Development and Characterization of a Floating Drug Delivery System Prepared via Hot-Melt Extrusion Technology Coupled with Pressurized CO2 for a Thermo-Labile API

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Purpose
The main objectives of this study were to develop a continuous single-step manufacturing platform to prepare a porous, low-density, floating multi-particle system (mini-tablet, 4 mm diameter) for a thermo-labile API via hot-melt extrusion technology coupled with pressurized CO2 (P-CO2/HME), and to characterize the porous hot-melt extrudates designed for floating strategies using a polymeric matrix of Eudragit® RL PO (EUD) and Compritol® 888 ATO as a processing aid and lubricant.

Methods
Ranitidine Hydrochloride (RH) was selected as a model drug for this study. EUD was sieved and blended with 10%-30% RH with or without Compritol® 888 ATO (10%-35%) using a V-shell blender (MaxiBlend™, GlobePharma, North Brunswick, NJ, USA) at 25 rpm for 15 min. The thermal stability of carriers with RH at the processing temperature was determined by thermogravimetric analysis (TGA, Pyris 1 TGA, Perkin Elmer). Pressurized carbon dioxide was injected through zone 6 of the extruder. The extrudates were obtained in the form of porous rods using a co-rotating twin-screw extruder (16 mm Euro Lab, Thermo Fisher Scientific). The resulting extrudates were further cut into mini-tablets (4 mm diameter) using a pelletizer (Type L-001-9482, Thermo Fisher Scientific) and then pulverized, using a comminuting mill (Model L1A, Fitzpatrick, Perth Amboy, NJ) to calculate the true density/porosity and surface area. True density of the milled solid dispersion powder was determined utilizing Micromeritics AccuPyc 1330 Gas pycnometer S/N-4011 (Norcross, GA). Prior to each run, calibration was performed. The sample was filled in a 10-cm³ 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. The surface morphology of the mini-tablets was studied by scanning electron microscopy (SEM). In-vitro release studies (n=3) were performed according to a USP dissolution method using apparatus II with 900 ml of 0.1N HCl maintained at 37 ± 0.5°C with a paddle speed of 100 rpm. Buoyancy efficiency in terms of lag time and floating time of the mini-tablets was determined by minutes and hours, respectively.

Results
TGA results indicated that all of the optimized formulations were stable at extrusion processing temperatures utilized. RH/ EUD/ Compritol® 888 ATO (30%/60%/10%) produced intact porous extrudates whereas RH/ EUD/ Compritol® 888 ATO (30%/35%/35%) exhibited non-uniform and difficult to handle extrudates for downstream processing. The milling efficiency of extrudates processed via P-CO2/ HME was better than the extrudates processed without P-CO2. The extrudates processed via P-CO2/ HME exhibited higher porosity (64%) and higher surface area, whereas regular extrudates processed via only HME exhibited lower porosity (52%) and lower surface area. Porous extrudates were obtained with a relatively low density compared to regular extrudates without the injection of pressurized carbon dioxide. SEM showed the porous nature of the mini-tablets with pores that ranged between 50 μm and 190 μm in size. In-vitro drug release profiles of the optimized formulation with RH in pH 1.2 buffer (simulated gastric fluid), demonstrated a sustained release profile with floating behavior. In-vitro drug release profiles of P-CO2 injected mini-tablets in acidic media provided the optimal sustained-release profile after 3 h (i.e. approximately 80% of RH was released). All of the processed formulations via combined P-CO2/ HME technology exhibited superior floating efficiency (lag time is equal to zero and floating period is more than 24 h). The formulation with Compritol® 888 ATO and EUD was extrudable at the lowest processing temperatures (80°C), while without the lipid lubricant higher processing temperatures were necessary (120°C). As a result of the higher temperatures, the API was degraded. Drug content and tablet content uniformity analysis of mini-tablets confirmed that the drug was uniformly distributed within the tablets with a standard deviation of <3%, indicating a good formulation and process. The extrudates with Compritol® 888 ATO exhibited a 101.7% drug content compared to those without Compritol® 888 ATO, in which RH was completely degraded.

Conclusion
Pressurized carbon dioxide mini-tablets were successfully prepared using EUD along with the aid of lubricant for a thermo-labile API. The porous matrices demonstrated promising in-vitro buoyancy efficiency and sustained release profiles. The described novel methodology can be used for the production of floating devices incorporating other thermo-labile APIs with lower density and higher surface area.

Acknowledgments
This project was partially supported by Grant Number P20GM104932 from the National Institute of General Medical Sciences (NIGMS), a component of NIH. The authors would also like to thank Dr. Vijayasankar Raman of the National Center for Natural Products Research, School of Pharmacy, The University of Mississippi, for his valuable assistance with the SEM imaging studies. A special thanks is also extended to Evonik and Gattefosse for providing gift samples.