SSPC, the SFI Research Centre for Pharmaceuticals

Development of Lipophilic Salts to Eliminate Variable Food Effect. Case Study with Venetoclax.

Callum D. Ryan, Joseph P. O'Shea, Brendan T. Griffin
School of Pharmacy, University College Cork, Ireland
SSPC, the SFI Research Centre for Pharmaceuticals

Introduction

In excess of 40% of medicines licenced by the FDA / EMA since 2010 display a pharmaceutical food effect (FE), whereby absorption of the drug varies between the prandial state of the patient. Lipid-based formulations (LBF) have been used as a method of overcoming FE and increasing bioavailability through enhancing the solvation capacity of GI fluids [1].

However the use of LBFs is restricted to drugs which can be dissolved in the lipid vehicle of the LBF. As a high number of drugs that display FE also display inherently poor solubility formulating LBFs can be challenging [2,3]

Research has demonstrated that conversion of pure forms of poorly soluble drugs to lipophilic salt forms allows for an increase in solubilisation capacity and resultingly a higher dose loading. This increase in solubility stems from two mechanisms (1) the crystalline forces of the ion drug pair is disrupted through steric hinderance of the bulky counterion (2) lipophilicity of the counterion increases the lipophilicity of the salt [2,3].

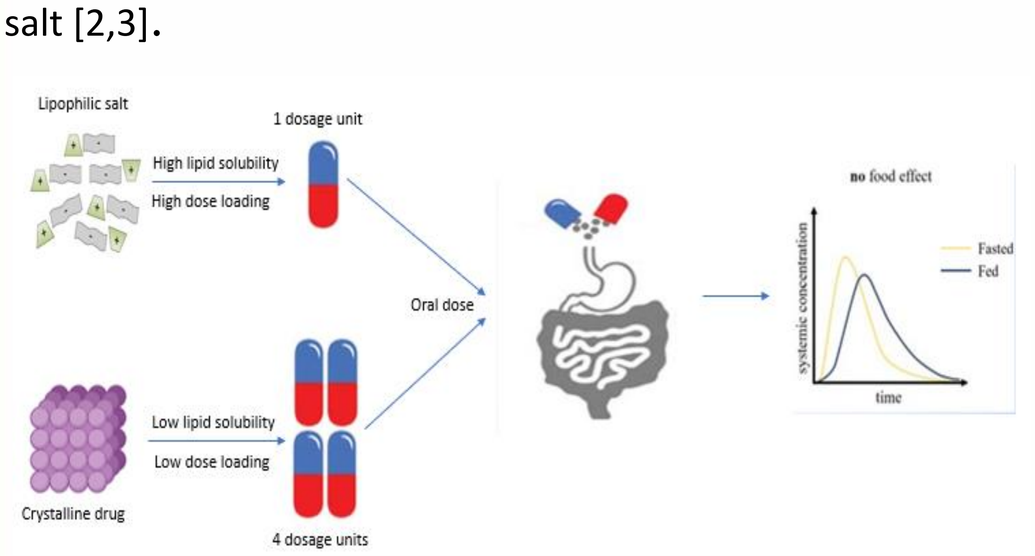
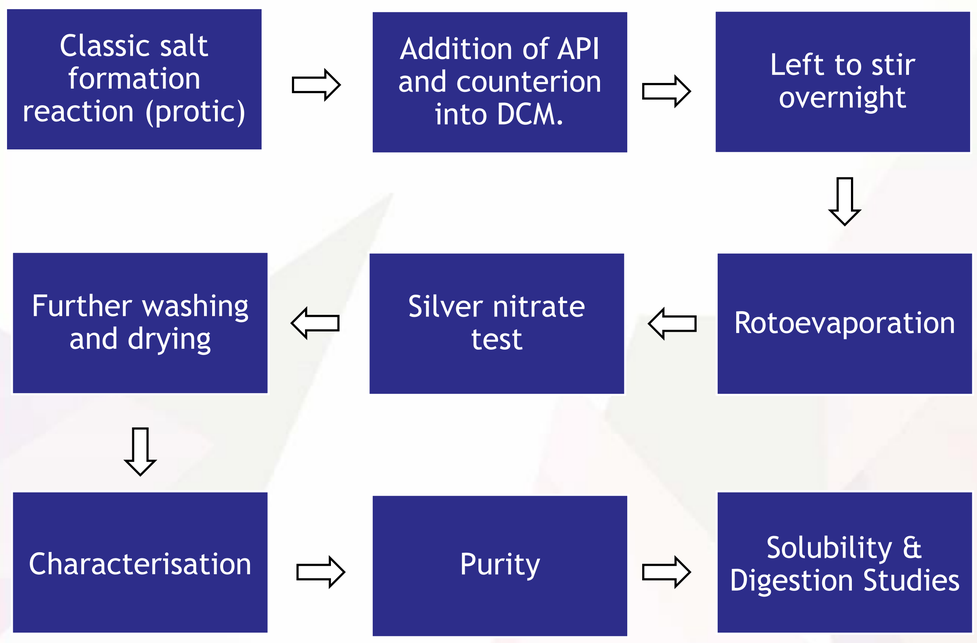


Figure 1: Schematic depicting the benefits of lipophilic salt technology. Adapated from Sahbaz et al., 2015 [2]

Objectives

- To assess the formation of a lipohilic salt of a BCS class IV API using a variety of counterions.
- To investigate the drug loading and solubility increases in LBFs using the lipohilic salt form compared to the free form of the API.
- Perform in-vitro biorelevant dissolution and digestion studies.

Methods



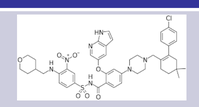
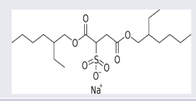
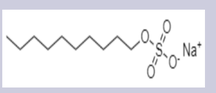
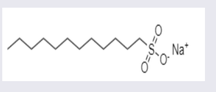
Molecule	Molecular Weight (g/mol)	Molecular Structure	pKa	Tm (°C)
Venetoclax	868.4		3.4 & 10.3	140
Sodium Docusate	444.6		0.21	153
Sodium Lauryl Sulfate	372.5		-1.5	211-213
Sodium Octadecyl Sulfate	288.4		-1.5	206
Sodium Decyl Sulfate	260.3		-1.5	198
Sodium Dodecane Sulfonate	272.4		-0.59	204

Table 1: Table containing a list of physicochemical properties and molecular structures of molecules used in the lipophilic salt synthesis.

Results & Discussion

Solubility (mg/ml)		
Molecule	Medium-Chain SEDDS	Surfactant Only SEDDS
Venetoclax	6.83+/- 0.62	5.11 +/- 0.83
Venetoclax Docusate	53.66 +/- 2.82	35.33 +/- 4.29
Venetoclax Octadecyl Sulfate	42.23+/- 1.9	38.08+/- 2.22
Venetoclax Lauryl Sulfate	61.84+/- 8.3	46.12+/- 1.84
Venetoclax Decyl Sulfate	39.87 +/-3.97	33.62+/- 2.19
Venetoclax Dodecane Sulfonate	52.19+/-6.37	41.12 +/- 1.28

Table 3: Table containing a list of solubility results of venetoclax free base and venetoclax lipophilic salts in prototype SEDDS.

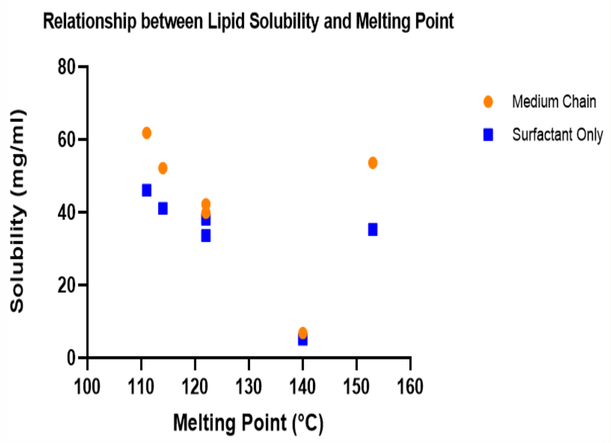


Figure 2: Scatter graph depicting the relationship between melting point and solubility.

- As shown in figure 2, a clear relationship exists between melting point and solubility of the salt complex in the formulation vehicle.
- The most pronounced reduction in melting point appears to occur in the carbon 10 and 12 chain lengths, while the presence of a sulfonate group does not appear to affect solubility or melting point – however it may affect stability of the complex.
- The increases in solubility relative to the free base form can allow for a lower amount of dosage units of venetoclax to be taken by the patient for a therapeutic effect to be achieved.

Conclusion + Future Perspectives

- Venetoclax was successfully synthesised as a lipophilic salt with a 1:1 equimolar ratio of venetoclax to counterion in the salt complex.
- A relationship between melting point and lipid solubility was demonstrated.
- Alkyl sulfates act as suitable counterions for lipophilic salt synthesis.
- Future working will involve *in-vitro* tests to assess performance of lipophilic salts under conditions reflective of *in-vivo*.

References

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Acknowledgements

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