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Feasibility of AquasolveTM HPMC-AS Lg via Hot-melt Extrusion: Effect of Pressurized CO2 on Physico-mechanical Properties

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FEASIBILITY OF AQUASOLVE™ HPMC-AS LG VIA HOT-MELT EXTRUSION:
EFFECT OF PRESSURIZED CO₂ ON PHYSICO-MECHANICAL PROPERTIES

A thesis
presented in partial fulfillment of requirements
for the degree of Master of Science
in the Department of Pharmaceutics and Drug Delivery
The University of Mississippi

by
MASHAN ALMUTAIRI

May 2018
ABSTRACT

The objective of the current study was to investigate the processability of Aquasolve™ HPMC-AS LG via hot-melt extrusion, and to examine the effect of pressurized carbon dioxide (P-CO$_2$) on the physico-mechanical properties of Efavirenz (EFA)-loaded extrudates (EXT). EFA is a poorly water-soluble drug and HPMC-AS LG was chosen as a carrier for this study. To optimize the process parameters and formulations, various physical mixtures were prepared with the following composition: EFA (30-40-50% w/w) and HPMC-AS LG (70-60-50% w/w) respectively. Physical mixtures were extruded through the co-rotating twin-screw extruder (16mm Prism Euro Lab, Thermo Fisher Scientific) utilizing a standard screw configuration. P-CO$_2$ was injected into eight zone of extruder using a high-pressure regulator connected to flexible stainless-steel hose with armor casing. The thermal characterization of extrudates was obtained by using differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA). A scanning electron microscopy (SEM) was conducted to study morphology and porosity of formulations. The macroscopic morphology changed to a foam-like structure, resulting in increased specific surface area, porosity and dissolution rate. Thus, HPMC-AS LG extrudates with P-CO$_2$ injection exhibited relatively higher dissolution rate than extrudates without P-CO$_2$. Additionally, HPMC-AS LG was able to physically and chemically stabilize the amorphous state of high-loading EFA in the extrudates. The milling efficiency was improved for extrudates with P-CO$_2$ injection due to porous nature and morphology changes.
DEDICATION

This thesis is dedicated to my dear parents, Mr. Salem Almutairi and Mrs. Sabha Almutairi, my brothers and sisters, to my gorgeous wife Haylaa AlMutairi and five daughters, Taif, Hanin, Ghala, Ward, and Assal for all their support, help and affection all through these years. They all have made me what I am today with their unending encouragement and guidance in every aspect of my life.
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1. INTRODUCTION

In the last two decades, hot melt extrusion has evolved as one of the most promising pharmaceutical processing technology. [1]. HME technology has several advantages over conventional pharmaceutical processing technologies including short processing time, continuous process, does not demand the use of water or toxic organic solvents[2,3]. HME is generally utilized for solubility enhancement[5]. HME has also revealed significant value for manufacturing various dosage forms such as pellets, tablets, transmucosal products as well as various usages such as controlled release formulations, targeted drug delivery including taste masking formulations.[6]. HME pharmaceutical applications have not been wholly appreciated, mainly attributed to the complex design of HME as well as the non-predicted performance of materials during the HME process[7].

Recently, several HME-enabled products have commercially approved, which gives this technology more interest in the pharmaceutical industry. However, it is hard to ignore the fact that many of pharmaceutical polymeric systems shown thermal and/or viscoelastic challenges during HME process. Moreover, active pharmaceutical ingredients exhibit their own individual limitations such as high melting temperatures and/or the low degradation temperatures [8]. The physicochemical properties of the active pharmaceutical ingredient (API), including the glass transition and the melting point temperatures, the degradation temperatures, and the miscibility or solubility of the API in the polymer carrier, have to be considered carefully, since they have a significant effect on the hot-melt extrusion processes as well as the final output[9–12].
The polymer carrier system is regularly the principal component within the formulation. Thus, the physicochemical properties of the polymer carrier including molecular weight, viscosity, $T_g$, etc., can have the significant influence on HME processing conditions and the performance of the HME drug products [13,14]. The degradation temperature and viscoelastic properties of the polymeric carrier system are two major factors and must be well-thought-out during HME process [15]. Therefore, the fully realizing of thermal and viscoelastic properties of the various drug/polymer mixtures help to establish the HME processing parameters (such as extrusion temperatures, screw speed, feeding rate, and motor load) as well as provide insight into the properties of the final output [16].

More than 50% of common pharmaceutical polymers for HME processing could not be processed as neat by HME. The reason of this problem attributes that those polymers reveal viscosities exceeding the defined maximum viscosity limit within HME processing window. Normally, this issue could be solved by plasticizing these polymers through adding the APIs, in which reducing the viscosities to be smoothly extrudable. When the APIs can’t adequately plasticize the polymeric carriers, in this case, it requires an alternative formulation or processing strategies to utilize these carriers. Moreover, the feasibility of thermally unstable APIs becomes less when the polymeric carriers processing at high temperatures during HME processing window [8].

One of the strategies to process the polymers within acceptable processing conditions is addition of plasticizers [17]. Typically, plasticizers perform to increase the free volume between polymer chains, causing a depression of the $T_g$ and the melt viscosity [18]. Normally, traditional plasticizers are utilized in a concentration between 5–30 % w/w of the extrudable physical mixtures[19–21]. The additional 5–30% w/w to the total weight of formulations, is a drawback,
since that may be result in large dosage forms [17]. Therefore, it would be necessarily to find an alternative to traditional plasticizers in pharmaceutical extrusion. Lately, supercritical carbon dioxide (sc-CO₂), and subcritical (pressurized) carbon dioxide have been investigated as temporary plasticizer by reducing the HME processing temperatures without adding weight to the final formulations [22,23]. It has been examined that sc-CO₂, or P-CO₂ act as a foaming agent [24]. Thus, the increasing surface area and the porosity of the polymers resulting in enhanced dissolution [25].

HPMC-AS has been exhibited to be a very effective crystallization inhibitor in amorphous solid dispersions ASDs [26,27]. HPMC-AS polymers have a T_g of 120°C, however they regularly require extrusion temperatures in excess of 170°C, even with plasticization, to reduce the higher motor torque due to melt viscosity[28]. Then, these facts put HPMC-AS LG a desirable candidate for the current research to provide a fully understanding of the relationship between the physical and mechanical properties of physical mixtures of model drug and HPMC-AS LG to assess their suitability, as well as the correlation with the actual hot-melt extrusion process parameters. In this current study the effect of carbon dioxide as a foaming agent was examined, and understand the impact on the physico-mechanical properties and performance of the extrudates.
2. MATERIALS AND METHODS

2.1. Materials

Aquasolve™ Hydroxypropyl Methylcellulose Acetate Succinate HPMC-AS LG grade and Efavirenz (EFA), Ibuprofen (IBU), and Theophylline (THEO) were obtained as gift samples from Ashland Inc. (Wilmington, DE). Carbon dioxide (CO₂) was supplied in gas cylinders (pure clean) from Airgas (Tupelo, MS). All other chemicals and reagents used in the present study were of analytical grade and obtained from Fisher Scientific (Fair Lawn, NJ).

2.2. Methods

2.2.1. Thermogravimetric analysis (TGA)

TGA studies were performed for materials EFA and HPMC-AS LG to establish processing temperatures for extrusion and stability using a Perkin Elmer Pyris 1 TGA running Pyris manager software (PerkinElmer Life and Analytical Sciences, 719 Bridgeport Ave., Connecticut, USA). Five to seven milligrams of the sample were weighed in an aluminum pan and heated from 25°C to 200°C at 10°C/min heating rate under nitrogen atmosphere.

2.2.2. Hot Melt Extrusion processing

The co-rotating twin-screw intermeshing extruder (16mm Prism Euro Lab, Thermo Fisher Scientific, Waltham, MA) was utilized to perform the HME processes. The extruder is divided into 10-barrel zones adjacent to the gravimetric feeder. Thermo Fisher Scientific standard screw
configuration was used for this study, which consists of four conveying zones and three mixing zones. Carbon dioxide (CO₂) was pressurized and injected into the extruder using a high-pressure regulator connected to flexible stainless-steel hose with armor casing. The other end of the hose was connected to the four-way connection, fitted with a pressure gauge, bleed valve, check valve (ball type for unidirectional flow of gas), with the latter being connected to the injection port at the conveying zone (conveying zone) of the extruder (Figure 1). Metering of P-CO₂ was regulated using the regulator knob. The preliminary studies were conducted to determine the processing temperature of pure polymer over a temperature range of 140 to 190 °C with 75 & 100 rpm. At 190 °C extrusion was investigated in the presence of P-CO₂. Similarly, the extrusion was investigated at 20%, 30%, 40% and 50% drug load with and without P-CO₂ (data not shown).

![Figure 1. Schematic representation for the set-up of the combined HME/P-CO₂ techniques](image)

### 2.2.3. Physical mixture

After optimizing the HME process parameters and formulation, various physical mixtures were prepared with the following composition: EFA (30-40-50% w/w) and HPMC-AS LG (70-60-50% w/w), respectively. The mixtures were blended using a V-shell blender (Maxiblend,
GlobePharma) at 25 rpm for 15 min. All the formulations mentioned in (Table 1) were studied and successfully extruded at the employed processing conditions.

Table 1. Conditions and outcomes for optimized formulations during HME processes

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Processing Temperature (°C)</th>
<th>Screw Speed (rpm)</th>
<th>Barrel Torque (%)</th>
<th>P-CO₂ (PSI)</th>
<th>P-CO₂ Injection Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% EFA/70% HPMC-AS LG EXT</td>
<td>140</td>
<td>100</td>
<td>46</td>
<td>300-400</td>
<td>Zone 8</td>
</tr>
<tr>
<td>30% EFA/70% HPMC-AS LG EXT</td>
<td>140</td>
<td>100</td>
<td>46</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40% EFA/60% HPMC-AS LG EXT</td>
<td>140</td>
<td>100</td>
<td>46</td>
<td>300-400</td>
<td>Zone 8</td>
</tr>
<tr>
<td>40% EFA/60% HPMC-AS LG EXT</td>
<td>140</td>
<td>100</td>
<td>46</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>50% EFA/50% HPMC-AS LG EXT</td>
<td>140</td>
<td>100</td>
<td>27</td>
<td>300-400</td>
<td>Zone 8</td>
</tr>
<tr>
<td>50% EFA/50% HPMC-AS LG EXT</td>
<td>140</td>
<td>100</td>
<td>27</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>30% EFA/70% HPMC-AS LG EXT*</td>
<td>150</td>
<td>75</td>
<td>25-30</td>
<td>250-300</td>
<td>Zone 8</td>
</tr>
<tr>
<td>30% EFA/70% HPMC-AS LG EXT*</td>
<td>150</td>
<td>75</td>
<td>25-30</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>40% EFA/60% HPMC-AS LG EXT*</td>
<td>150</td>
<td>75</td>
<td>25-30</td>
<td>250-300</td>
<td>Zone 8</td>
</tr>
<tr>
<td>40% EFA/60% HPMC-AS LG EXT*</td>
<td>150</td>
<td>75</td>
<td>25-30</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>50% EFA/50% HPMC-AS LG EXT*</td>
<td>150</td>
<td>75</td>
<td>13-20</td>
<td>250-300</td>
<td>Zone 8</td>
</tr>
<tr>
<td>50% EFA/50% HPMC-AS LG EXT*</td>
<td>150</td>
<td>75</td>
<td>13-20</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* These formulations were selected for further studies based on preliminary studies results.

2.2.4. Milling Efficiency

Prior to analysis, the HME extrudates were milled using a Fitz lab scale mill (Model L1A, Fitzpatrick, Perth Amboy, NJ) and particle size distribution and milling efficiency was studied using a vibrating sieve shaker (Gilson, performer III SS-3). The fraction below 600 μm was utilized for further investigation. To study the milling efficiency of formulations before and after injection of P-CO₂, 25 g of each melt extruded sample was milled for 3 min, 3000 rpm with a Fitz laboratory mill and particle size distribution was estimated using the vibrating sieve method. A set of sieves with known mesh size (respectively 75, 125, 250, 420, 600 and 840 μm) and known tar weight, was placed on top of each other and known amount of the powder was placed in the top sieve. The whole stack was placed on a vibrating plate for 10 min at an amplitude of 1.5 mm after which each sieve was weight to obtain a particle size average distribution.
2.2.5. Drug content and degradation

UV analysis was conducted to determine the uniformity of weight, drug content and degradation after extrusion with or without P-CO$_2$ injection. The assay methods detailed in the USP were performed. The EFA content in the extrudates was determined by dissolving the contents in phosphate buffer solution (pH 6.8) and assayed spectrophotometrically against a blank comprising the buffer solution. The analysis was performed by UV spectrophotometer at 247 nm (Genesys 6, Thermo Fisher Scientific, Madison, WI, USA); a value at which the absorbance of the polymer is negligible. The percent drug content was compared to the calculated value. The experimental value was the average of triplicate.

2.2.6. Dissolution studies

*In-Vitro* dissolution testing was conducted on milled and 40# sieved extrudates samples and compared with a pure crystalline EFA. A USP dissolution apparatus II (Hanson SR8; Hanson Research, Chatsworth, CA, USA) was utilized with pH 6.8 phosphate buffer, at 37±0.5 °C, using a paddle rotating at 50 rpm, for 2 h. At predetermined time points, 2 mL of an aliquot was withdrawn and filtered through a filter tip 10 µm (Rockwood, TN, USA) and replaced with an equal volume of fresh dissolution medium after each sampling. EFA was assayed by UV spectrophotometer maximum wavelength of 247 nm (Genesys 6, Thermo Fisher Scientific, Madison, WI, USA). All dissolution tests were carried out in triplicate and the mean and SD were reported. Student’s t-test was used for statistical analysis.
2.2.7. Solid State Characterization

The nature of EFA in the extrudates was determined by using differential scanning calorimetry (DSC) and confirmed by powder x-ray diffraction (PXRD).

2.2.7.1. Differential Scanning Calorimetry (DSC)

The nature of pure EFA, pure HPMC-AS LG, physical mixture and its corresponding extrudates was assessed by DSC. The analysis was preformed using a DSC (TA instruments DSC 25 Discovery series) coupled with a refrigerated cooling system. Samples of between 4 and 8 mg were weighed out using a Mettler Toledo scale. Samples were then placed in non-perforated aluminum pans, which were crimped before testing, with an empty crimped aluminum pan being used as a reference cell. Calorimetry scans were carried out from 50 to 200 °C for each sample. All DSC measurements were carried out at a scanning rate of 10 °C/min. Volatiles were removed from the purging head with nitrogen at a rate of 20 ml/min. Calibration of the instrument was preformed using indium as standard. After each scan was completed the melting points were analyzed and Trois manager software was used for the data analysis.

2.2.7.2. Powder X-ray Diffraction Measurements (PXRD)

The confirmation of crystallinity degree of pure EFA, pure HPMC-AS LG, EFA in the physical mixture and respective extrudates was investigated using, powder X-ray diffraction (PXRD) analyses using a Bruker D8 Focus X-ray diffractometer operated at voltage of 40 kV and a current of 40 mA. Powder was packed into the sample holder. Data for each sample were collected in the 2Θ angle range of 4–40° over 10 min in continuous detector scan mode. The process parameters were set as scan-step size of 0.02° (2Θ) and scan-step time of 0.3 s.
2.2.7.3. Scanning electron microscopy (SEM)

The morphological characteristics and degree of porosity of extrudates at different drug loads of 30, 40 and 50% with and without P-CO$_2$ treatment was studied using SEM (JEOL JSM-5600) that was operated at an accelerating voltage of 5 kV under analysis mode. Each specimen was fixed by conductive double-sided carbon adhesive tape and gold-sputter coated by a Hummer® 6.2 sputtering system (Anatech LTD, Springfield, VA) in a high-vacuum evaporator prior to the test to avoid electrostatic charging. Four magnificent (25, 50, 100, 250) were employed to give more accurate and clear understanding of results.

2.2.8. Density and porosity

True density of powdered extrudates for all the formulations as well as the pure polymer with and without P-CO$_2$ was measured utilizing Micromeritics AccuPyc 1330 Gas pycnometer S/N-4011 (Norcross, GA). Prior to each run, calibration was performed. The sample was filled in 10-cm$^3$ sample cup and the weight of the sample was noted. True density was measured at an equilibration rate of 0.0050 psig/min and the number of purges was set to 10. Bulk and tapped density was calculated by measuring the volume of a 5 g milled extrudates in a 10 mL graduated cylinder. Porosity was calculated by the following equation [29].

\[
\% \text{Porosity} = 1 - \frac{\text{Bulk Density}}{\text{True Density}} \times 100
\]
3. RESULTS AND DISCUSSION

3.1. HME processing

The physicochemical properties of the API, and the polymeric carrier have to be considered carefully, since they have a significant effect on the hot-melt extrusion processes as well as the final output [9]. Therefore, the process parameters of hot-melt extrusion should be accustomed based on the physicochemical properties of each formulation component. Theoretically, as a rule the temperature of extrusion is required to set at 10-20 °C above the $T_g$ of the polymers for flow consideration during the extruding process. In addition, there are many properties that could also be critical in HME process such as the melt viscosity of polymer, molecular weight, and miscibility. Furthermore, the plasticization effect of the drug on polymer may also plays an important role in extrudability of materials [16]. Many research studies have shown that the P-CO$_2$ behaves as a plasticizer for some pharmaceutical polymers[17,23–25,30,31].

In this study, the temperature of extrusion and drug/polymer ratio have a major influence on HME process. During early stage of HME process optimizing, the extrudability of plain pure polymer was impossible when we set the temperature of the extruder below 160 °C since it led to reach the maximum level of motor load. At 160, 165, and 170 °C, the motor load was almost at 96 %. This could be attributed to high viscosity of the polymer. To reduce the motor load, the speed of extruder was lowered to 75 rpm at all temperatures studied. The processing enhancement was very limited, and the process was restricted to go further. Moreover, P-CO$_2$ did not indicate any sign of plasticizing effect on the polymer (reduction in the HME processing temperature and motor
load). Therefore, it was not logical to inject the P-CO₂ at such high motor load. Quite the contrary, it exhibited rise in motor load even with increasing the temperature of extruder which would be explained as inability of the P-CO₂ stream to penetrate the polymer. The relationship between the polymer, P-CO₂, and temperature directed to inject the P-CO₂ only at zone 8; neither zone 6 nor zone 4, which was very difficult to apply into the HME process. Table 2 lists the results of this relationship. Zone 4 and zone 6 provide relatively a long period of contact between the polymer and P-CO₂ until they reach the extruder die. At zone 8 (Figure 1), the polymer and P-CO₂ meet only at zone nine and ten of the extruder. Additionally, at zone 4 & 6 (Figure 1), the chance of back-pressure issue in extruder is high, which spread materials out of the feeding zone. However, it would be possible to inject the P-CO₂ at least at zone 6 with increasing temperature to above 190 °C. Nevertheless, the high temperature is not practical and having undesirable consequences upon formulation components and the extruder parts. Injection of P-CO₂ at zone 8 was desirable to successfully produce a foaming, porous extrudates (Figure 1).

3.2. Screening of appropriate API

The type of drug, and its ratio in the formulations was very critical during the optimizing of the HME process. The low melting point drugs were supposed to be a suitable choice since those drugs could melt at low temperature and might act as plasticizing agents for HPMC-AS LG and provide smooth HME processing. Ibuprofen (Tₘ is about 78 °C) as a model drug provided a plasticizing effect as it was expected for the goal that it was selected for. However, the accumulated sticky materials caused a blockage at the feeding zone which is because of the low Tₘ of ibuprofen. Consequently, these sticky materials hindered obtaining a continuous HME process. It was concluded that not all low-melting point drugs act as plasticizers to HPMC-AS LG while injection of P-CO₂. It was clearly observed that the steam of P-CO₂ became hot after getting inside the
barrel, beside the temperature of extruder, which facilitated melting of ibuprofen and accumulating at the neck of funnel in the feeding zone. Additionally, a high melting point drug was investigated to avoid the blockage issue at the feeding zone. Theophylline ($T_m$ is around 273 °C) was studied while HME processing. The initial results displayed that there is no blockage at the neck of the funnel at the feeding zone while processing theophylline through the HME. In the other hand, theophylline did not demonstrate significant persuasive impact on the HME process, because the motor load was high, even with the extruder temperature set up at 165 °C. This explains that there is no plasticizing effect of theophylline on HPMC-AS LG. Thus, intermediate melting point drug EFA ($T_m$ is about 138 °C) was selected as the main model drug in this study. EFA showed very impressive influence on HPMC-AS LG via HME process. It overcame the blockage issue at the feeding zone and provided a strong plasticizing effect on HPMC-AS LG even with low ratio within the formulations (Table 2). While increasing the ratio of EFA, the motor load was going down, which means very desirable plasticizing effect without causing any blockage at the feeding zone during the HME process. With such an influence, the HME process would have a high range of flexibility and capacity to control the process for reaching the optimizable conditions. Moreover, The great character of polymers when they prove the high ability to solubilize a large amount of drug [32]. HPMC-AS LG has demonstrated its excellence by dissolving 50% of EFA in complete amorphous state as confirmed by DSC, and PXRD studies.

3.3. Drug content and degradation

TGA data demonstrated that all formulations utilized in this study were stable under the employed processing temperature (data not shown). UV analysis indicated acceptable uniformity of drug and drug content and no degradation of EFA as a function of temperature and pressure during the hot melt extrusion process with and without carbon dioxide injection. This confirmed
that the EFA was uniformly distributed in formulations with a higher yield. The combined HME/P-CO$_2$ processes showed relatively lower process loss. The average weights (± SD) of two series of 20 capsules contents is equivalent to 100 mg of EFA. The reproducibility indicated by these results were considered to be satisfactory for the purposes of the present study. The analysis of drug content confirmed the theoretical value of the formulations, with values ranging from 96% to 102%.

3.4. Differential scanning calorimetry (DSC)

DSC studies were conducted on all formulations including pure EFA and HPMC-AS LG, to ascertain the impact of P-CO$_2$ during the processing of formulations and if it had any effect on their thermal properties.

As it can be seen in Figure 2, the DSC thermograms of pure EFA showed apparent endothermic peak at around 140 °C. The sharp EFA peak was disappeared in all processed formulations except for their respective physical mixtures which shows less endothermic peak (less T$_m$) with less enthalpy of fusion. The absence of the peak indicates that the all processed formulations preserved the amorphous nature after HME coupled with P-CO$_2$ processing.

3.5. Powder X-ray Diffraction Measurements (PXRD)

The diffraction patterns Figure 3 obtained from pure EFA, pure HPMC-AS LG, all processed formulations and their respective physical mixtures confirmed the amorphous nature of EFA and is in accordance with DSC data. Analysis of the XRD pattern obtained from pure EFA sample showed the several crystal peaks including the characteristic sharp and intense peak of EFA. As shown in Figure 3, the X-ray diffraction patterns of various samples, including processed extrudates, physical mixture (PM), and pure API showed characteristic peaks attributed to its
crystalline nature of EFA structure. On the other hand, the diffraction pattern of pure HPMC-AS LG did not show any Peaks (hallow band), which indicates that its polymeric structure is amorphous. In the physical mixture of EFA and HPMC-AS LG, there still were less intense peaks due to presence of partial EFA in crystalline form. In the X-ray pattern of the EFA–HPMC-AS LG extrudates, showed absence of characteristic peaks indicating the transformation of crystalline EFA into amorphous form and suggests that EFA was present in amorphous state. Finally, the diffractograms of the processed formulations before and after P-CO₂ treatment assured that no modifications occurred after the treatment.

3.6. Dissolution Studies

To investigate the influence of P-CO₂ injection within the polymeric matrix on EFA release from the HPMC-AS LG extrudates, In-Vitro dissolution study was conducted. HPMC-AS LG demonstrated enhancement of EFA dissolution rate, which is unidirectional to the increasing percentage of HPMC-AS LG in the formulations. Figure 4 shows the dissolution of EFA from various extrudates in the dissolution medium (pH 6.8). Extrudates at all drug loads released EFA higher than the pure EFA, presumably by generating a supersaturated state in the dissolution medium. The formulation of 30% EFA / HPMC-AS LG which processed by the assistance of P-CO₂ showed relatively greater EFA release than the other formulations (40%, 50% EFA / HPMC-AS LG). This can be attributed to the media which is more specified for the HPMC-AS LG polymer and presence of polymer in a high percent. The order of improvement of drug dissolution for the formulations processed by this coupled technology (HME/P-CO₂) was 30% EFA / HPMC-AS LG EXT/ P-CO₂ > 40% EFA / HPMC-AS LG EXT/ P-CO₂ > 50% EFA / HPMC-AS LG EXT/ P-CO₂.
Table 2. Results and conditions of investigating the extruder parameters, (polymer/ drug) ratio, and the type of the drug on HME processes with and without P-CO₂ injection.

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Processing Temperature (°C)</th>
<th>Screw Speed (rpm)</th>
<th>Barrel Torque (%)</th>
<th>P-CO₂ Injection Zone</th>
<th>P-CO₂ (PSI)</th>
<th>Back Pressure Zone</th>
<th>Feeding Zone Blockage</th>
<th>HME Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% HPMC-AS LG</td>
<td>140</td>
<td>100</td>
<td>Maximum *</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Failed</td>
</tr>
<tr>
<td>100% HPMC-AS LG</td>
<td>140</td>
<td>75</td>
<td>Maximum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Failed</td>
</tr>
<tr>
<td>100% HPMC-AS LG</td>
<td>140</td>
<td>100</td>
<td>Maximum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Failed</td>
</tr>
<tr>
<td>100% HPMC-AS LG</td>
<td>140</td>
<td>75</td>
<td>Maximum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Failed</td>
</tr>
<tr>
<td>100% HPMC-AS LG</td>
<td>150</td>
<td>100</td>
<td>Maximum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Failed</td>
</tr>
<tr>
<td>100% HPMC-AS LG</td>
<td>150</td>
<td>75</td>
<td>Maximum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Failed</td>
</tr>
<tr>
<td>100% HPMC-AS LG</td>
<td>150</td>
<td>100</td>
<td>Maximum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Failed</td>
</tr>
<tr>
<td>100% HPMC-AS LG</td>
<td>150</td>
<td>75</td>
<td>Maximum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Failed</td>
</tr>
<tr>
<td>50% HPMC-AS LG/50 EFA</td>
<td>160</td>
<td>100</td>
<td>98%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Successful**</td>
</tr>
<tr>
<td>100% HPMC-AS LG</td>
<td>160</td>
<td>75</td>
<td>88%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Successful**</td>
</tr>
<tr>
<td>100% HPMC-AS LG</td>
<td>170</td>
<td>100</td>
<td>88-90%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Successful**</td>
</tr>
<tr>
<td>100% HPMC-AS LG</td>
<td>170</td>
<td>75</td>
<td>82%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Successful**</td>
</tr>
</tbody>
</table>

*The motor reached the maximum level that was impossible to move on.

**Very limit success which means obtaining final product, but under very high motor load and temperature.

H.T: very high temperature.
H.Q: very high the motor load.
Interestingly, even though that the number of pores within the extrudates is higher and larger in 50% drug load formulation (Figure 5) which might facilitate the drug release, but this can’t be compromised by the media which is highly preferable by the polymer. Furthermore, it was observed that HPMC-AS LG substitution level (LG grade) plays an important role in enhancing the solubility of EFA, which released faster and more completely from the EFA / HPMC-AS LG-grade extrudates (Figure 4). This result stems from EFA’s higher lipophilicity (logP of 4.6), which makes it dissolution-rate-limited, and from the higher succinoyl content of the LG-grade polymer, which offers higher hydrophilicity and thereby improves the dissolution rate. The same phenomenon has happened with a previous study.
The dissolution profiles are relatively higher for the CO$_2$-treated materials. These extrudates were all amorphous, indicating that the release can be controlled as a function of the carbon dioxide treatment [25]. It was found that the HPMC-AS LG matrix governs the dissolution rate of the extrudates. When the molecules of HPMC-AS LG were dissolved, the EFA molecules dissolved
simultaneously because EFA molecules (up to 50%) were in amorphous form as shown in Figure 2 and there was no need to overcome the lattice energy. Therefore, it has been confirmed that EFA was molecularly dispersed or nearly molecularly dispersed in the HPMC-AS LG matrix.

The dissolution rate depends on the surface area of the material exposed to the dissolution media [33]. Although the foamed extrudates exhibit an increased surface area, the unmilled foams had significantly slower dissolution than regular ground extrudates.

Moreover, although the porous matrix exhibited high surface area, the P-CO₂ processed formulation (50% EFA / HPMC-AS LG) that has the lower density value and higher porosity (Table 3), and larger pore size (Figure 5-P, Q, R) has almost the same dissolution profile as the formulation without P-CO₂ treatment (regular extrudates). This could be attributed to the particles being floated and accumulated on the surface of the media making these particles not fully accessible to all sides of the media resulting in limited contact between the two phases. Moreover, this can be attested by visually noticing the floating particles on the media surfaces throughout the dissolution study.

In contrast, the other formulations; the P-CO₂ processed formulations (30 & 40% EFA / HPMC-AS LG) sank into the dissolution media allowing the dissolution process to proceed faster through the fully accessible surfaces[34]. Since the P-CO₂-treated extrudates are more hygroscopic[25], water penetrates faster within the matrix whereas slower in regular extrudates.
3.7. Scanning electron microscopy (SEM)

The surface of all processed extrudates with P-CO2 treatment, shown in the SEM images of Figure 5, is quite different to the ones made by traditional extrusion process in which the extrudate is smooth compared to the foamed and porous extrudates. The specific surface area is clearly larger in the case of the foamed samples providing extended availability to the dissolving medium, which may increase the dissolution rate[34]. The internal and external porous structures of solid dispersions as seen in Figure 5 can alter the physico-mechanical properties of such a formulation.

On the other hand, as shown in Figure 5, the matrix had mesh-like framework, denoting that P-CO2 penetrated during the process uniformly through HPMC-AS LG matrix. Thereby, these images suggest that homogeneous or heterogeneous porosity behavior might occur depending on drug load; i.e. with an increase in drug load up to (50%), homogeneous pores are formed during the processing of dispersions assisted by P-CO2 treatment while in (30% drug load), heterogeneous pores are formed during the processing of dispersions assisted by P-CO2 treatment. These pores
are dominating structures of HPMC-AS LG matrices. This can be attributed to the plasticizing effect of EFA, which leads to less viscous matrices and facilitate the penetration of P-CO$_2$ homogeneously throughout the matrix within the extruder barrel[34]. This can be confirmed by seeing images of regular extrudates wherein the smoother surfaces are accompanied with higher drug load (50%) whereas the rougher surfaces are accompanied with less drug load 30%. The smoothness of surfaces is a sign of the plasticizing effect of EFA on the polymer. This is in accordance with previous reports[23,35]. After injecting P-CO$_2$ during the hot melt extrusion process and while the materials are exciting the extruder die, the pressure is expanded to atmospheric conditions, thereby, P-CO$_2$ is released from the extrudates. This results in foam formation as explained by Lee et al.[36] and Park et al.[37]. Also, they illustrated that the pore size can be altered as a function of CO$_2$ pressure and temperature. In addition, they obtained different morphologies ranging from a foamy-like structure to a fibrous-like structure[24].

3.8. Density and Porosity

As seen in Table 3, all density values were decreased in case of formulations prepared by the aid of P-CO$_2$. This would occur because of foamy and porous matrices that have been formed after P-CO$_2$ treatment. Furthermore, porosity values are higher with samples prepared by the aid of P-CO$_2$. This would allow for large surface area which leads to improved dissolution profile as well as tablet characteristics[23]. Also, it leads to high surface free energy that aids in stabilizing the amorphous form[38–41]. This low density and porous matrices might help in tablet characteristics which would be the theme of a continuing study.
Table 3. Bulk, tapped, true density and porosity of pure EFA, pure HPMC-AS LG, Physical Mixture (PM) and Extrudates (EXT) with and without P-CO$_2$ (g/ml)

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Bulk Density</th>
<th>Tapped Density</th>
<th>True Density</th>
<th>% porosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFA</td>
<td>0.225</td>
<td>0.338</td>
<td>1.450</td>
<td>84.440</td>
</tr>
<tr>
<td>HPMC-AS LG</td>
<td>0.462</td>
<td>0.470</td>
<td>1.289</td>
<td>64.164</td>
</tr>
<tr>
<td>30% EFA / HPMC-AS LG PM</td>
<td>0.369</td>
<td>0.447</td>
<td>1.416</td>
<td>73.912</td>
</tr>
<tr>
<td>40% EFA / HPMC-AS LG PM</td>
<td>0.351</td>
<td>0.421</td>
<td>1.474</td>
<td>76.192</td>
</tr>
<tr>
<td>50% EFA / HPMC-AS LG PM</td>
<td>0.317</td>
<td>0.404</td>
<td>1.532</td>
<td>79.261</td>
</tr>
<tr>
<td>30% EFA / HPMC-AS LG EXT</td>
<td>0.598</td>
<td>0.629</td>
<td>1.347</td>
<td>55.631</td>
</tr>
<tr>
<td>40% EFA / HPMC-AS LG EXT</td>
<td>0.612</td>
<td>0.668</td>
<td>1.362</td>
<td>55.066</td>
</tr>
<tr>
<td>50% EFA / HPMC-AS LG EXT</td>
<td>0.620</td>
<td>0.652</td>
<td>1.381</td>
<td>55.111</td>
</tr>
<tr>
<td>30% EFA / HPMC-AS LG EXT+P-CO$_2$</td>
<td>0.461</td>
<td>0.493</td>
<td>1.350</td>
<td>65.874</td>
</tr>
<tr>
<td>40% EFA / HPMC-AS LG EXT+P-CO$_2$</td>
<td>0.494</td>
<td>0.519</td>
<td>1.357</td>
<td>63.617</td>
</tr>
<tr>
<td>50% EFA / HPMC-AS LG EXT+P-CO$_2$</td>
<td>0.350</td>
<td>0.466</td>
<td>1.382</td>
<td>74.681</td>
</tr>
</tbody>
</table>

3.9. Milling Efficiency

Influence of P-CO$_2$ on milling efficiency for foamy structure extrudate was evaluated. Regular extrudates (i.e. without P-CO$_2$ treatment) are glassy form in nature, which make them very difficult to mill to obtain a suitable particle size distribution. Consequently, the milling efficiency was determined with and without P-CO$_2$ injection within HME process. Table 4 displays the results for this investigation. These results confirmed that the obtained amount of selected particle sizes (<600, 250, and 125 um) after milling process for formulation with P-CO$_2$ larger than the corresponding formulations without P-CO$_2$. Moreover, the resistance of milling machine during milling process for formulations with P-CO$_2$ was less than the corresponding formulations without P-CO$_2$. The enhancement of milling efficiency would be due the morphology changes into foam-like structure extrudates, as impact of P-CO$_2$ injection.
Figure 5. SEM images of all Extrudates without, and with P-CO2: A, B, and C 30% Extrudate (30% EFA / 70% HPMC-AS LG without P-CO2), D, E, and F 30% Extrudate (30% EFA / 70% HPMC-AS LG with P-CO2), G, H, and I 40% Extrudate (40% EFA / 60% HPMC-AS LG without P-CO2), J, K, and L 40% Extrudate (40% EFA / 60% HPMC-AS LG with P-CO2), M, N, and O 50% Extrudate (50% EFA / 50% HPMC-AS LG without P-CO2), P, Q, and R 50% Extrudate (50% EFA / 50% HPMC-AS LG with P-CO2)
Table 4. Results of the Milling Efficiency

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Torque (Amps)</th>
<th>Particles &lt; 600 um (%)</th>
<th>Particles &lt; 250 um (%)</th>
<th>Particles &lt; 125 um (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% EFA / HPMC-AS LG EXT</td>
<td>1.08</td>
<td>78.44</td>
<td>9.57</td>
<td>1.03</td>
</tr>
<tr>
<td>40% EFA / HPMC-AS LG EXT</td>
<td>0.85</td>
<td>84.99</td>
<td>15.33</td>
<td>2.74</td>
</tr>
<tr>
<td>50% EFA / HPMC-AS LG EXT</td>
<td>0.79</td>
<td>77.90</td>
<td>3.37</td>
<td>0.98</td>
</tr>
<tr>
<td>30% EFA / HPMC-AS LG EXT P-CO₂</td>
<td>0.79</td>
<td>92.14</td>
<td>14.88</td>
<td>1.97</td>
</tr>
<tr>
<td>40% EFA / HPMC-AS LG EXT P-CO₂</td>
<td>0.74</td>
<td>97.70</td>
<td>24.41</td>
<td>4.75</td>
</tr>
<tr>
<td>50% EFA / HPMC-AS LG EXT P-CO₂</td>
<td>0.72</td>
<td>98.08</td>
<td>13.64</td>
<td>1.79</td>
</tr>
</tbody>
</table>

Conclusion

The comprehensive understanding of the relationship between the physico-chemical properties and physico-mechanical properties for physical mixtures of medium melting point EFA and higher Tₜ HPMC-AS LG, as well as the correlation with the actual hot-melt extrusion process parameters, and impact of P-CO₂ successfully leads to obtain high-loading EFA within plasticized foamy matrix as a final output. HPMC-AS LG improved the release profile for all EFA-loaded extrudates with and without P-CO₂ injection. However, EFA-loaded extrudates with P-CO₂ revealed relatively higher drug release than extrudates without P-CO₂. The morphologic changes of extrudates as a foam-like structure after P-CO₂ injection, resulting in an increased surface area and porosity. Thus, the milling efficiency of the extrudates was improved. HPMC-AS LG demonstrates a promising carrier to produce physically and chemically stable amorphous solid dispersion systems which are processed by HME.
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VITA

Mashan Salem Almutairi, proud son of Mrs. Sabha Almutairi and Mr. Salem Almutairi, was born in Hafr Albatin, Saudi Arabia on March 9, 1982. He attended the School of Pharmacy at King Saud University, Riyadh, Saudi Arabia, and received his Bachelor’s degree in 2011, and since that time he has been a registered pharmacist with The Saudi Commission for Health Specialties. Immediately after graduation, he had worked for Saudi Food Drug Authority for about two years, until he has accepted the offer from The University of Hail to be a faculty of the Department of Pharmaceutics in the School of Pharmacy, and awarded a full scholarship to get his Master and Ph.D. degrees in the United States of America. In 2015, Mr. Almutairi was accepted into the Master program of Pharmaceutical Science with an emphasis on Pharmaceutics and Drug Delivery at the University of Mississippi, which is the one of the best programs in the US. He is an active member of the American Association of Pharmaceutical sciences (AAPS). His work has been presented at national as well as international conferences. He received his Master in Pharmaceutical Sciences in May of 2018 under the supervision of Dr. Michael A. Repka. In the next summer, Mr. Almutairi will pursue his Ph.D. program in Pharmaceutical Science with an emphasis on Pharmaceutics and Drug Delivery at the University of Mississippi.