Tailoring Drug Release and Utilization of Process Analytical Techniques by FT-IR Imaging employing HME Systems

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ABSTRACT SUMMARY
The present studies were to compare the influence of Eudragit® RSPO and RLPO blends on drug release for water soluble and insoluble drugs from hot melt extruded formulations and also to assess the feasibility of FT-IR Chemical Imaging as a process analytical technique.

INTRODUCTION
Sustained Release (SR) dosage forms should possess pH-independence and robust drug release properties due to the variable pH values observed in the gastric tract (GIT), as well as numerous biopharmaceutical variables and reduce intra- and inter-individual variations in bioavailability¹. Moreover, SR dosage forms containing water-soluble drugs need more compact fabrication within polymers². However, poorly water-soluble drugs require solubilization techniques and release-modulation for maximized therapeutic efficacy³. Thus, the present study has employed hot-melt extrusion (HME) techniques.

Among the extrudable polymers, which have the effects of solubilizer as well as sustained release, Eudragit® RSPO and RLPO (methacrylic resins) were selected due to their high chemical stability, good extrudability and pH independent properties⁴. Theophylline (TP) was selected as a water soluble and Carbamazepine (CBZ) as a water insoluble model drug.

The objectives of the present study were, (1) to establish the robust sustained release formulations using Eudragit® RSPO and RLPO blends on drug release for water soluble and insoluble drugs from hot melt extrusion, and (2) to evaluate the feasibility of FT-IR imaging as a PAT or QbD tool compared to content uniformity data determined by HPLC.

EXPERIMENTAL METHODS
Preparation of HME containing TP or CBZ
100g batches of various formulations with Eudragit® RSPO and/or RLPO (alone or in combination at different ratios) containing TP (10-30%) and CBZ (10-30%) were extruded (Table I) with barrel temperatures ranging from 140°C-150°C and a screw speed of 80 rpm utilizing a lab scale twin-screw hot-melt extruder (Prism 16mm EuroLab, Thermo Fisher Scientific). Further, the extrudates were cooled to room temperature and the cooled extrudates were milled using a comminuting mill (Fitzpatrick, Model "L1A") and then passed through a 30-mesh sieve to change the shape to granules or pellets.

Physico-Chemical Properties
A Perkin-Elmer (Waltham, USA) Diamond differential scanning calorimeter (DSC) was used to study the crystallinity of the drug and to characterize drug miscibility in the extrudates of the formulations.

A D5005 diffractometer (Bruker, Germany) using Cu-K radiation at a voltage of 40 kV, 50 mA, was used to investigate PXRD patterns of all samples, pure TP, CBZ and Eudragit® RSPO, RLPO, and hot-melt extrudates.

Drug Release Study
Drug release studies were performed by filling milled extrudates into capsules using a USP II paddle method. For theophylline (TP), the dissolution medium was 900 mL of deionized water and maintained at a constant temperature of 37±0.5°C. The rate of rotating paddle was 50 rpm. The dissolution method was followed on “Theophylline Tablets” (USP 36-NF 31). For carbamazepine (CBZ), 900 mL of deaerated deionized water containing 1% sodium lauryl sulfate was used and paddle speed was 75 rpm. The dissolution method was followed on “Carbamazepine Tablets” (USP 36-NF 31).

Content uniformity study
Extrudates containing TP or CBZ were accurately weighed, equivalent to 10mg of TP and 20mg of CBZ, and transferred individually, dissolved with 100ml of mobile phase and mixed, respectively. The mixtures were then assayed using an appropriate analytical method. All experiments were carried out with 10 replications.

Fourier transform-infrared spectroscopy (FT-IR) and Its Imaging
A FT-IR spectrophotometer (Cary 660 FT-IR) and microscope with a 64×64 pixel FPA (Cary 620) were used. Hot-melt extrudates were checked to investigate the interaction between API and polymer.

Table I. 10% or 30% drug loaded formulations (w/w %)

<table>
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<th>No.</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
<th>0.6</th>
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<tr>
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<td>60</td>
<td>45</td>
<td>30</td>
<td>0</td>
<td>70</td>
<td>46</td>
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<tr>
<td>RLPO</td>
<td>0</td>
<td>30</td>
<td>45</td>
<td>60</td>
<td>90</td>
<td>0</td>
<td>24</td>
<td>35</td>
<td>46</td>
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</table>

RESULTS AND DISCUSSION
DSC and PXRD showed that the crystallinity of both APIs changed into fully amorphous forms in the hot-melt extrudates regardless of water solubility of API and drug loading (Fig. 1).

Increasing Eudragit® RLPO increased the in vitro drug release whereas increasing Eudragit® RSPO sustained the drug release for up to 12 hours (Fig. 2).

Fig. 3 showed the individual distributions of the API contents. According to the USP criteria, the upper limit concentration (ULC) was set to 115% and the lower limit concentration (LLC) was 85%. All extrudates were within the specifications of the content uniformity study. The results obtained in this study showed that the hot-melt extrusion process with Eudragit® RSPO and RLPO could have very high homogeneity regardless of the API’s water solubility and drug loading.

Fourier transform infrared (FT-IR) imaging is becoming an increasingly applied technique in biomedical spectroscopy. However, FT-IR imaging technique also is amenable to Quality by Design (QbD) and Process Analytical Techniques (PAT). FT-IR imaging provides a practical chemical image and a visual distribution as well as concentration of chemical components according to the unique spectroscopic signature. Before checking the FT-IR imaging, selection of the unique spectroscopic wavelength from FT-IR is very important to obtain the exact imaging. Chemical imaging demonstrated excellent content uniformity/drug distribution for both APIs within the extrudates (Fig. 4).

CONCLUSIONS

TP and CBZ with varying ratios of Eudragit® RSPO and RLPO melt extrudes can be employed to tailor drug release profiles. The drug content uniformity analyzed by FT-IR chemical imaging correlated well with HPLC analysis.

REFERENCES


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