing an extended release profile for CPM at the used concentration of the polymer and the method used for matrix tablet preparation. These findings are in agreement with previous reports on the effect of Eudragit and Compritol on drug release (Perez et al., 1993; Skoug et al., 1993; Abd-Elbary et al., 2012). Rapid dissolution or weakening of the bonds between the particles in the compressed tablets prepared using hydrophobic polymer, Eudragit S100 at 37°C and pH 7.4 can explain the failure of that polymer to control initial drug release (Skoug et al., 1993). The fast release from matrix tablets made from hydrophobic polymers may be also explained by their inability to absorb water and form a viscous gel layer around the drug particles as in the case of some hydrophilic polymers, such as HPMC.

**Accelerated stability testing**: Stability of a pharmaceutical product may be defined as the ability of a particular product to retain the same physical, chemical, microbiological and toxicological properties possessed at the time of its packaging, in a specific closure system, throughout its period of storage and use (Gorog, 2000; Bajaj et al., 2012). Stability studies are a pre-requisite for marketing approval. A variety of factors can affect the stability of a pharmaceutical product, such as stability of the active ingredients, their interactions with other ingredients and excipients, the manufacturing process, the type of dosage form the container/closure system used for packaging, the light, heat and moisture conditions encountered during shipment, storage and handling of the product (Bajaj et al., 2012).

Therefore, stability testing are carried out to give an insight on how the quality of a drug substance or drug product might vary with time under the influence of a variety of environmental factors. Stability testing also provides reliable information and guidance for the selection of adequate formulations, excipients and container closure systems for the development of new products. In addition, it is used for the determine shelf-life, re-test periods and the ideal storage conditions (Gorog, 2000; Bajaj et al., 2012).

The results of the accelerated stability study carried out on the prepared matrix tablet formulae showed that in all tested batches, the percentage of CPM remaining was more than 94% indicating good stability of the prepared matrix tablets after a 6-months storage period (Fig. 2 and Table 4). Statistical analysis of the data showed that there was no significant differences in the

<table>
<thead>
<tr>
<th>Time (month)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>96.6±0.46</td>
<td>97.6±0.20</td>
<td>98±0.15</td>
<td>98±0.75</td>
<td>97±0.85</td>
<td>96±0.92</td>
<td>98±0.15</td>
<td>97±0.44</td>
</tr>
<tr>
<td>1</td>
<td>95.9±0.27</td>
<td>95.4±0.24</td>
<td>97±0.47</td>
<td>98±0.64</td>
<td>96±0.76</td>
<td>96±0.14</td>
<td>97±0.20</td>
<td>96±0.55</td>
</tr>
<tr>
<td>3</td>
<td>95.4±0.08</td>
<td>95.0±0.18</td>
<td>95±0.87</td>
<td>96±0.25</td>
<td>95±0.04</td>
<td>95±0.81</td>
<td>95±0.67</td>
<td>96±0.71</td>
</tr>
<tr>
<td>6</td>
<td>94.3±0.98</td>
<td>94.0±0.39</td>
<td>95±0.32</td>
<td>95±0.37</td>
<td>94±0.54</td>
<td>94±0.89</td>
<td>95±0.05</td>
<td>94±0.83</td>
</tr>
</tbody>
</table>

All values are expressed as Mean±SD, n = 3
Fig. 2: HPLC chromatogram of matrix tablet showing peak for CPM, $t_r \sim 4.885$ min used to
determine the remaining concentration for accelerated stability study

percentage remaining for CPM at $p<0.005$. It also provided evidence that the storage condition had
no significant effect on the physical properties of the matrices.

CONCLUSION

Matrix tablets of CPM were prepared by direct compression using different types and
concentrations of hydrophilic and hydrophobic polymers. The Polymer type and concentration had
no significant effect on the flow properties of the powder mixtures or the physical characteristics
of the prepared tablets and their short-term stability, except for the incorporation of low amount
(10%) of Compitol, which resulted in poor flow properties. The effect of polymer type and
concentration on the release of CPM from matrix tablets was more significant on the release of the
drug from matrix tablets. The incorporation of Hypermellose at 28% w/w resulted in a better ability
to control the release of CPM from matrix tablets over a period of 12 h when compared to formulae
prepared using a lower concentration of hypermellose (10% w/w), those containing different
different concentration of Carbopol 934 P or matrices containing hydrophobic polymers. Therefore,
hypermellose in concentration of 25% w/w could be considered as a potential candidate for
formulating controlled CPM matrix tablets.

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