Flavored Self Microemulsifying Lipid Formulations for Masking the Organoleptic Taste of Pharmaceutical Actives

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ABSTRACT

The field of SMEDDS is designed to enhance bioavailability of poorly-water soluble compounds. Yet, these systems have the capacity to solubilize aqueous-based materials within its lipid matrix as L2 phase (W/O microemulsion). This characteristic is utilized in this investigation to incorporate aqueous flavors within oil vehicle as an approach to mask bitter taste of drugs. Miscibility profiles and self-micro-emulsifying regions for various lipid composites were screened by constructing ternary phase diagrams using different types of oil, cosurfactant and surfactant. Solubility of bitter taste model drug was measured in various optimized vehicles. Dynamic equilibrium phase studies were performed and phase boundaries were determined for the lipid-aqueous flavors-water systems. Self-micro-emulsifying system comprising Crodamol GTCC/ Glycerox 767HC /Croduret 40 ss at ratios of [0/80/20], [6/54/40] or [10/40/50] have shown capacity to solubilize, aqueous-based materials including; strawberry flavor, sucrose and citric acid as L2 phase. Phase behavior study has revealed that clear dispersions can be obtained at all dilutions with water. Potential flavored self-microemulsifying lipid formulations representing type III lipid class system were developed. Aqueous flavors loaded into these vehicles can be used to mask bitter tastes in oral pharmaceuticals.

INTRODUCTION

Self-micromulsifying drug delivery systems (SMEDDS) are isotropic mixtures of oils and non-ionic surfactants which spontaneously emulsify in water upon gentle agitation producing fine dispersions of particle size between 5 to 150nm. These systems exhibit one of the most successful approaches in improving the dissolution, absorption and hence bioavailability of poorly water-soluble compounds.

They provide a reservoir of drug dissolved in the lipid matrix, which upon administration and making contact with gastrointestinal fluids spontaneously emulsify producing oil-in-water dispersions with large surface area available for drug diffusion. However, In order to facilitate formulation design of lipid based formulations, these systems were classified into type I, II, III and IV (Pouton, 2006) based on the hydrophilicity of oil mixture, particle size of resultant dispersion and formulation digestibility (Table 1). Taste is crucial to oral pharmaceutical dosage forms as undesirable taste is one of the important formulation problems encounters many drugs.

Taste is the conscious experience produced when a ligand binds to its taste receptor cell (TRC) housed in the taste buds on different areas of the tongue. There are approximately 2000-5000 taste buds in the oral cavity (Miller, 1995). Each contains around 100 heterogeneous taste receptor cells (TRCs) and thus responds to all stimuli (Chandrashekar et al., 2006). Currently, there are five accepted taste primaries: salty, sweet, sour, bitter, and umami. Bitter or obnoxious taste of drugs leads to lack of patients' compliance and therefore, bitterness masking becomes essential. There are various known taste masking technologies which are used in pharmaceutical industry which include; addition of sweeteners and flavoring agents (Kalaskar and Singh, 2014), microencapsulation (Sharma and lewis, 2010; Alkire et al., 1997), granulation (Wadhwa and Puri, 2011; Ishikawa and Watanbe, 1999), pro-drug (Kalaskar and Singh, 2014), viscosity enhancers (Deepti et al., 2011; Skranga and Tully, 2000), pH modifiers (Deepti et al., 2011), inclusion complexation (Leea et al., 2010), ion exchange resins (Puttevara et al., 2010), multiple emulsions (Khan et al., 2006) and the use of bitter taste inhibiting agents such as; neodesmin, aryl urea sulfonic acids (Roy et al., 1991), adenosine 5-monophosphate (ATP) (McGregor, 2004) and organic acids.

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Microemulsion application for taste masking is discussed in literature (Patel et al., 2006; Silva et al., 2012) yet; there is no single available product on the market which uses this technology. Our findings (un-published data) have demonstrated that oil-water interface for emulsion dispersions is not rigid enough to conceal unpleasant taste of drugs and hence provide adequate protection from activating taste receptor cells on the tongue. Hence, the objective of the present study is to design and develop stable flavored o/w micro-emulsions comprising various oils, co-surfactants, oil/aqueous based flavors and non-ionic surfactants using Paracetamol as bitter-taste hydrophilic model drug.

MATERIALS AND METHODS

Materials

Crodamol GTCC (medium chain triglyceride), Crodamol PC (propylene glycol dicaprylate / caprate), Glycerox 767HC (PEG 6 caprylic/ capric glycerides) and Croduret 40ss (PEG 40 Hydrogenated Castor Oil) were all supplied by Croda as gift samples. Cremophor RH 40 (PEG 40 Hydrogenated Castor Oil) was obtained from BASF Corporation, Oleic acid (USP) PRS-Codex purchased from Panreac, Spain and Peppermint oil by Hemway Germany. Aqueous based strawberry flavor food grade by Foster Clark Product LTD was purchased from the local market. Paracetamol 98% was obtained from Aldrich Company. Ethanol absolute was obtained from Scharlau, Spain.

Methods

Miscibility profiles of lipid mixtures

Regions of mutual solubility of various lipid formulations comprising various oils (Crodamol GTCC, Peppermint oil and Oleic acid), co-surfactants (Glycerox 767HC, Crodamol PC) and surfactants including;Croduret 40 ss and Cremophor RH40 were constructed using ternary phase diagrams. Formulations of 2 grams which represent various percentages of Cremophor RH40 were constructed using ternary phase diagrams.

Table 1: Typical Properties of Type I, II, III and IV Lipid Formulations (Pouton, 2006).

<table>
<thead>
<tr>
<th>Typical Composition (%) Triglycerides or Mixed Glycerides</th>
<th>Type I</th>
<th>Type II</th>
<th>Type IIIA</th>
<th>Type IIIIB</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactants</td>
<td>20 - 60</td>
<td>20 - 50</td>
<td>20 - 50</td>
<td>&lt; 20</td>
<td>0</td>
</tr>
<tr>
<td>Hydrophilic Cosolvents</td>
<td>0</td>
<td>0</td>
<td>0 - 40</td>
<td>20 - 50</td>
<td>0 - 80</td>
</tr>
<tr>
<td>Particle Size of Dispersion (nm)</td>
<td>100 - 250</td>
<td>50 - 100</td>
<td>50 - 100</td>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td>Significance of Aqueous Dilution</td>
<td>Limited Importance</td>
<td>Solvent Capacity Unaffected</td>
<td>Some Loss of Solvent Capacity</td>
<td>Significant Phase Change and Potential Loss of Solvent Capacity</td>
<td>Significant Phase Change and Potential Loss of Solvent Capacity</td>
</tr>
<tr>
<td>Significance of Digestibility</td>
<td>Crucial requirement</td>
<td>Not Crucial But Likely to Occur</td>
<td>Not Crucial But May be Inhibited</td>
<td>Not Required and Unlikely to happen</td>
<td>Not Required and Unlikely to happen</td>
</tr>
</tbody>
</table>

Mixtures were then kept for 24-48 hours in an oven set up at 25°C before visual assessment. Mixtures which formed a continuous single phase were classified as miscible formulations. Samples that displayed two or more phases were described as immiscible systems.

Self-Emulsification profiles of lipid mixtures

Mixtures of the various oils, co-surfactants and surfactants were produced by accurately weighing ingredients into glass test tubes and then wrapped by cling film followed by vortexing. Test tubes were held at 50 °C in a thermostated water bath held for 2 minutes before lipid mixtures were thoroughly vortexed. Lipid formulations were then left to equilibrate overnight in an oven set up at 25°C. Emulsions were prepared under conditions of gentle agitation at a controlled temperature of 37°C. An amount of 1g of each lipid mixture was introduced into 100ml of distilled water in a 500-ml glass beaker held at 37°C in a thermostated water bath. Emulsification under agitation conditions considered to be a reasonable simulation of the in vivo situation was carried out. Agitation was provided by gentle shaking on a mechanical shaker at 100 oscillations per min for 15 minutes. Visual assessment of resulting dispersions was carried out and systems which produced clear micro-emulsions were identified as SMEDDS.

Phase behaviour study

Selected lipid formulations with and without aqueous based strawberry flavor and Paracetamol were blended. Phase composition changes were made by adding water sequentially at 10 % w/w intervals. Mixtures were vortexed until homogeneity is achieved and then allowed to stabilize for phase identification.

Calibration curve of Paracetamol

Calibration curve was constructed according to the method described by Pawar et al. (2013). An amount of 0.1g of extracted Paracetamol was dissolved in 100 ml ethanol. Series of dilutions were made to obtain Paracetamol concentrations ranging from 1µg to 10 µg. Absorbance of the various solutions were
Solubility of Paracetamol in various lipid mixtures

Paracetamol is added in excess to various lipid solutions. Lipid suspensions are then vortexed for 3 minutes and then stored for 72 hours in a controlled temperature oven at 25°C to reach equilibrium (samples were vortexed in between). Oil suspensions are centrifuged at maximum speed (10,000 rpm) for 15 minutes. The clear saturated oil solution is then removed and assayed analytically by UV spectrophotometry at λ max 250 nm.

RESULTS AND DISCUSSION

Emulsification profiles of lipid formulations

Lipid systems containing flavored nonpolar oil

The Emulsification profile of a lipid system composed of Oleic Acid (LCT oil), Peppermint Oil (Flavored Oil) and Cremophor RH40 (non-ionic surfactant) is shown in figure 1. As figure 1 suggests, a very limited area of SMEDDS is obtained which reflects the optimized capacity of the surfactant to solubilize the non-polar content of the lipid mix, Oleic Acid and Peppermint Oil, in a stable o/w microemulsion system after aqueous dispersion. At least 60% w/w of Cremophor RH40 is needed to be mixed with Peppermint Oil to produce SMEDDS. On the other hand, the maximum amount of Oleic acid to be included in the lipid mixture of Peppermint Oil/Cremophor RH40 and thus form SMEDDS is only about 10% w/w at minimum surfactant concentration of 70% w/w. Furthermore, replacing Oleic Acid (LCTs) with Crodamol PC (MCTs) has slightly extended SMEDDS area as depicted in figure 2 as generally, MCTs are more soluble and have higher mobility in the lipid/water interfaces. Optimized SMEDDS area can be obtained at maximum Oleic concentrations of 30% w/w in the lipidic mix w/w using minimum Cremophor RH40 concentrations of 60% w/w.

Lipid systems containing aqueous flavors

Figure 3 shows the emulsification profile of a lipid system composed of Crodamol GTCC (oil), Glycerox 767HC (co-surfactant) and Croduret 40 ss (non-ionic surfactant). An extended area of SMEDDS is formed which widens the number of robust self-micro-emulsifying formulations that may be selected from this lipid composite. This may suggest the fact that due to the polar characteristics of Corduret 40 ss as measured by its HLB value (13) has, from one hand, improved the mixing properties of the lipid pre-concentrate and moreover with Glycerox 767HC (HLB = 13.2) have produced oil droplets with a total HLB value that would enhance degree of aqueous dispersion. Interestingly, self-micro-emulsifying dispersions can be obtained by blending a binary mix composed of Glycerox 767HC and Corduret 40 ss at only a 10% w/w minimum concentration of the non-ionic surfactant Corduret 40 ss, see line AB depicted on figure 3. Each of the lines AC, AD, AE and AF which are shown on figure 3 represents formulations at fixed ratio of Crodamol GTCC: Glycerox 767HC diluted with increasing concentration of Corduret 40 ss. Ratios of Crodamol GTCC: Glycerox 767HC for the representative formulations on lines AC, AD, AE and AF are 2:8, 3:7, 4:6 and 5:5, respectively. The progressive inclusion of Crodamol GTCC (source of triglyceride) in the lipid composite (i.e. moving from line AC to AF) entails gradual increase of the concentration of the non-ionic surfactant Corduret 40 ss to produce SMEDDS. Based on the emulsification profile of Crodamol GTCC/Glycerox 767HC/Croduret 40 ss system, SMEDDS formulations numbered 1-12 presented in table 2 are selected. These formulations are categorized into group A; binary mix of Glycerox 767HC/Croduret 40 ss using concentrations of Corduret 40 ss between 20-50% w/w, group B; binary mix of Crodamol GTCC/Glycerox 767HC at ratio of {1:9} blended with increasing concentrations of Corduret.
40 ss between 20-50% w/w and group C; binary mix of Crodamol GTCC/Glycerox 767HC at ratio of [2:8] blended with increasing concentrations of Corduret 40 ss between 20-50% w/w. Furthermore, formulations numbered 13 to 19 in table 2 were selected based on emulsification behavior of lipid system composed of Crodamol PC, Oleic Acid and Cordurate 40 ss. Formulations 1-19 are considered pre-concentrate lipidic mixtures which will act as recipients to incorporating aqueous flavors within lipid matrix and hence producing as W/O microemulsion system.

Dynamic phase behavior resulted from the interaction of increasing concentrations of strawberry flavor with the various lipidic formulations is shown in figure 4. Formulations numbered 1-12 and 19 were able to solubilize 20% w/w of aqueous-based strawberry flavor forming stable w/o microemulsion identified as L₁ phase. This reflects synergistic effect of Corduret 40 ss (HLB value =13) with Glycerox 767HC (HLB = 13.2) which have interplayed to forming the right HLB of the lipid mix to maximize solubilization of aqueous flavor into lipid matrix. Role of various lipid constituents on enhancement in the water-solubilized region (L₁) and hence, the impact on the mechanism of emulsification process is thoroughly investigated by Hasan (2014). Nonetheless, formulations from 13 to 18 have produced, on dilution with the aqueous flavor, a number dynamic intermediate transient phases passing from L₁ phase → either L₁+L₂ (turbid mixtures) or gel phase. This will either compromise the stability of these systems or might unnecessarily extend emulsification time after aqueous dispersion of the formulation. These systems were deemed unsuccessful and hence were excluded from further evaluation.

Dynamic phase behavior of formulations 1 to 12 and 19 containing 20% w/w aqueous flavor resulted from the sequential dilution with water from 0-100% w/w was investigated and presented in figure 5. Formulations 1-4 (group A), 7 and 8 (group B) and 12 (group C) on dilution with water have produced all the way through clear W/O → O/W microemulsions which may suggest that these systems are good candidates to form the bases of producing flavored SMEDDS. On the other hand, formulations 5 and 6 (group B); 9, 10 and 11 (group C) and 19 have produced intermediate dynamic transient phases including L₁+L₂, Gel or L₁+L₂+Gel phases which may undermine the suitability of these systems and hence were excluded from further analysis.

Due to possible irritant effect of the non-ionic surfactant (Corduret 40 ss) present in these lipidic systems, formulations which have the minimal surfactant concentrations and still produce, on dilution with water, all the way through clear micromulsions were selected for further development. Formulations which fulfill the aforementioned criteria are; formulation number 1 (group A) composed of Glycerox 767HC /Corduret 40 ss (80/20) % w/w, formulation 7 (group B) composed of Crodamol GTCC/Glycerox 767HC /Croduret 40 ss (6/54/40) % w/w and formulation 12 (group C) composed of Crodamol GTCC/Glycerox 767HC /Croduret 40 ss (10/40/50) % w/w.

Aqueous-based strawberry flavor containing 5-10% w/w sucrose was sequentially added to lipid formulations 1, 7 or 12. Dynamic phase behavior resulting from diluting lipidic formulations with increasing concentration of flavor containing sucrose is shown in figure 6 a. Clear W/O microemulsions as L₁ phase were obtained at all added concentrations of flavor. This suggests that these formulations have high polarity to encapsulate enough hydrophilic sweetened flavors within the lipid matrix which can exert taste masking effect. Sucrose was used here as a natural sweetening agent.
However, synthetic sweeteners such as sucralose, aspartame and saccharin in combination sugar alcohols like lactitol, maltitol and sorbitol to decrease after-taste perception (Vummaneni and Nagpal, 2012) can also be used. Natural or synthetic flavors in combination with sweeteners can mimic taste masking efficiency. Strawberry flavor was here chosen as an example of aqueous-based flavor and cane by replaced by any other flavor according to the designed application.

Formulations 1, 7 or 12 containing 20% w/w (strawberry flavor plus 5-10% sucrose) were further diluted with 0-100% w/w of water to highlight changes in the dynamic phases formed due to gradual penetration of water during emulsification process, see figure 6 b. Clear W/O \( \rightarrow \) O/W micromulsions (\( L_2 \rightarrow L_1 \)) are formed at all dilution percentages of water. This can improve patient's satisfaction and compliance as optical clear dispersions are obtained after dispersing formulation in any amount of water.

Lipidic formulations 1, 7 and 12 are considered archetypical examples of type III lipid class systems according to the classification by Pouton (2006). Therefore, ‘Diffusion and Stranding’ mechanism is considered to be the predominant process of emulsification of these lipid systems. The role of co-surfactant (Glycerox 767HC) in these lipid mixtures is to aid in the emulsification process by the virtue of its high polarity. It is thought that co-surfactant can stabilize the interface by penetrating into the void spaces among surfactant molecules in the surfactant film around the oil droplet and hence lowering the interfacial tension and increasing the interfacial fluidity (Hasan, 2014).

Lipidic formulations 1, 7 and 12 were also titrated with increasing concentrations of strawberry flavor containing 10% w/w sucrose and 5% w/w citric acid. Equilibrium dynamic phase behavior has revealed clear W/O microemulsions (\( L_2 \) phase) which suggests that these lipid systems have the capacity to solubilize...
solution of sucrose and citric acid, see figure 7 a. Furthermore, on
dilution with water of lipid systems containing 20% w/w
(strawberry flavor, 10% sucrose and 5% citric acid), clear W/O →
O/W microemulsions ($L_2 \rightarrow L_1$) are obtained, see figure 8 b. Water
soluble organic acids such as tartaric acid, ascorbic acid
or citric acid and their salts can be used with hydrophilic polymers,
surfactant or oils for achieving taste masking. These acids promote
salivation and thus viscosity in the mouth which can coat taste
buds, and therefore can act as potential taste masking agent
(Vummaneni and Nagpal, 2012). Furthermore, citric acid not only
can increase taste masking efficiency of sweeteners but also can
compete within the channel receptors with the bitter stimuli.

Fig. 6: Dynamic phase behavior resulting from diluting (a) Formulations 1, 7 or 12 with increasing concentration of aqueous-based strawberry flavor containing 5-10% w/w sucrose (b) Formulations 1, 7 or 12 containing 20% w/w (strawberry flavor plus 5-10% sucrose) with 0-100% w/w of water.

Fig. 7: Dynamic phase behavior resulting from diluting (a) Formulations 1, 7 or 12 with increasing concentration of aqueous-based strawberry flavor containing 10% w/w sucrose and 5% w/w citric acid (b) Formulations 1, 7 or 12 containing 20% w/w (strawberry flavor, 10% sucrose and 5% citric acid) with 0-100% w/w of water.
Inclusion of a bitter-taste model drug

Paracetamol is widely used as analgesic and antipyretic drug in all age groups; pediatric and geriatric patients. It was selected here as a model bitter-taste hydrophilic drug with a threshold concentration of 350µg/ml (Cavallari et al., 2004; Sharma et al., 2012). Saturated solubility of Paracetamol in various lipidic solutions is measured and data is presented in figure 8.

Solubility of Paracetamol in pure lipid formulations 1, 7 or 12 was found approximately in the range of 80 to 90 mg/g lipid; with the highest value observed in formulation 1. However, when incorporating 20% w/w of either water or flavor 1 (pure strawberry flavor) in the lipid formulations, solubility of Paracetamol was almost doubled in comparison to the pure lipidic systems. Approximately 160 to 180 mg/g lipid is the solubility of Paracetamol in lipid formulations 1 or 7 containing 20% w/w of either water or flavor 1. This is attributed to the fact that, as Paracetamol is a water soluble drug, increasing hydrophilic content within lipid matrix will ensue in enhancing solubility of Paracetamol in these systems. However, there is reduction in Paracetamol solubility in the case of including in the lipid systems, 20% of either flavor 2 (strawberry flavor + 10% sucrose) or flavor 3 (strawberry flavor + 10% Sucrose + 5% citric acid), relatively to formulations containing 20% of either water or pure strawberry flavor (flavor 1). This might be due to the competition of sucrose or citric acid solutes present in flavor 2 or 3 with Paracetamol within aqueous core of the lipidic solution. Nonetheless, solubility of Paracetamol in all lipid formulations containing 20% w/w of either flavors 2 or 3 lies between 140 -160 mg/ g lipid. It is worth noting here that, for the solubility data, it is important here to elucidate the effect of incorporating drug in the lipid matrix on the phase behavior after dispersion of the formulation. Generally, hydrophobic drugs included in SMEDDS affect dynamic mechanistic of emulsification process as transient intermediate phases might appear before reaching L1 phase (clear O/W microemulsion).

This might be attributed to the effect of drug on the polarity of the oil droplet or by blocking charge transfer between molecules during emulsification. Yet, if this system were to be applied as a method to enhance oral bioavailability of poorly water soluble compounds, the formation of intermediate phases might help solubilization of drugs and thus avoiding crystallization of drugs during emulsification in the GIT. However, in the case of using SMEDDS as taste masking approach, the formation of such transient intermediate phases might compromise physical characteristics the resultant dispersions at certain percentage of water dilution. Therefore, it is important for these systems with and without drugs to form all the way through clear dispersion during dilution with water.

Equilibrium dynamic phase behavior resulting from the gradual dilution with water of lipid formulation 7 containing 20 % w/w pure strawberry flavor and Paracetamol at concentrations of either 50 mg or 100 mg/ g lipid is presented in figure 9. Clear W/O → O/W micromulsions (L2→L1) are obtained at both concentrations of the drug. This suggests that Paracetamol as a hydrophilic material does not interfere in the mechanistics of emulsification process and thus may add value to this system as a potential approach for taste masking.

Nonetheless, hydrophobic drugs can interfere in the mechanistic processes of emulsification by blocking charge movement through the system, via the direct complexation of the drug with some mixture components through its interaction with the liquid crystalline phase or by penetration into the surfactant interfacial monolayer.
Fig. 9: Equilibrium dynamic phase behavior resulting from the gradual dilution with water of lipid formulation 7 containing 20 % w/w pure strawberry flavor and Paracetamol at concentrations of (A) 50 mg or (B) 100 mg/ g lipid.

CONCLUSION

Potential flavored self-microemulsifying lipid formulations representing type III lipid class system which comprise Crodamol GTCC / Glycerox 767HC / Croduret 40 ss at ratios of (0/80/20), (6/54/40) or (10/40/50) were developed. Aqueous-based strawberry flavor, sucrose, citric acid and Paracetamol could be loaded into these lipid systems forming stable O/W microemulsion which can have taste masking abilities. These systems depending on formulation constituents can solubilize up to 140 to 180 mg Paracetamol/gm lipid. Furthermore, clear microemulsions are obtained on further dilution with water, which adds value to these systems as potential taste masking vehicles.

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REFERENCES


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