The influence of the composition and charges of the acrylic resins, the hydrophilic polymer, and the other excipients on the release rate of drug from the matrices.

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Running Title: The influence of composition and charges of the acrylic resins on drug release

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Abstract

The effect of the hydrophilic polymers such as sodium carboxymethyl cellulose, (NaCMC) and the hydrophobic polymers such as Eudragit RL100 and Eudragit RS 100 on the dissolution and the release rate of drug when prepared as controlled release matrices were studied. Tablets were prepared by a direct compression technique. The dissolution tests were performed by both the basket and the paddle methods. In the present study the acrylic resins Eudragit RS 100 and Eudragit RL 100 are separately mixed with the anionic and hydrophilic polymer NaCMC and the other excipients in an attempt to prepare controlled release matrices and to investigate the effect of the charge and composition of these polymers on the drug release. Also the research will study the effect of the pH of the dissolution medium, and the storage of the matrices at different temperatures, on the release rate of the drug. It was found that percent, charge of the polymers, pH of the dissolution medium and storage of matrices at different temperatures affect the release rate of the drug. The experiments were performed in vitro and the data obtained were plotted according to four kinetic models to study the release kinetic. These models were zero order release, first order release, Higuchi equation, and Korsmeyer equation. Zero order release was observed in the formulation with a high percent of the hydrophilic polymers, while high percent of hydrophobic polymers didn’t show zero order release and the drug was liberated in a less time from the matrices.

Keywords: propranolol HCl, matrix, controlled release, Eudragit RS100, Eudragit RL100, Sodium Carboxymethylcellulose.

Introduction

The polymers are widely used in the preparation of controlled release matrices due to their simplicity, safety and it should be economical use [1-4]. Among these polymers celluloses have been extremely popular in controlling the release rate of soluble drug from solid dosage form. The ease of compression, their ability to accommodate large amount of drugs and the minimum processing variables on the release rate are the main reasons for their popularity [1-2]. Sodium carboxymethylcellulose is a widely used polymer, due to its availability in a range of viscosity grades and good swelling and erosion characteristics, which can be used to modulate the release of various drugs [5 – 10]. Many active substances have a short half-life, such as propranolol hydrochloride 3 to 4 hours [11]. So, the patients have to use the drug three to four times a day. As a result, controlled release formulations are necessary to reduce the patient participation in the process of therapy and to improve his compliance to the medicine [12].

Several researches investigated the effect of combination of the hydrophilic and hydrophobic polymers which caused a modification of the drug release from the matrices [13- 17].

Also a number of studies investigated the effect of the inclusion surfactants on the release rate of drugs from the
controlled release matrices [18 – 22]. The studies showed increase of drug release when both the drug and the surfactant have the same charges and a decrease of drug release when they have different charges. A number of publications have reported the interactions between some anionic polymers and the cationic drugs in the dissolution medium that lead to decrease in drug release. [23- 26].

The purpose of the present study was to investigate the effect of the polymer composition, its charge on drug release from the matrices. It also reports the effect of different parameters such as pH of the dissolution medium, and the storage conditions of the tablets on the release rate of the drug.

**Experimental**

**Materials**

To prepare the matrices the following materials were employed: Propranolol HCl, dextrose, sorbitol and lactose.

<table>
<thead>
<tr>
<th>Ingredient</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>
<th>F9</th>
<th>F10</th>
<th>F11</th>
<th>F12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol HCl</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
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</tr>
<tr>
<td>Eudragit RL100</td>
<td>69%</td>
<td>69%</td>
<td>69%</td>
<td>79%</td>
<td>59%</td>
<td>40%</td>
<td>20%</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dextrose,* or sorbitol or lactose</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium stearate.</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
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<td>1%</td>
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<td>1%</td>
</tr>
<tr>
<td>Eudragit RS100</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>NaCMC</td>
<td></td>
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</tr>
</tbody>
</table>

* F1 = 10% lactose, F2 = 10%, sorbitol, F3 =10% dextrose.

**Preparation of tablets**

The acrylic resin Eudragit RL100 and RS100 were powdered in a Ball Mil and sieved through a 300 μm sieve and further blended with propranolol HCl and the other additives for five minutes in a blender. The different formulations prepared, are shown in table 1.

The powder mixture was compressed to prepare tablets of 400 mg using the direct compression technique, an instrumental single punch tabletting machine, (Korch-Erweka).

The diameter and the thickness of the cylindrical tablets were 1 cm, and 0.4 cm respectively and the weight of each tablet was 400 mg. The hardness level of the tablets was about 9 kg and a schleuniger – 2 hardness tester was employed for its determination.

**Physical evaluation of tablets**

**Weight deviation**

20 tablets were weighed individually and together in an electrical balance and the average weight was recorded and the standard deviation was calculated. According to the USP limits for weight variation in case of tablet weighting up to 130 mg is ± 10 %, less than 324 mg ± 7.5 %, and more than 324 mg ± 5%.

were sponsored by the Arab Pharmaceutical Manufacturing- Jordan (APM), Magnesium stearate was purchased from BDH, Eudragit RL100 and Eudragit RS 100 were sponsored by Rohm Pharma, and Sodium carboxymethyl cellulose was purchased from FMC. All chemicals were reagent grade.

**Friability test**

The friability of 20 tablets was determined using a Roche friabilitor (Érweka, Germany). A total 20 tablets from each formulation were weighed and tested at a speed of 25 rpm for 4 minutes. After removing the dust the tablets were re- weighed. All the tablets passed the test as per the following equation.

\[
\% \text{ of friability} = \left( \frac{W_1 - W_2}{W_1} \right) \times 100
\]

N.B. W1: is the weight the tablets before the friability test and W2 is after the friability test.
In vitro dissolution test

The United States Pharmacopoeia (USP) basket and paddle methods (Erweka, DT 6R, Heusenstamm, Germany) were used for all the in vitro dissolution studies. The test was performed at 37 ± 0.1 °C with a rotation speed of 50 and 100 rpm using 900 ml of the dissolution medium.

Assay

Samples of 5 ml were withdrawn after each hour from the dissolution medium and replaced immediately with an equal volume of the respective dissolution medium maintained at 37 ± 0.1°C. Test samples were filtered through 0.45 μm filter, and assayed spectrophotometrically at 289 nm using a blank solution as a reference with a UV-Vis double-beam spectrophotometer (Systronic 2202). The mean of three determinations was used to calculate the drug release rate from each of the formulations.

Kinetic of release analysis

The following equations were applied to interpret the kinetics of drug release from the matrices.

Zero order equation:

\[ C = k_0 t \]

C = the cumulative of drug amount release versus time t and \( k_0 \) is the zero-order rate constant.

First order release:

\[ \log C = \log C_0 - K_1 t / 2.303 \]

Log cumulative percent of drug remaining plotted versus time, t. \( C_0 \) is the initial concentration and \( K_1 \) is the first order constant.

Higuchi equation:

\[ Q = KH t^{1/2} \]

Q = cumulative percentage of drug release plotted versus square root of time, t

KH : is the Higuchi dissolution constant.

Korsmeyer equation:

\[ Mt/M_a = Kk t \]

\( Mt/M_a \) = log cumulative percentage of drug release versus log time, t and \( Kk \) is the Korsmeyer release rate constant.

Results and Discussion

Several publications report that effect of surfactant solubility, charge and concentration on drug release from the matrices. And the results of these studies indicate a very interesting effect on the release rate of drug [8 – 10, 18 -20]. Moreover several studies have shown the effect of hydrophilic and hydrophobic polymers on drug release [1, 8 -10, 13-15]. Most of these studies focused on the mechanisms of the drug release from the hydrophilic matrices may be because of. Disintegration of the tablets [1, 19]; Attrition (erosion) of the tablets [18 -20]; Destruction of the matrices [1, 19, 27]; the release rate of the drug from the hydrophilic matrices was mainly due to the swelling and sometimes due to the erosion and destruction of the tablets when the formulation is a mixture of the hydrophobic/hydrophilic polymers. [8 -10, 1-4]

In the formula F1 with 10 % lactose, the tablets were disintegrated within two hours and the entire drug was released, while in the formulations F2 and F3 the tablets were disintegrated within three hours and the entire drug was released, inspite of the least solubility of lactose in comparison with sorbitol and dextrose [11]. These results may be due to the formation of a more viscous solution around the tablets in the case of sorbitol and dextrose and not in tablets containing lactose. (Figure.1). In formula F4 the entire drug was released in less than four hours because the drug started to dissolve in the dissolution medium and pores were formed within the tablets which led to destruction of the tablets and release the entire drug.

In the formulations F5 to F8, it was observed that as the percent of the hydrophilic sodium carboxymethyl cellulose increased in the matrices, the release rate of drug decreased, while when this percent decreased the release rate of drug from the matrices increased. Conversely as the percent of Eudragit RL100 increased in the matrices the release rate of drug increased. In formula F5 when the Eudragit RL100 was 59 % and the sodium carboxymethyl cellulose (NaCMC) was 20 % from the weight of the tablet the release of drug was completed in 5 hours (Figure.1). The percent of drug release in formula F6 reached 95 % after the eighth hour and 70 % in the formula F7. (Figure.1) the lowest release rate of drug was observed in formula F8 (56 %) where the hydrophilic NaCMC was the highest (69 %) from the weight of the tablet the hydrophobic polymers RL100 was 10 % from the weight of the tablet (F8). All these experiments were done in dissolution medium of 1.2 and stirring speed of 50 rpm by the paddle method.
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The formula F9 where the hydrophilic polymer NaCMC was 20% from the weight of the tablets and Eudragit RS100 was 69%, the entire drug was released in 4 hours. While in formula F12 when NaCMC was 69% from the weight of the tablet and Eudragit RS100 was 10%, from the weight of the tablet the release rate of the drug in the eighth hour was 64%. The percent of drug release from formula F10 was 98% in the eighth hour and 73% in the case of formula F11 (Figure 2). All these experiments were done in dissolution medium of 1.2 and stirring speed of 50 rpm by the paddle method.

From the results obtained it was observed that as the percent of the hydrophilic NaCMC increased the release rate of drug decreased, these findings may be because of; The ability of the hydrophilic polymer to swell and absorb an extra amount of the dissolution medium with a result of reducing or controlling the drug release [8-10, 21]; The slowly erosion or attrition of the hydrophilic NaCMC from the tablets which resulted in a decrease of drug release [1, 18-20]; Propranolol hydrochloride is a cationic drug and NaCMC is an anionic polymer so, they may form a complex which decrease the drug release, these phenomena were reported in many studies when the anionic surfactants and the cationic drugs were used to prepare controlled release matrices, [1, 13]; The cationic ammonium groups in the Eudagit RL100 make it slightly cationic polymer which may enhance the complex formation and reinforce the decrease of the drug release [19]; The amount of the soluble ammonium groups in the Eudragit RL100 increased the penetration of the dissolution medium into the matrices and increases the swellability of the tablet which decreases the release rate of the drug [19].

These results also, gave an evidence that the ammonium groups have an effect on the swelling rate of the tablets because the formulations F9 to F12 contain Eudragit RS100 that contain less amount of ammonium groups and this showed more increase in the release rate of the drug. The release of the drug from the tablets may occurred by attrition and disintegration while, in the formulations (F5 – F8) that contained Eudragit RL100 with a higher amount of the ammonium groups absorbed and enhances the swelling rate of the tablets which reduce the diffusion of the drug from the matrices (Figure 2).

In formula F11 the concentration of propranolol Hydrochloride is 20%, Eudragit RS100 20%, Sodium carboxymethyl cellulose 59% and Mg stearate 1% from the tablet weight, the effect of different parameters such as...
the pH of the dissolution medium, the stirring speed and the storage conditions were studied. The results revealed that the dissolution medium of a pH $\approx 7.4$ increased the release rate of drug. The percent of drug release was 97% at stirring speed of 50 rpm after eight hours. These results may be due to both of the erosion and diffusion effect of this medium on the swollen matrices of NaCMC (1, 23). While the release rate of the drug was 64% at the same stirring speed when the dissolution medium was simulated gastric fluid at pH $\approx 1.2$ after eight hours. These results may be due to the diffusion of drug only from the matrices (Figure.3). It was also observed from the experiments that the increase of the stirring speed from 50 rpm to 100 rpm in the dissolution medium of a pH $\approx 7.4$ increased the release rate of the drug from 97% in the eighth hour at 50 rpm to 100% in the sixth hour at the 100 rpm; while when the stirring speed increased from 50 to 100 rpm in the pH $=1.2$ the release rate increased from 64 to 73% after eight hours. These results were due to the increase of agitation of the dissolution medium which increased diffusion and erosion of the matrices. (Figure.3)

The effect of storage at a higher temperature was investigated. Tablets from the formula 11 were stored for 100 days at 25 °C, 45° C and 60° C to study the effect of temperature on the drug. The results revealed a decrease of drug release after the eighth hour from (72 %) at 25° C to 63% at 45°C and (48 %) at 60°C at a stirring speed of 50 rpm and dissolution medium of pH $\approx 7.4$, (Figure.3). These results may be due to the decomposition of the drug during the storage at these temperatures.

Table: 2 Release kinetic study

<table>
<thead>
<tr>
<th>formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi equation</th>
<th>Korsmeyer</th>
</tr>
</thead>
<tbody>
<tr>
<td>F6</td>
<td>0.999287</td>
<td>0.57766</td>
<td>0.991412</td>
<td>0.86887</td>
</tr>
<tr>
<td>F7</td>
<td>0.997296</td>
<td>0.84551</td>
<td>0.967432</td>
<td>0.87278</td>
</tr>
<tr>
<td>F8</td>
<td>0.997632</td>
<td>0.84425</td>
<td>0.927041</td>
<td>0.85191</td>
</tr>
<tr>
<td>F10</td>
<td>0.985719</td>
<td>0.86636</td>
<td>0.918766</td>
<td>0.90348</td>
</tr>
<tr>
<td>F11</td>
<td>1</td>
<td>0.84574</td>
<td>0.948083</td>
<td>0.85909</td>
</tr>
<tr>
<td>F12</td>
<td>0.998399</td>
<td>0.84263</td>
<td>0.977348</td>
<td>0.89344</td>
</tr>
</tbody>
</table>

Kinetic assessment of the release mechanism

To know the mechanism of drug release from the formulations (F6, to F12) the data were analyzed according to zero order (cumulative percentage of drug release vs. time), first order (log percentage of drug remaining vs. time), Higuchi’s equation (cumulative percentage of drug release vs. square root of time), and Korsmeyer equation (log cumulative percentage of drug release vs. log time). F9 was not assessed because the entire drug was released in less than 4 hours. The results of the of the regression value are shown in Table 2. When the data were plotted according to the zero order release the higher linearity was observed in the formula F11 in which the value of $(r²) =1$. The other regression values were between 1 and 0.985 which suggest a high linearity. When the data were plotted according to the first order release a good linearity was observed in all the formulation except formulation F6 in which the amount of the hydrophilic and hydrophobic polymers in the tablets approximately equals which suggest that the drug release from the matrices occurred by two mechanisms the diffusion and the erosion of the tablets in the specified hours the regression values were between 0.57766 and 0.886636. When the data were plotted according to the Higuchi equation in the formulations (F6, to F12) the higher regression values was 0.991 which suggest that the release of the drug occurred by erosion and diffusion from the tablets. To confirm the diffusion mechanism, the data were fit to korsmeyer equation and the formulation showed a good linearity with slope (n) values ranging from 0.90348 to 0.85191. These values appears to indicate the release of drug occurred by anomalous diffusion. Finally from the formulations above (Table 2), we propose that the drug release is controlled by more than on mechanism.
Conclusion

The dissolution data obtained show that it is possible to prepare dosage form that delivers the drug at constant rate by changing the ratios of the polymers and the excipients. The data also indicates that the acrylic resin used has an interesting effect on the release rate of the drug due to the differences in the composition of the resin that is the amount of the soluble quaternary ammonium groups in each polymer. The charges of the drug and the polymer (hydrophilic and hydrophobic) have its effect on the release rate of drug. Finally the pH, the dissolution medium, the temperature had an effect on the release of drug.

References

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