Introduction

Chronic bronchopulmonary diseases are common health problems that are characterized by abnormal mucus secretion and impaired mucus transport. They are often associated with infectious microorganisms and thus treated with potent antibiotics, anti-tuberculosis drugs and antifungal agents. Mucolytic agents are useful in adjunctive therapy of respiratory tract disorders producing a modest improvement in symptom control and lung function. It has been demonstrated that there is a synergism between mucolytics and antibiotics in the treatment of exacerbation of chronic bronchitis. Moreover, mucolytics act as scavengers of reactive oxygen species overexpressed by the body especially during periods of oxidative stress when they can significantly damage cell structures.[2]

Ambroxol (trans-4-(2-amino-3,5-dibromobenzyl)-aminocyclo-hexanol) is an active metabolite of bromhexin that has been used to increase surfactant secretion in the lungs and as mucolytic to breakdown acid mucopolysaccharide fibers making the sputum thinner and less viscous thus more easily removed by coughing.[1] Ambroxol has also been reported to have a cough-suppressing effect[3] and anti-inflammatory action through inhibition of mediator release involved in the pathogenesis of allergic inflammation.[4] Therefore, it is frequently used in the treatment of bronchial asthma and chronic bronchitis,[5] and also used in pulmonary alveolar proteinosis and infant respiratory distress syndrome.[6] It is rapidly absorbed after oral administration with an onset of action that occurs after about 30 min followed by fast elimination with a half-life of 3–4 h only thus requiring three dosings per day for optimum therapeutic efficacy. This high dosing frequency may increase the risk of exacerbation of gastrointestinal side effects such as diarrhea, heartburn, indigestion as well as intense headaches, shortness of breath and weakness and possible allergic reactions to the skin.[7] Therefore, several sustained release formulations of Ambroxol have been developed that are based on pellet, capsule dosage

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Abstract

A series of either hydrophilic or hydrophobic polymers were used to prepare controlled release Ambroxol hydrochloride (AMX) matrix tablets by direct compression. Both the compatibility and flow properties of AMX/polymer mixtures were investigated. The effect of the amount and type of polymer on the physical properties and in vitro drug release was studied and compared to commercially available Ambroxol® SR capsules. A kinetic study of the release profile of AMX from the prepared matrix tablets was performed. All excipients used in the study were compatible with the model drug. AMX/drug mixtures containing sodium alginate (NA) and hydroxypropylmethyl cellulose (HPMC) showed better flow properties than other polymers used in the study. The in vitro drug release studies showed that matrix tablets formulae containing 10% HPMC (S7) or a combination of 30% NA and 5% HPMC (Ah) exhibited a higher ability to control the release of AMX. The kinetic study revealed that a diffusion controlled mechanism prevailed except when carbopol was used. Formula Ah followed a non-fickian diffusion mechanism similar to Ambroxol® SR capsules. Both formulae S7 and Ah could be considered as potential candidates for formulation of AMX controlled release matrix tablets.

Keywords: Controlled release, formulation, release kinetics, hydrophilic polymers, hydrophobic polymers

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forms[6] or in situ gelling pectin formulations[9] to improve patient compliance by allowing once daily administration of the drug and therefore avoiding undesirable fluctuation of drug levels, improving efficiency enhancing therapeutic action and eliminating toxic side effects.[10]

Controlled drug release is usually accomplished using a matrix or membrane. Matrix-based formulations are prepared from either swellable hydrophilic or non-swellable hydrophobic excipients or polymers[10,11] and can be considered as an alternative approach to control the release of Ambroxol. Drug release from matrix tablets is controlled by either the dissolution or erosion of the polymeric matrices[12,14] or the formation of a hydrated viscous film around the tablet which acts as a barrier to drug release by opposing water penetration into tablet and also exit of dissolved solutes from the matrix tablets.[12,14] Water-soluble drugs are commonly released by diffusion across the gel layer, whereas poorly water-soluble drugs are usually released by erosion mechanisms. The contribution of each release mechanism to the overall drug release profile is influenced not only by the nature of the drug but also by the hydration characteristics of the polymer and the subsequent physical and mechanical properties of the hydrated gel layer that forms around the tablet.[15] When hydrophilic polymers such as xanthan gum (XG), guar gum (GG), sodium alginate (NA), Carbopol 934, hydroxypropylmethyl cellulose (HPMC), hydroxypropyl cellulose (HPC), methyl cellulose (MC) and chitosan (CH) are used for the preparation of matrix tablets, hydration and gellation of the polymer at the tablet/liquid interface progresses, a viscous gel barrier is formed and the drug is released at a much slower rate.[16] It has been confirmed that drug release from these polymer matrices is controlled by polymer erosion and/or drug diffusion through the polymer matrix or pores in the matrix. On the other hand, hydrophobic matrices prepared by addition of hydrophobic polymers such as ethyl cellulose (EC), cellulose acetate butyrate (CAB) and cellulose acetate phthalate (CAP) as well as lipidic hydrophobic polymers such as Compritol® 888 ATO, Precirol® ATO 5 and hydrophobic polymers (EC, CAB, CAP, Compritol®, 888 ATO, Precirol® ATO 5). The physical and chemical compatibilities and flow properties of the drug/polymer mixtures were evaluated and the physicochemical properties and in vitro release profile of AMX matrix tablets were determined. In addition, a kinetic study of the release profile of AMX was performed in order to gain insight into the release mechanism of the prepared matrix tablets.

Materials and methods

Materials

AMX and Ambroxol® SR 75 mg Capsules were obtained from GlaxoSmithKline (Cairo, Egypt), HPMC type 2208, viscosity 4000 cps, was obtained from Dow Chemicals (Charlotte, NC), Magnesium stearate (NF grade) was obtained from Alfa Chemicals (Kings Port, NY). Carbopol 934P was purchased from Goodrich Chemical Co. (Cleveland, OH). Compritol® 888 ATO (glyceryl behenate) and Precirol® ATO 5 (glyceryl palmitostearate) were purchased from Gattefosse Co. (St priest, France). CAB and CAP were acquired from Eastman Chemical (Kingsport, TN). Lactose, EC (Ethocel 100), MC (Methocel), XG, GG and NA were purchased from Sigma (St Louis, MO). Hydrochloric acid and trisodium orthophosphate were obtained from El-Nasr pharmaceutical & chemicals Company (Cairo, Egypt).

Compatibility study for drug/excipient mixtures

Preparation of drug/excipient mixtures

Physical mixtures of AMX with various excipients namely, magnesium stearate, XG, GG, HPMC 4000 cps, NA, Methocel, Ethocel, CAB, CAP, Carbopol 934P, Compritol® 888 ATO and Precirol® ATO 5 were prepared by mixing AMX with each excipient in the ratio of 1:1 (w/w) in a glass mortar at room temperature.

Differential scanning calorimetry (DSC)

Samples of the drug/excipient mixtures were hermetically sealed in a flat-bottomed aluminum pans and heated in the DSC-50 (Shimidzu, Kyoto, Japan) in an atmosphere of nitrogen to eliminate the oxidative and pyrolytic effects. A temperature range of 25–300°C was used and the heating rate was 10°C/min. The DSC thermograms were recorded and the results were compared to those of control groups consisting of similar amounts of individual components of each mixture.

Fourier-transform infrared spectroscopy

Samples of 2–3 mg of the drug/excipient mixtures were mixed with about 400 mg of dry potassium bromide powder then compressed into transparent discs under pressure of 10,000–15,000 pounds per square inch. The IR spectra of the pure drug, excipients and drug/excipients mixtures were recorded using Fourier-Transform Infrared
FT-IR spectrophotometer (Shimadzu IR-345-U-04, Japan).

**Formulation and characterization of flow properties tablet blends**

Tablet formulae containing drug, lactose as filler, and magnesium stearate as lubricant were prepared by direct mixing. In all formulae, the drug concentration was held constant at 75 mg AMX per 300 mg of formulation and the lubricant concentration was kept constant at 1% w/w. The blends were prepared in a glass mortar using geometrical dilution. Subsequently, random samples of the blends were analyzed to determine the uniformity of mixing. The type and amount of polymers used in the preparation of matrix tablets are given in Table 1.

**Determination of the angle of repose (θ)**

The flow properties of the prepared blends was determined using the fixed height cone method. Briefly, a cut-stem glass funnel was tightened at a height 2.5 cm from the horizontal plane. The powder sample (either the drug alone or its blends) was allowed to flow gently through the funnel till a cone was formed and has reached the surface of the funnel orifice. Powder flow was then stopped and the average diameter of the formed cone (d) was determined. The area of the base of the cone formed was taken as a measure of the internal friction between particles. The angle of repose (θ) was calculated from the equation \( \tan \theta = 2h/d \); where h and d are the height and the diameter of the cone, respectively. The measurement was done in triplicate, and the average angle of repose was calculated for each sample.

**Determination of Carr’s index and hausner ratio of the blends**

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 5 g of the drug or its blends and the volume occupied was recorded as \( V_b \) initial bulk volume, and thereafter the initial or poured bulk density \( D_b \) was calculated as \( D_b = \text{powder weight} / V_b \). The cylindrical graduate was tapped at a constant velocity till a constant volume is obtained, the final bulk volume \( V_f \) was then recorded and the final or tapped density \( D_f \) was calculated as powder \( D_f = \text{powder weight} / V_f \). The percentage compressibility, Carr’s index, was then determined from the equation \( \text{Carr’s index} = (1-V_f/V_b) \times 100 \). And Hausner ratio was obtained by dividing \( V_f \) by \( V_b \). The experiments were done in triplicate and the average bulk density, Carr’s compressibility index, and Hausner ratio of each of the prepared formulae were computed.

**Preparation of AMX matrix tablets**

AMX matrix tablets were prepared using the same blends mentioned previously in section 2.4. The drug, hydrophilic or hydrophobic polymer, and lactose were blended using a flexible mixer (Turbula T2C, Switzerland) for 15 min at 40 rpm. Then, 1% magnesium stearate was added and the mixture was blended using the same mixer for 5 min. The blends were compressed using a tablet single punch press machine (model TDP, Shanghai Tianhe Pharmaceutical machinery factory, Shanghai, China) into 300 mg tablets using 9 mm flat punch and die where the force of compression was kept constant at 10 ± 0.5 kN and a compression rate of 54 tablets per minute.

**Determination of content uniformity**

The uniformity of drug content in the compressed tablets was determined by individually crushing ten tablets from each formula and dissolving the resulting fine particles in 100 ml 0.1 N HCl. The solution was then filtered, properly diluted and the absorbance was measured spectrophotometrically at the predetermined \( \lambda \text{max} \) of AMX of 244 nm using UV/VIS spectrophotometer, UV-1601 PC (Shimadzu, Kyoto Japan).

### Table 1. Polymer composition and physical properties of powder blends.

<table>
<thead>
<tr>
<th>Name</th>
<th>Polymer type</th>
<th>Polymer content (% wt/wt)</th>
<th>Name</th>
<th>Polymer type</th>
<th>Polymer content (% wt/wt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>Guar Gum</td>
<td>10%</td>
<td>S17</td>
<td>Precirol</td>
<td>10%</td>
</tr>
<tr>
<td>S2</td>
<td>Guar Gum</td>
<td>30%</td>
<td>S18</td>
<td>Precirol</td>
<td>30%</td>
</tr>
<tr>
<td>S3</td>
<td>Xanthan Gum</td>
<td>10%</td>
<td>S19</td>
<td>Methocel</td>
<td>10%</td>
</tr>
<tr>
<td>S4</td>
<td>Xanthan Gum</td>
<td>30%</td>
<td>S20</td>
<td>Methocel</td>
<td>30%</td>
</tr>
<tr>
<td>S5</td>
<td>NA</td>
<td>10%</td>
<td>S21</td>
<td>Ethocel</td>
<td>10%</td>
</tr>
<tr>
<td>S6</td>
<td>NA</td>
<td>30%</td>
<td>S22</td>
<td>Ethocel</td>
<td>30%</td>
</tr>
<tr>
<td>S7</td>
<td>HPMC 4000</td>
<td>10%</td>
<td>S23</td>
<td>CAB</td>
<td>10%</td>
</tr>
<tr>
<td>S8</td>
<td>HPMC 4000</td>
<td>30%</td>
<td>S24</td>
<td>CAB</td>
<td>30%</td>
</tr>
<tr>
<td>S9</td>
<td>Carbopol 934</td>
<td>10%</td>
<td>S25</td>
<td>CAP</td>
<td>10%</td>
</tr>
<tr>
<td>S10</td>
<td>Carbopol 934 P</td>
<td>30%</td>
<td>S26</td>
<td>CAP</td>
<td>30%</td>
</tr>
<tr>
<td>S13</td>
<td>HPC</td>
<td>10%</td>
<td>S14</td>
<td>Ac</td>
<td>30% NA + 5% compritol</td>
</tr>
<tr>
<td>S14</td>
<td>HPC</td>
<td>30%</td>
<td>S15</td>
<td>Ap</td>
<td>30% NA + 5% precirol</td>
</tr>
<tr>
<td>S15</td>
<td>Compritol</td>
<td>10%</td>
<td>S16</td>
<td>Ah</td>
<td>30% NA + 5% HPMC 4000</td>
</tr>
<tr>
<td>S16</td>
<td>Compritol</td>
<td>30%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Per 300 mg/tablet.*
Physical  characterization  of  AMX  matrix  tablets

The  determination  of  physical  properties  of  the  prepared matrix  tablets  was  performed  after  a  relaxation  period of at  least 24 h,  at  room temperature.  Determination of weight variation  was  carried  out  according  to  the British  Pharmacopoeia,  where 20 tablets  from  each formula were  individually weighed  (model AC210 S,  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 measured individually  using an electronic micrometer  (model G, Peacock, Japan)  and the mean thickness and diameter  were calculated.  The friability was determined by using  a friabilator (Digital test apparatus,  Model DF11, Vego, Bombay, India) using 20 tablets and  rotating  for 4 min  at  a speed  of 25 rpm.  The tablets were then  brushed  and reweighed.  The percentage loss  in weight  was calculated and taken  as a  measure of friability.[26] The hardness of ten tablets  was determined using hardness  tester (model PTB311, Pharmatest, Germany).

In vitro release  studies

The dissolution and release studies  were carried out using USP dissolution apparatus,  type II  (Type PTW, Pharma Test, Germany) equipped with paddles  which was operated  at the speed of 50 rpm.  Studies were carried out  at 37 ± 0.5°C in 900 ml of 0.1 N HCl (pH 1.2)  for  a  period of 2 h followed  by release in phosphate buffer  (pH 7.4)  for 10 h.  The amount  of drug  released was measured  at the  suitable  time intervals  (0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8 and 12h)  and then  determined spectrophotometrically (UV-1601 PC, Shimadzu, Kyoto Japan) at λmax 244 nm using 0.1 N HCl (pH 1.2)  as a  blank  for  first 2 h then phosphate buffer (pH 7.4)  as a blank for the remaining samples.  Each in vitro release study was performed in triplicate and compared to the release of  the drug from the commercially available Ambroxol® SR capsules.

Kinetic analysis of the release data

The mechanism of  drug release  from matrix tablets during dissolution tests  was determined  by applying  zero order  kinetics,  first order  kinetics,  Higuchi  and Korsmeyer–Peppas models.  The following  linear regression equation were  employed for  zero order  kinetics:  \( F_t = Kt \),[26] where  \( F_t \) represents the fraction of drug released in time \( t \) and \( K \) is the apparent release rate constant or zero order release constant.  First order kinetics was determined  according to the equation Ln \( (1-F) = -Kt \); Where \( F \) represents the fraction of drug released in time \( t \) and \( K \) is the first order release constant.  Drug release following Higuchi model was determined using the equation \( F = Kt^{1/2} \), where \( F \) represents the fraction of drug released in time \( t \) and \( K \) is the Higuchi dissolution constant. The Korsmeyer–Peppas equation \( \frac{M_t}{M_i} = Kt^n \), is often used to describe the drug release behavior from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved;[24] where \( K \) is a kinetic constant incorporating the structural and geometric characteristics of the matrix tablets, \( n \) is the diffusional exponent which depends on the release mechanism and \( \frac{M_t}{M_i} \) represents the drug dissolved fraction at time \( t \). When determining the \( n \) exponent, only the portions of the release profile where \( \frac{M_t}{M_i} \leq 0.6 \) were employed to provide the accurate values.

Results and discussions

Compatibility of drug/polymer mixtures

DSC was performed for AMX, excipients and their physical mixtures prepared at 1:1 weight ratio (Figure 1A) to determine any possible physicochemical interaction between the drug and polymers used in formulation of the matrix tablets.  The DSC thermogram of AMX showed a characteristic sharp melting endothermic peak with an onset at 245.00°C and an end set at 260.06°C with peak at 243.75°C corresponding to the melting point of the drug, followed by an exothermic peak due to degradation of the drug.[25] The thermograms of the physical mixtures of AMX with all selected polymers showed the presence of an endothermic peak similar to that of the drug.  This indicates the existence of the crystalline form of AMX in the physical mixture and the absence of any physical drug/polymer incompatibility.

The compatibility of AMX with each polymer was further investigated by FT-IR Spectroscopy of the drug/polymer mixtures to detect any chemical changes in the drug structure that could not be identified by DSC (Figure 1B).  The FT-IR spectrum of AMX, showed the characteristic bands corresponding to the functional groups of the drug at 3193.89–3281.13 cm⁻¹ (ν -NH₂), 1630.01–1411.78 cm⁻¹ (ν -OH), 2587.08 cm⁻¹ (ν -NH), 1630.01–1411.78 cm⁻¹ (ν C = C aromatic), and 2705.00–2940.03 cm⁻¹ (ν C-H aliphatic).  The FT-IR spectra of the investigated physical mixtures did not show any significant shifts with respect to the FT-IR spectra of the individual components which indicates the absence of any chemical interaction between the drug and polymers and confirm the compatibility of all polymers used in the study with AMX in 50% w/w physical mixture.

Characterization of the flow properties of the powder blends

The flowability of tablet blend is important due to its direct effect on uniformity of die fill and the corresponding uniformity of tablet weight and content.  The reproducible filling of tablet dies improves the weight uniformity and allows the production of tablets with more consistent physicochemical properties.  Additionally, the flowability is essential for blending and powder homogeneity because uneven powder flow can result in excess entrapped air which may promote capping or lamination and may also increase the particle-die-wall friction resulting in lubrication problems.[26,27]
Powder flow and compaction are influenced by many physical, mechanical and environmental factors. Physical factors such as particle shape, size, size distribution, purity, crystallinity and surface energy affect the powder flow. Elastic and plastic deformations are examples of mechanical factors that affect the powder flow properties while a number of environmental factors such as humidity, adsorbed impurities, consolidation load and time have also important influences on flowability of powder blends. Therefore, powder flow is a complicated matter, and no single parameter is likely to meet every need. Therefore, several parameters were combined to be indicative of powder flow. In this study, the flow properties of the powder mixtures were determined by measuring of the angle of repose $\theta$ and computing Carr’s index (compressibility index) and Hausner ratio. The angle of repose $\theta$ is a characteristic of the internal friction or cohesion of the particles and is used as an indirect method of quantifying powder flowability, because of its relationship with interparticle cohesion, friction, or resistance to movement between particles. In general, the value of the angle of repose increases with more cohesive powders. Accordingly, powders with angle of repose above 50° have unsatisfactory difficult flow properties; those with angles from 25 to 40° have reasonable flow potential, whereas powders with minimum angles close to 25° correspond to very good flow properties. However, angle of repose measurement has generally not been considered as a reliable predictor of powder flow in part due to lack of sensitivity of the method to distinguish between two “slightly” different flowing materials and also due to unavoidable experimental difficulties such as powder-bed consolidation, particle segregation, and aeration in forming the powder cone which cannot be easily avoided. Therefore, Carr proposed that the angle of repose should be just one of several methods used in characterizing powder flow. The results of angle of repose ($\theta$) measurements (Figure 2A) showed that almost all formulae (except S6, S8, Ah) have an angle of repose between 25° and 40° indicating reasonable flow, while angles of repose for (S6, S8 and Ah) were less than 25° indicating very good flow properties.

Compressibility index or Carr’s index ($C_i$) is another simple, fast and popular method for predicting powder flow characteristics beside its use as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials since all of these can influence the observed compressibility index. Carr’s index value between 16 and 21 generally indicates good flow properties. Nevertheless, compressibility should be used with other measures of flow since no single type of measurement adequately assesses all the factors influencing flow. Carr’s index determination (Figure 2B) showed that almost all formulae had fair flow except formulae (S6, S8, Ah) which showed good flow while formulae (S1, S3, S15, S17 and S26) had poor flow properties. These results correlate to those of angle of repose measurements in showing that blends S6, S8, and Ah had

![Figure 1. Physical and chemical compatibility of AMX and its 1:1 w/w mixtures with different hydrophilic and hydrophobic polymers. (A) DSC thermograms and (B) IR spectra.](image)
superior flow properties than the other blends. However, it has to be noted that Carr’s index is a one-point determination and does not reflect the ease or speed with which consolidation occurs. Indeed some materials have a high index suggesting poor flow but may consolidate rapidly, which is essential for uniform filling on machine.\cite{31}

Hausner’s ratio is related to interparticle friction, therefore used to predict powder flow properties. Powders with low interparticle friction have ratios of ~1.2, while more cohesive, less flowing powders have ratios greater than 1.6.\cite{31} Hausner ratio values for tested blends (Figure 2C) showed that most formulae had values of ~1.2–1.6 indicating more cohesive and less flowing powders except formulae S6, S8, S20 and Ah which had Hausner ratio >1.2 indicating low interparticle friction which also correlates with the results obtained from angle of repose measurements and Carr’s index determination. These results indicate that blends containing 30% NA, HPMC,
Methocel and mixture of 30% NA and 5% HPMC showed the best flow properties due to cross-linking between polymer molecules which increase their particle size and enhance their flow properties. On the other hand, Carr’s index results showed that tablet blends containing gums and Precirol are the least flowable owing to the high cohesive nature of these polymers.

Physical characterization of AMX matrix tablets

The determination of the mean weight of 20 tablets from each formula showed that none of these tablets deviated from the average weight (300 mg) by >5% (Table 2) having an acceptable weight variation range (from 297.85 to 304.10 mg). The average thickness and diameter of ten tablets from each formula measured by a micrometer was found to be in the range 4.21–4.67 mm and 9 mm, respectively (Table 2), which shows the uniformity of the tablet compression process and excludes variations in drug release due to changes in tablet diameter or force of compressions.

The determination of average drug content showed that all tested matrix tablets formulae are in compliance to the pharmacopoeial limits where the average drug content of all formulae lied within the range of 85–115% of the label claim and the standard deviation was <6% (Table 2).

All tested matrix tablet formulae showed a friability value <1% (Table 2) except S1, S2, S3 and S4 which have friability >1% and thus were excluded from subsequent release studies as a maximum loss of 1% of the mass of the tablets tested is considered to be acceptable for most products. This decision was further supported by hardness testing where all formulae showed acceptable hardness values (Figure 3) except S1, S2, S3 and S4 also which had low average hardness value of 2.2–2.5 kg. These results correlates with previous studies which showed that using gums in preparation of matrix tablets by direct compressions results in brittle tablets with high tendency of being friable. The obtained hardness values for the remaining formulae confirm the excellent compactability properties of the used polymers which allowed direct compression even in the absence of other excipients.

Drug release from matrix tablets

Drug release from the Ambroxol® SR capsules was essentially complete after 6 h showing that the study design and selection of media can be considered appropriate for studying the release of AMX from matrix tablets. Releasing of 20–50% of the drug after 3 h ensures that there is no dose dumping from the dosage form. In addition, the purpose of the 12-h sampling time interval is to confirm the complete dissolution of the drug in controlled release.

Table 2. Physical properties of matrix tablets prepared by direct compression.

<table>
<thead>
<tr>
<th>Name</th>
<th>Average weight (mg) ± SD*</th>
<th>Average thickness (mm) ± SD**</th>
<th>Average diameter (mm)**</th>
<th>% Drug content ± SD*</th>
<th>Average friability (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>300.91 ± 0.91</td>
<td>4.17 ± 0.48</td>
<td>9</td>
<td>92.98 ± 1.40</td>
<td>1.28</td>
</tr>
<tr>
<td>S2</td>
<td>299.17 ± 0.54</td>
<td>4.56 ± 0.04</td>
<td>9</td>
<td>97.80 ± 0.76</td>
<td>1.16</td>
</tr>
<tr>
<td>S3</td>
<td>301.35 ± 1.01</td>
<td>4.34 ± 0.66</td>
<td>9</td>
<td>98.33 ± 4.27</td>
<td>1.41</td>
</tr>
<tr>
<td>S4</td>
<td>299.81 ± 0.98</td>
<td>4.40 ± 0.25</td>
<td>9</td>
<td>95.07 ± 2.26</td>
<td>1.37</td>
</tr>
<tr>
<td>S5</td>
<td>299.37 ± 1.08</td>
<td>4.58 ± 0.70</td>
<td>9</td>
<td>102.11 ± 1.95</td>
<td>0.26</td>
</tr>
<tr>
<td>S6</td>
<td>299.69 ± 0.47</td>
<td>4.66 ± 0.51</td>
<td>9</td>
<td>104.40 ± 2.09</td>
<td>0.33</td>
</tr>
<tr>
<td>S7</td>
<td>299.89 ± 0.37</td>
<td>4.72 ± 0.50</td>
<td>9</td>
<td>99.84 ± 0.42</td>
<td>0.47</td>
</tr>
<tr>
<td>S8</td>
<td>301.55 ± 1.14</td>
<td>4.50 ± 0.26</td>
<td>9</td>
<td>89.83 ± 1.54</td>
<td>0.26</td>
</tr>
<tr>
<td>S9</td>
<td>301.94 ± 0.88</td>
<td>4.66 ± 0.66</td>
<td>9</td>
<td>87.99 ± 0.89</td>
<td>0.13</td>
</tr>
<tr>
<td>S10</td>
<td>303.42 ± 0.69</td>
<td>4.47 ± 0.20</td>
<td>9</td>
<td>88.79 ± 1.44</td>
<td>0.053</td>
</tr>
<tr>
<td>S13</td>
<td>299.68 ± 0.76</td>
<td>4.54 ± 0.88</td>
<td>9</td>
<td>108.00 ± 1.34</td>
<td>0.82</td>
</tr>
<tr>
<td>S14</td>
<td>301.86 ± 0.48</td>
<td>4.46 ± 0.05</td>
<td>9</td>
<td>106.20 ± 1.94</td>
<td>0.11</td>
</tr>
<tr>
<td>S15</td>
<td>301.31 ± 1.11</td>
<td>4.58 ± 0.59</td>
<td>9</td>
<td>101.00 ± 4.27</td>
<td>0.17</td>
</tr>
<tr>
<td>S16</td>
<td>300.71 ± 1.05</td>
<td>4.62 ± 0.83</td>
<td>9</td>
<td>96.33 ± 2.75</td>
<td>0.29</td>
</tr>
<tr>
<td>S17</td>
<td>300.51 ± 0.97</td>
<td>4.73 ± 1.39</td>
<td>9</td>
<td>102.00 ± 1.43</td>
<td>0.23</td>
</tr>
<tr>
<td>S18</td>
<td>301.77 ± 0.41</td>
<td>4.57 ± 0.71</td>
<td>9</td>
<td>100.05 ± 2.38</td>
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<td>S19</td>
<td>299.52 ± 1.62</td>
<td>4.78 ± 0.82</td>
<td>9</td>
<td>99.10 ± 2.26</td>
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</tr>
<tr>
<td>S20</td>
<td>300.11 ± 1.04</td>
<td>4.49 ± 0.67</td>
<td>9</td>
<td>96.88 ± 1.86</td>
<td>0.53</td>
</tr>
<tr>
<td>S21</td>
<td>304.52 ± 0.98</td>
<td>4.57 ± 0.86</td>
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<td>98.08 ± 1.67</td>
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</tr>
<tr>
<td>S22</td>
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<td>4.69 ± 0.93</td>
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<td>S23</td>
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<td>S25</td>
<td>298.99 ± 0.99</td>
<td>4.40 ± 0.59</td>
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<tr>
<td>S26</td>
<td>299.89 ± 1.98</td>
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<tr>
<td>Ac</td>
<td>302.00 ± 1.49</td>
<td>4.68 ± 0.77</td>
<td>9</td>
<td>100.10 ± 1.55</td>
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<tr>
<td>Ap</td>
<td>300.19 ± 0.84</td>
<td>4.60 ± 0.67</td>
<td>9</td>
<td>99.98 ± 2.39</td>
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</tr>
<tr>
<td>Ah</td>
<td>303.14 ± 0.97</td>
<td>4.56 ± 0.53</td>
<td>9</td>
<td>90.97 ± 2.84</td>
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* n = 3, ** n = 10.
The release profiles of AMX from matrix tablets (Figures 4, 5 and 6) showed that the drug release was influenced by the amount and type of polymer used in the formulation of matrix tablets.

The drug release from hydrophilic matrix tablets was studied using formulae each containing 10 or 30% of NA, HPMC, carbopol 934P and HPC (Figures 3A and 3B). 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 from matrix tablets containing 10% polymer concentration. Matrix tablets formulae S5, S13 and S14 containing 10% NA and 10 and 30% HPC, respectively, failed to sustain the drug release over 12-h release period and showed a dose dumping where >89% of the drug was released after 3 h. The inability of NA to sustain the release of the drug may be due to the insufficiency of the polymer concentration to form a gel and retard the drug release. The results of drug release from formulae containing HPC agreed with previous studies that showed that HPC is not suitable for the preparation of modified ketoprofen hydrophilic matrix tablets due to lower hydration even after long water exposure periods. On the other hand, formulas S8, S9 and S10 containing 30% HPMC and 10% and 30% carbopol 934P, respectively, showed good retardation of drug release after 3 h; however, they all failed to release >75% of the required drug amount after 12 h. These findings are in agreement with previously reported studies on the effect of HPMC and Carbopol on drug release. The reduction in drug release from high concentrations of HPMC in matrix tablets is due to increased viscosity of the gel matrix which leads to a reduction in the effective diffusion coefficient of the drug. Matrix tablets containing 10–30% Carbopol polymers showed a significant swelling after 2 h which caused a significant reduction in the release of the drug. The swelling may be due to the ionization of the carboxylic acid group of the Carbopol.
causing the ionic repulsion of the polymer at pH 7.4, or it may also be due to the hydration of the polymer which results in an increase in the radius of gyration and end-to-end distances of the polymer chains.\[40\]

Matrix tablets S6 and S7 containing 30% NA and 10% HPMC, respectively, showed a better release profile especially after 3 h where only 56 and 59% of the drug was released from S6 and S7, respectively. However, after 6 h, 85% of AMX was released from formula S6 while only 76% was released from formula S7. Therefore, the presence HPMC at low concentration of 10% w/w enabled the reduction of the rate of drug release to closely match the requirements for controlled release dosage forms.

AMX matrix tablets prepared by direct compression of the drug with 10 or 30% hydrophobic polymers showed complete release of the drug after 12 h (Figures 4A and 4B) except for S16 and S24 containing 30% Compritol® 888 ATO and 30% CAB, which showed 48.78% and 89.29% release after 12 h, respectively (Figure 5B). Similar to hydrophilic polymers, matrix tablets containing a lower concentration of hydrophobic polymers generally showed a faster release than those containing a higher concentration of the same polymer probably due to a greater reduction in drug diffusion into the medium in the presence of a large polymer concentration. In addition, drug release from all matrix tablets containing 10% hydrophobic polymers was faster than that of Ambroxol® SR capsules showing a dose dumping effect where >85% of the drug was released after 3 h. Similar, results were obtained for matrix tablets formulae S18, S20, S22, S24 and S26 where >67% of the dose was released after 3 h. Therefore, none of the hydrophobic polymers used in the study was capable of providing an extended-release profile at the used concentration of the drug and the method used for matrix tablet preparation. The dose dumping effect and the inability of hydrophobic polymers to control the drug release may be due to greater loss of structure or weakening of bonds between particles at 37°C in the compressed matrices prepared from hydrophobic polymers especially those with low melting point such as Precirol® ATO 5. It 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 NA and HPMC. The fast release of drug from matrix tablets prepared from hydrophobic cellulose derivatives was also reported previously where a release modifier such as poly ethylene oxide is essential to aid the sustained release of the drug from matrix tablets containing EC.\[37\]

**Kinetic analysis of the release data**

Drug release from polymer-based matrix tablets is a complex process that may be purely diffusion or erosion controlled, or may exhibit a combination of these mechanisms.\[41,42\] In order to determine the model of drug release, the *in vitro* release data were analyzed according to zero order, first order, Higuchi model and Korsmeyer–Peppas equation (Table 3). Higuchi model is applicable when the release of drug is largely governed by diffusion through water-filled pores in the matrix. The preference of a certain mechanism was based on the determination of coefficient of determination ($r^2$) for the parameters studied only for the early
stages (≤60%) of drug release, where the highest coefficient of determination is preferred for the selection of the order of release. The release of AMX followed the diffusion mechanism from all matrix tablets formulae containing hydrophilic polymers except S9 and S10 which followed first order kinetics. Similar results were obtained for all matrix tablets formulated using hydrophobic polymers or a combination of two polymers where the release of the drug from the matrix followed diffusion mechanism.

A good fit to Korsmeyer–Peppas equation indicates combined effect of diffusion and erosion mechanisms for drug release.\(^{24}\) It depends on the release mechanism and the shape of the drug delivery system.\(^{43}\) In case of cylindrical tablets, \(n \leq 0.45\) corresponds to a Case I Fickian diffusion release. In Case II transport or relaxation-controlled release, the exponent \(n\) is 0.89 for the release from cylinders. The non-Fickian release or anomalous transport of drug occurs when the \(n\) value lies between the limiting values of Fickian and Case II transport. This non-Fickian kinetics corresponds to coupled diffusion/polymer relaxation. Occasionally, values of \(n > 0.89\) for release from cylinders have been observed, which has been regarded as a Super-Case II transport that may result from an increased plasticization at the relaxing boundary.\(^{36,44,45}\) The values of release parameters, \(n\) and \(k\), are inversely related where a higher value of \(k\) may suggest burst drug release from the matrix. The equation is, however, valid only for the early stages (≤60%) of drug release\(^{24}\) where three points at least should be ≤60%. Therefore, in formulas S13, S14, S17, S19, S20, S21, S22, S23 and S25 there was no enough data for fitting to this model.

The fitting of drug release data to Korsmeyer–Peppas model from Ambroxol\textsuperscript{®} SR capsules, and directly compressed matrix tablets containing hydrophilic and hydrophobic polymers showed that Ambroxol\textsuperscript{®} SR capsules and all prepared matrix tablets had \(n\) in the range 0.45–0.89 indicating anomalous (non-Fickian) transport; except formulae S5, S7, S8, S24, S26 were \(n\) was ≤0.45 indicating Fickian diffusion (Table 3).

To this end, only matrix tablets formula S7 containing 10% HPMC showed a suitable release profile that fits the requirements for extended-release dosage forms compared to other hydrophilic or hydrophobic polymers used in this study. However, the amount of drug released from formula S7 after 3h was 59% which is still slightly higher than the maximum required amount (50%) of the drug to be released after this time period. In addition, although the drug release from S7 did not follow zero order kinetics characteristic for controlled release dosage form, the drug was released by diffusion from the matrix tablets which matches the mechanism of drug release from commercially available sustained release Ambroxol\textsuperscript{®} SR capsules. Therefore, an attempt was made to optimize the drug release from the prepared matrix.
tablets using combinations of hydrophilic polymers or hydrophilic/hydrophobic polymers (Figure 6). Formula Ac, Ap and Ah containing combinations of 30% NA and 5% HPMC, precirol and compritol, respectively, showed a better sustained release profile than that of Ambroxol® SR capsules. However, only Ah combination significantly reduced the amount of drug released from matrix tablets to 41.8, 59.73 and 81.68% after 3, 6 and 12 h, respectively. This may be due to the combination of gel properties of alginites and the viscosity-enhancing ability of HPMC which interacted synergistically to modify the release of the drug from matrix tablets. These results correlate with previous studies which showed in situ gel-forming ophthalmic solutions using alginate as a gelling agent in combination with HPMC as a viscosity-enhancing agent, and concluded that the gel formed in vitro produced sustained drug release over an 8-h period. In addition, the release of AMX from formula Ah followed an anomalous non-fickian diffusion mechanism similar to Ambroxol® SR capsules (Table 3) suggesting that adding NA resulted in a shift in release kinetics from Fickian diffusion in presence of HPMC alone to a coupled diffusion/polymer relaxation mechanism.

The results of the release study and kinetics modeling therefore showed that matrix tablets of both formulae S7 containing 10% HPMC and Ah containing a combination of 30% NA and 5% HPMC displayed a strong compatibility with the official release requirement for extended-release dosage form. Both formulae also showed acceptable physical properties. Although S7 and Ah followed the Higushi diffusion model for drug release, Ah showed more similarity to commercially available Ambroxol® SR capsules by following the same mechanism of drug diffusion. Therefore, both S7 and Ah matrix tablet formulae are potential candidates for subsequent stability and in vivo studies.

Conclusion

Matrix tablets were successfully prepared by direct compression of AMX/hydrophilic or AMX/hydrophobic polymers mixtures. The amount and type of polymer significantly affected the physical properties and drug release from the matrix tablets. Using 10% HPMC or a combination of 30% NA and 5% HPMC resulted in higher ability to control the release of AMX from matrix tablets. The release kinetics was shifted from fickian diffusion when HPMC was used to non-fickian diffusion using a 30% NA and 5% HPMC polymer combination. The results suggest that formulation of AMX controlled release matrix tablets can be achieved using 10% HPMC or a combination of 30% NA and 5% HPMC.

Acknowledgments

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References


