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Transformation of Biopharmaceutical Classification System Class I and III Drugs Into Ionic Liquids and Lipophilic Salts for Enhanced Developability Using Lipid Formulations

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ABSTRACT

Higher lipid solubility of lipophilic salt forms creates new product development opportunities for high-dose liquid-filled capsules. The purpose of this study is to determine if lipophilic salts of Biopharmaceutical Classification System (BCS) Class I amlodipine and BCS Class III fexofenadine, ranitidine, and metformin were better lipid formulation candidates than existing commercial salts. Lipophilic salts were prepared from lipophilic anions and commercial HCl or besylate salt forms, as verified by ^{1}H-NMR. Thermal properties were assessed by differential scanning calorimetry and hot-stage microscopy. X-ray diffraction and polarized light microscopy were used to confirm the salt's physical form. All lipophilic salt forms were substantially more lipid-soluble (typically >10-fold) when compared to commercial salts. For example, amlodipine concentrations in lipidic excipients were limited to <5-10 mg/g when using the besylate salt but could be increased to >100 mg/g when using the docusate salt. Higher lipid solubility of the lipophilic salts of each drug translated to higher drug loadings in lipid formulations. *In vitro* tests showed that lipophilic salts solubilized in a lipid formulation resulted in dispersion behavior that was at least as rapid as the dissolution rates of conventional salts. This study confirmed the applicability of forming lipophilic salts of BCS I and III drugs to promote the utility of lipid-based delivery systems.

Introduction

Lipid formulations are widely used in drug development to improve the oral absorption of poorly water-soluble Biopharmaceutical Classification System (BCS) Class II or IV drugs.[1-3] There are many other reasons, however, why lipid formulations may be pursued for development, where the intent is not to enhance oral bioavailability. These include (1) improved content uniformity of high potency/low dose drugs; (2) requirements for fast onset of action; (3) consumer preference; (4) taste masking; (5) delivery of low melting drugs; (6) modified release; and (7) to increase drug permeability.[4] In many of these applications, lipid formulations are used for water-soluble BCS Class I and III drugs either as liquid-filled capsules or lipid multi-particulate finished dosage forms.

Hywel D. Williams and Leigh Ford are joint first authors.
Chemical compounds studied in this article: amlodipine (PubChem CID: 2126), amlodipine besylate (PubChem CID: 60496), fexofenadine (PubChem CID: 3348), fexofenadine hydrochloride (PubChem CID: 63002), metformin (PubChem CID: 4091), metformin hydrochloride (PubChem CID: 14219), ranitidine (PubChem CID: 3001055), and ranitidine hydrochloride (PubChem CID: 3033332).
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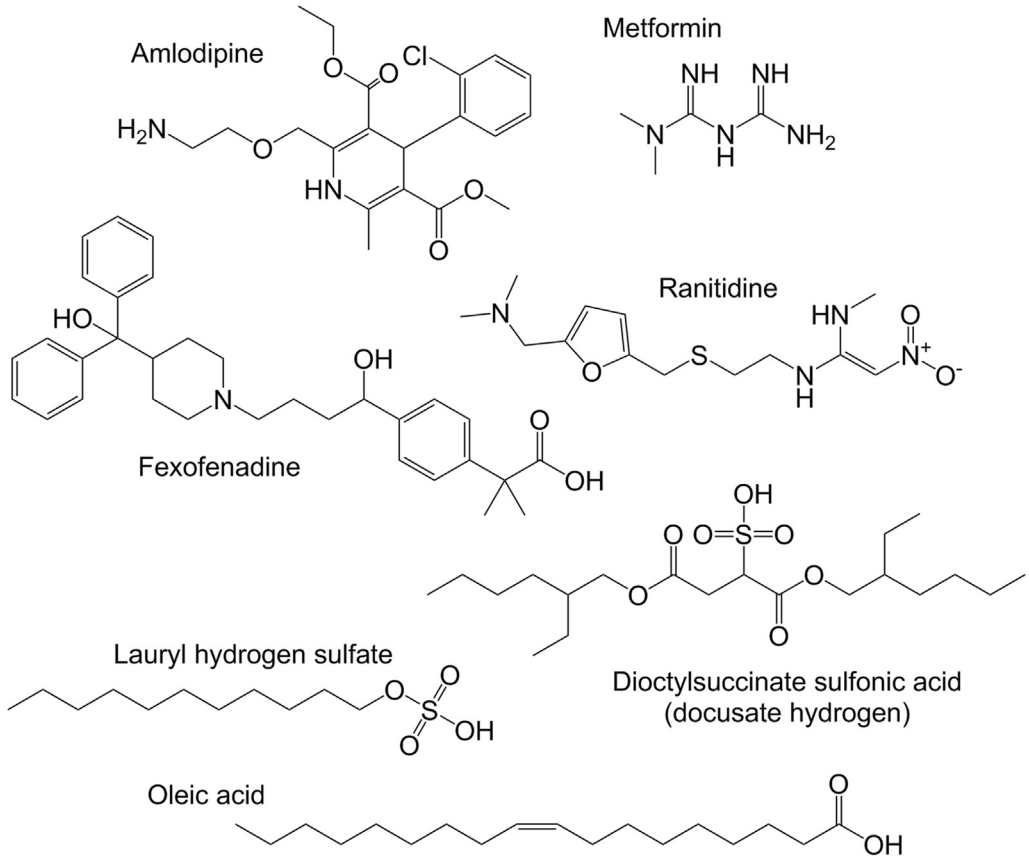

Figure 1. The chemical structure of the BCS Class I and III drugs and primary counterions investigated in this study.

Pharmaceutical and consumer healthcare product examples containing such water-soluble drugs in lipid formulations include Tirosint® (levothyroxine, BCS Class III), Zyrtec® Liquid Gels (cetirizine, BCS Class III), Depakene® (valproic acid, BCS Class I), and Zmax® (azithromycin, BCS Class III).

A potential constraint to the broader use of lipid formulations in delivering BCS Class I and III drugs is low solubility in commonly used lipidic excipients and lipid formulations such that the complete dose cannot be delivered in a single dosage unit, for example, a capsule. In these instances, lipid suspensions can be a viable alternative approach although there may also be scenarios where lipid solution type formulations are preferable biopharmaceutically, for example, where a fast onset of action is required. Approaches that improve drug solubility in lipid formulations are therefore desirable because they reduce the formulation:drug ratio, and in turn allow a reduction in capsule size and capsule number.

One approach to improve solubility in lipids (and therefore drug loading) is to decrease the strength of the crystal lattice forces, for example, by using an isolated amorphous form of the drug. This approach is commonly used to improve the aqueous solubility of poorly water-soluble compounds,[5,6] particularly where strong crystalline forces limit solubility and dissolution, and where the hydrophobicity of a compound precludes the formation of favorable intermolecular forces with water (e.g., dipole interactions, hydrogen bonds).[7] Applying the same philosophy to improve drug solubility in lipids, however, is unlikely to achieve the long-term physical stability needed for lipid formulation development, with likely reversion on storage to the more stable and ultimately less lipid-soluble crystalline form.

Lipophilic salts are an alternative and promising approach to achieving higher solubility in lipids.[8,9] Depending on the intrinsic properties of the drug and the choice of counterion, lipophilic salts may exist as solids or liquids at room temperature. Those salts with melting points/glass transition temperatures below 100°C are typically described as ionic liquids.[10,11] In addition to ionic liquids, salts that exhibit a melting point between 100°C and the melting point of the free acid/base can also exhibit high solubility in lipids. The utility of a salt approach to improve solubility in lipids therefore extends beyond the ionic liquid definition. Taking this into consideration, the term “lipophilic salts” offers a broader classification to cover all salts that exhibit enhanced lipid solubility over the respective free acid/free base forms.

Recent work by Sahbaz et al.[12] showed that lipophilic salt forms (ionic liquid and non-ionic liquid salts) of weakly basic drugs could achieve high solubility in lipid formulations. This allowed much higher drug loadings in lipid formulations, and the combination of lipophilic salts and lipid formulations was highly effective in promoting the oral absorption of poorly water-soluble weak bases, including itraconazole, when compared to the current commercial formulation.

Lipophilic salts of water-soluble drugs have been previously described.[11,13,14] In these cases, the altered salt form was employed to improve aqueous solubility, to provide for controlled release, or to facilitate dual pharmacological functions (where the counterion also had pharmacological activity). In contrast, the potential for lipophilic salt forms to facilitate the use of lipid formulations for water-soluble drugs, as a means to, for example, increase drug loading, has not been investigated.

Here, lipophilic salts of amlodipine, fexofenadine, metformin, and ranitidine were prepared (Fig. 1). These were selected as model drugs to illustrate potential lipophilic salt applications toward a broader set of drugs that meet the following criteria: (1) BCS Class I or III; (2) having at least one ionizable group to form salts with an