Introduction

Over the years, various techniques and formulations have been employed to enhance the bioavailability of drugs without disturbing patient acceptability and compliance.\(^1\,^2\)

The gastrointestinal tract continued to be the major and most common route of drug entry to the systemic circulation.\(^3\,^4\) However, a delay in the onset time might happen to drugs taken orally due to interpersonal variation in the gastric emptying, creating a lag time between administration and onset of intestinal absorption.\(^5\) Moreover the blood that drains from the gastrointestinal tract (GIT) goes directly to the liver giving chance to many drugs to lose some to most of their bioavailability if swallowed by this route due to first-pass metabolism.\(^6\,^8\)

Currently there was a growing interest to use other administration routes where rapid and effective drug absorption occurs.\(^9\)

Many drugs were successfully formulated and absorbed through the mucosal cells of the oral cavity, mainly by the buccal or sublingual mucosa.\(^10\,^12\)

Both absorption sites share common benefits including rapid onset of action with increased blood levels. Furthermore, drugs are protected from the hostile environment of the GIT, bypass first-pass effect and hence save their bioavailability.\(^9\,^13\)

Among the different pharmaceutical forms that were found applicable in the oral cavity,\(^11\,^18\) rapidly disintegrating tablets continued to gain much popularity and clinical usefulness among patients,\(^19\,^22\) especially with children and elderly who experience problems in swallowing.

Metoclopramide hydrochloride (MH) is an antidiopaminergic and gastrointestinal stimulant that exerts antiemetic properties through antagonism of central and peripheral dopamine receptors. Onset time was found to be between 30 and 60 min after oral tablet intake.\(^23\)
Attempting to decrease onset time by proper optimization of the formulation parameters would be beneficial especially in case of critical situations with patients receiving anticancer drugs or those suffering from severe dehydration.

Beside, it is noteworthy that ideal delivery of drugs would follow zero-order kinetics, so that blood level of drugs could be maintained constant throughout the delivery period. This concept was mostly applicable in controlled delivery devices, where gradual release of candidate drug overtime would be done at constant rate.[24–26]

The new objective of our present work was to design a sublingual tablet formulation of MH, possessing both fast and constant zero-order release profile, through proper optimization of different formulation excipients.

Materials and methods

Materials
Disodium hydrogen phosphate, dihydrogen potassium phosphate, and magnesium stearate (Adwic Co., Cairo, Egypt)
Crosscarmelose sodium (ac-di-sol) type SD-711 (FMC Corporation, Philadelphia, PA)
Crosspovidone XL (CP) (FMC Corporation, Philadelphia, PA)
Microcrystalline cellulose (Avicel PH 102) (FMC Corporation, Philadelphia, PA)
Low substituted hydroxypropyl cellulose (LSHPC) Shin- Etsu Chemical Co. (Tokyo, Japan)
Glycolys, pearlitol flash and mannitol BP (Roquette, France)
MH was kindly supplied from Cid Pharmaceutical Co. (Guiza, Egypt)

Methods

Preparation of tablets
Seven formulations F1 to F7 containing each 10 mg MH along with different types & percent of excipients were directly compressed using a single punch tablet press (KorschEK0, Germany) using 6 mm flat level edged punch. A moderate compression force (3–5 KN) was applied so as to provide a constant value for hardness (~3 kg) for all tested formulae (measured with Monsanto hardness tester). The total weight of the compressed tablets was maintained at 80 mg.

Evaluation of tablet characteristics
Friability
The friability of tablets was measured according to the USP methods & criteria.[25] Tablets were weighed before and after the measurement and the weight loss was calculated. Results were mean of four determinations.

Weight variation
Weight of tablets was determined according to USP specifications,[26] where the mean weight of 20 tablets (±SD) was calculated.

Content uniformity
Each tablet was crushed and then dissolved in buffer pH 6.8 by the aid of magnetic stirring (Pierce, Rokford). The content of MH was then assayed spectrophotometrically at wave length of 272 nm using a Shimazu UV-160 V ultraviolet/visible spectrophotometer (Shima Corp, Tokyo, Japan). Results were mean of six determinations (±SD) for each formulation.

Disintegration time
A simple method for determination of disintegration time (DT) of sublingual tablets was performed according to Rawas Qalajii et al. in two successive publications,[28,30] where in brief; each tablet was dropped into a 10-ml glass test tube filled with 2 ml distilled water. The time required for complete tablet disintegration (i.e completely dispersed fragments were obtained) was observed and recorded with a stop wash. The test tube was gently rotated at 45° during the visual inspection. Results were mean of six determinations (±SD).

Wetting time
By a slight deviation from the method reported by Schiermeier et al.[31] wetting time of tablets was measured by a rather simple and discriminating procedure such that each tablet was placed in a circular glass petri dish. By the aid of a dropper, one drop of methylene blue solution was allowed to fall on the center of the tablet. The spreading of the dye was visually observed and the time for complete propagation of the dye at the upper surface of the tablet was recorded with a stop watch. Results were expressed as mean of ten determinations (±SD).

Water absorption ratio
Tablets were weighed before and after wetting procedure. Water absorption ratio was determined according to the following equation:

\[ R = \frac{100(w_a - w_b)}{w_b} \]

were \( w_a \) and \( w_b \) are the weight before and after water absorption, respectively.[32–34]

In vitro release study
The release study was carried out using USP dissolution apparatus ll at a rotation speed of 50 rpm.[35] The dissolution medium was phosphate buffer pH 6.8 (300 ml)[36,37] equilibrated at 37°. Samples were withdrawn at suitable time intervals and determined spectrophotometrically at 272 nm. Each experiment was performed in triplicate. The mean and SD were calculated.

Kinetic analysis of release data
Kinetic analysis was performed using linear regression analysis, adopting models for zero order, first order, and Higuchi diffusion model.
Differential scanning colorimetry
The possibility of interaction and/or complexation between CP and MH was studied using differential scanning colorimetry (DSC) (DSC-60, Shimazu, Kyoto). Physical mixtures of drug and CP at two predetermined weight ratios viz: 1:0.8 (F5) and 1:0.4 (F6) along with drug and CP alone were sealed each in an aluminum pan. The samples were heated at 10°C/min to 250°C.

FTIR analysis
Infrared (IR) spectra was recorded for MH and CP alone besides a physical mixture of drug and CP at ratios equivalent to that present in F5 and F6 with a FT-IR spectrophotometer (Perkin Elmer Co, CA, USA). Samples were scanned from 500 to 4000 cm⁻¹.

SEM analysis
The surface topography of tablet formulations (F5 & F6) before and after wetting as well as a cross section in tablet matrix was studied by SEM (Jeol Ltd, Tokyo, Japan). Samples were sputter-coated with a layer of Au under argon atmosphere, 20 kV acceleration voltages was used.

Results and discussion
Disintegration time
Values for disintegration time of tested formulae ranged between 1.16 and 1.51 min with an average (Av) of 1.28±0.12 min. (Figure 1). This could ensure the suitability of all tested superdisintegrants for sublingual application. However, different types and percent of excipients contributed differently in the extent and rate of drug dissolution from tablet formulations. Therefore, discrimination was performed on the light of the calculated dissolution rate constants.

Wetting time
Five percent Glycolys (F7) in tablet formulations gave the fastest wetting time if compared with ac-di-sol and CP at the same tested concentration (Table 2). The additional amount of mannitol present in F7 might be the cause of enhanced wetting. It was also remarkable that for ac-di-sol and Cp, complete wetting of tablet surface was accelerated by the increase in the percent of added superdisintegrant. This could be reasonable due to their well known strong hydration capacity. Affinity to drag water into their porous structure was enhanced with increase in concentration, thereby allowing water to spread and absorb more rapidly into tablet matrix. However, 10% CP was superior to the same concentration of ac-di-sol in fastening the wetting of tablet probably due to less swelling energy and hence easier water uptake (Table 1 and Figure 2).

Table 1. Physicochemical characteristics of tablet formulations.

<table>
<thead>
<tr>
<th>Formula Code</th>
<th>Weight %a</th>
<th>%Friabilitya</th>
<th>Disintegration time (min, s)</th>
<th>Wetting time (min, s)</th>
<th>Water absorption ratio</th>
<th>Drug contentb</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>4.646</td>
<td>0.613</td>
<td>1.51±0.064</td>
<td>1.11±0.010</td>
<td>45.93</td>
<td>90.4±3.34</td>
</tr>
<tr>
<td>F2</td>
<td>0.479</td>
<td>3.312</td>
<td>1.37±0.135</td>
<td>1.14±0.031</td>
<td>42.93</td>
<td>90.8±2.83</td>
</tr>
<tr>
<td>F3</td>
<td>4.250</td>
<td>3.330</td>
<td>1.25±0.01</td>
<td>0.95±0.346</td>
<td>17.23</td>
<td>91.6±2.26</td>
</tr>
<tr>
<td>F4</td>
<td>4.580</td>
<td>0.690</td>
<td>1.26±0.049</td>
<td>0.40±0.064</td>
<td>48.03</td>
<td>90.1±2.63</td>
</tr>
<tr>
<td>F5</td>
<td>0.830</td>
<td>0.500</td>
<td>1.16±0.029</td>
<td>0.20±0.015</td>
<td>62.23</td>
<td>97.6±4.21</td>
</tr>
<tr>
<td>F6</td>
<td>1.170</td>
<td>2.330</td>
<td>1.26±0.029</td>
<td>1.20±0.076</td>
<td>53.26</td>
<td>93.5±3.93</td>
</tr>
<tr>
<td>F7</td>
<td>4.125</td>
<td>8.052</td>
<td>1.16±0.032</td>
<td>0.29±0.062</td>
<td>54.34</td>
<td>92.5±2.54</td>
</tr>
</tbody>
</table>

aData represent % variation from the mean, calculated as 100 – mean%.

bData are expressed as % from the theoretical content.

Table 2. Composition of tablet formulations.

<table>
<thead>
<tr>
<th>Added Excipients</th>
<th>Tablet formulations (respective weights in mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel PH102 (microcrystalline cellulose)</td>
<td>F1 61.74</td>
</tr>
<tr>
<td>LSHPH C</td>
<td>6.86</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.372</td>
</tr>
<tr>
<td>Mannitol</td>
<td>–</td>
</tr>
<tr>
<td>Ac-di-sol (cross linked sodium carboxymethylcellulose)</td>
<td>–</td>
</tr>
<tr>
<td>Crosspovidone (cross linked N-vinyl-2-pyrolidone)</td>
<td>–</td>
</tr>
<tr>
<td>Glycols (sodium carboxymethyl starch)</td>
<td>–</td>
</tr>
<tr>
<td>Pearlitol flash (a compound of mannitol and maize starch)</td>
<td>–</td>
</tr>
</tbody>
</table>
The use of mannitol in formulations might be accused for poor tablet cohesion (Table 1). Addition of 1% of the latter in formulae (F2, F3, and F6) (Table 2) caused a significant increase in percent friability if compared to F1 devoid of mannitol. The use of 45% Pearlitol flash in F7 resulted in the highest record. On the other hand, the good compaction property of cross povidone and ac-di-sol seemed to overshadow the effect of added mannitol. This was elucidated by a less friability percent upon increasing the concentration of the two latters to 10% of tablet weight (F4 and F5, respectively).

In vitro release study
Kinetic treatment of release data (Table 3 and Figure 3) revealed that tablet formulation (F1) containing only MCC and HPC had the lowest release rate constant. This was reflected on dissolution half-life which showed the highest value (~16 min.). Hence, MCC & HPC alone were not sufficient to attain the goal for a fast release sublingual tablet.

Addition of 1% mannitol to the formulation (F2) caused a slight decrease in $t^{1/2}$ to 9 min. Being an osmotic diuretic,[38] mannitol might drag more effectively dissolution medium inside the tablet, where it dissolved first, leaving behind a porous matrix with more channels. Faster disintegration with subsequent drug dissolution occurred in consequence. Furthermore, the facilitated inward diffusion of dissolution medium caused an amount of drug (5%) to dissolve from the surface layer of tablet matrix giving a higher percent of flush release than that present in F1 devoid of mannitol.

For more enhancement of drug release rate, ac-di-sol was added in formulations F3 and F4 in concentrations, 5 and 10%, respectively. Although a slight fastening in $t^{1/2}$ occurred to 5.6 min in F3, doubling the % of the excipient did not further enhance the rate of drug release. This might be interpreted on the light of the dual action of the added excipient on drug disintegration and dissolution. The well known fibrous nature of ac-di-sol might cause a water wicking effect that pulled aqueous medium into the core of the tablet thereby enabling faster drug dissolution. Its cross linked chemical structure created an insoluble hydrophilic and highly adsorbent matrix, which upon swelling to many times its original volume caused a rapid disintegration of tablet with subsequent outer release of the drug included.[39] Therefore, the enhancing in rate of drug dissolution was partially limited by the swelling capacity of ac-di-sol, that might attain equilibrium at the lower concentration used.

On the other hand, drug release at zero time (flush release) increased from 0.4 to about 1.9 mg% by increasing the % of ac-di-sol from 5 to 10%, respectively (Table 3). This
could be a result of more water uptake into the tablet causing instant drug dissolution from the superficial layers of the matrix before swelling and subsequent disintegration took place.

The addition of 5% CP into the tablet core (F6) resulted in a flush release almost the same as in F3 having 5% ac-di-sol, indicating possible similarity in efficiency of water uptake for the two tested superdisintegrants. However, F6 showed a much faster release as \( t^{1/2} \) dropped from 5.6 min (F3) to 0.8 min. This result could be due to the higher porous nature of CP, creating a matrix from which MH could be released much faster, before disintegration could even be completed.

Increasing the concentration of CP to 10% (F5) did not cause a remarkable variation in \( t^{1/2} \), only a change in drug release mechanism occurred from first to zero-order kinetics (Table 4) accompanied by a disappearance of flush release and a lag time of 0.57 min. appeared instead.

Attempting to explore a reasonable interpretation for such result, one or more suggestions were expected to influence the change in release kinetics of MH at higher concentration of CP.

- Existence of physical and/or chemical interaction between the drug and excipient, which was concentration dependent.
- Contribution of the spacial alignment of polymeric network inside tablet matrix at either concentration studied.

In order to study the first suggestion, DSC and IR spectra were performed for MH, CP each alone and their physical mixture corresponding to weight ratios in F5 and F6. However, according to Figures 4 and 5 no sign of

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Slope</th>
<th>Y intercept</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1 2.1146</td>
<td>−0.019</td>
<td>16.386</td>
<td>0.6805879</td>
</tr>
<tr>
<td>F2 2.4052</td>
<td>−0.0322</td>
<td>14.414</td>
<td>0.58957</td>
</tr>
<tr>
<td>F3 19.96</td>
<td>−0.4596</td>
<td>13.686</td>
<td>0.89067</td>
</tr>
<tr>
<td>F4 2.0218</td>
<td>−0.0537</td>
<td>15.524</td>
<td>0.703349</td>
</tr>
<tr>
<td>F5 58.69</td>
<td>−0.7713</td>
<td>119.75</td>
<td>0.9478924</td>
</tr>
<tr>
<td>F6 23.784</td>
<td>−0.3672</td>
<td>78.534</td>
<td>0.94244</td>
</tr>
<tr>
<td>F7 4.8837</td>
<td>−0.0715</td>
<td>26.206</td>
<td>0.87578536</td>
</tr>
</tbody>
</table>

Figure 5. IR spectra for optimized tablet formulae.
chemical or physical interaction between the drug and excipient was revealed.

Second, the spacial alignment of polymeric network inside tablet matrix was elucidated by SEM analysis (Figure 6). Surface topography of tablet at lower CP concentration (F6), showed almost smooth non porous surface. However, increasing the concentration of CP (F5) revealed a significant change, in the form of rough reticulations with occasional pores on the surface. These porous reticulations were extending to the interior of tablet core as shown in the cross-section.

Tablet matrix also showed narrow passages in F6, which were changed to wide interconnected pores at high concentration of the excipient (F5). Furthermore the observed pores became much wider after inward access of dissolution medium into the core.

From the previous observations it could be reasonable to postulate that, inward diffusion of buffer system was facilitated through such wide interconnected pores, without preliminary dissolution of drug from tablet surface. That’s why flush release was eliminated and instead a lag time appeared. This was equivalent to the time taken by dissolution medium to access tablet core before fast outward drug release was achieved. Furthermore, the alignment of polymeric network could match with the geometrical model proposed by Landgraf et al. In this model, polymeric structure resembled an infinite number of superimposed cylinders creating almost equal path lengths for the outward emergence of the drug. In such case a constant zero-order release profile could be approached. The presence of large number of interconnected cavities permitted fast release of the drug from tablet matrix which was completed almost before disintegration went to completion.

Conclusion

Polymers possessing highly porous nature like cross povidone could be helpful in the design of a proper formulation. The physicochemical properties of such polymer could be tailored at optimum concentration so as to create a variation in the geometry inside tablet matrix offering a well organized interconnected structure. Release of drug from such assembly could satisfy the goal of the present research being fast and constant zero order with time.

Declaration of interest

The author reports no conflicts of interest. The protocol of the present work was approved by Experiments and Advanced Pharmaceutical Research Unit (EAPRU), Faculty of Pharmacy, Cairo University.

References
