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Creating Drug Solubilization Compartments via Phase Separation in Multicomponent Buccal Patches Prepared by Direct Hot Melt Extrusion−Injection Molding

Muqdad Alhijjaj,[†,‡] Jacob Bouman,[§,∥] Nikolaus Wellner,[⊥] Peter Belton,[#] and Sheng Qi*[,†]

[†]School of Pharmacy, University of East Anglia, Norwich, Norfolk, U.K., NR4 7TJ

[‡]College of Pharmacy, University of Basrah, Basrah, Iraq

[§]Laboratory of Physical Chemistry and Colloid Science, Wageningen University, Wageningen, The Netherlands

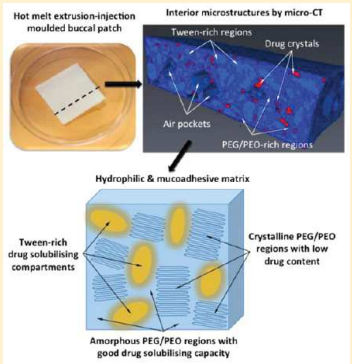
[∥]Physics and Physical Chemistry of Foods, Wageningen University, Wageningen, The Netherlands

[⊥]Institute of Food Research, Norwich Research Park, Colney Lane, Norwich, Norfolk, U.K., NR4 7UA

[#]School of Chemistry, University of East Anglia, Norwich, Norfolk, U.K., NR4 7TJ

Supporting Information

ABSTRACT: Creating in situ phase separation in solid dispersion based formulations to allow enhanced functionality of the dosage form, such as improving dissolution of poorly soluble model drug as well as being mucoadhesive, can significantly maximize the in vitro and in vivo performance of the dosage form. This formulation strategy can benefit a wide range of solid dosage forms for oral and alternative routes of delivery. This study using buccal patches as an example created separated phases in situ of the buccal patches by selecting the excipients with different miscibility with each other and the model drug. The quaternary dispersion based buccal patches containing PEG, PEO, Tween 80, and felodipine were prepared by direct hot melt extrusion−injection molding (HME-IM). The partial miscibility between Tween 80 and semicrystalline PEG-PEO led to the phase separation after extrusion. The Tween phases acted as drug solubilization compartments, and the PEG-PEO phase had the primary function of providing mucoadhesion and carrier controlled dissolution. As felodipine was preferably solubilized in the amorphous regions of PEG-PEO, the high crystallinity of PEG-PEO resulted in an overall low drug solubilizing capacity. Tween 80 was added to improve the solubilization capacity of the system as the model drug showed good solubility in Tween. Increasing the drug loading led to the supersaturation of drug in Tween compartments and crystalline drug dispersed in PEG-PEO phases. The spatial distribution of these phase-separated compartments was mapped using X-ray micro-CT, which revealed that the domain size and heterogeneity of the phase separation increased with increasing the drug loading. The outcome of this study provides new insights into the applicability of in situ formed phase separation as a formulation strategy for the delivery of poorly soluble drugs and demonstrated the basic principle of excipient selection for such technology.



KEYWORDS: *buccal, solid dispersions, hot melt extrusion, injection molding, X-ray micro-CT*

INTRODUCTION

The highly hydrophobic nature of many active pharmaceutical ingredients is often the major rate-limiting step responsible for their poor dissolution following oral administration, which consequently leads to low systemic bioavailability.[1,2] In addition, some of them also have some level of first-pass metabolism, which makes their delivery across the buccal mucosa a potential approach to improve their bioavailability, especially for potent drugs and those with narrow therapeutic windows.[3] Felodipine, a dihydropyridine calcium antagonist widely used as a potent antihypertensive drug, is one such example: the currently available oral felodipine formulations are extended release tablets which often lead to high inter- and intrapatient variations in pharmacokinetics and absorption.[4] This is because the dissolution of the drug is slower than the permeation of the drug and leads to overall absorption being formulation-dependent.[5] Due to the low oral bioavailability, in literature buccal patches and films of felodipine have been proposed with the attempt to avoid the first-pass metabolism and improve the bioavailability.[6] Most of these buccal formulations (mainly being tablets and films) were produced using conventional solvent film casting or direct compression.[3] Film casting often requires the use of organic solvents, and the removal of the solvent and the detection of residual solvents are associated with increased cost, safety, and environmental issues. In addition, patches prepared by solvent casting often have uneven surfaces and heterogeneous thickness due to the

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