ABSTRACT SUMMARY
The purpose of this study was to formulate and characterize nicotinic acid (niacin) entrapped polylactide-co-glycolide (PLGA) nanoparticles (NPs) using two differing concentrations (0.1% and 0.25% w/v) of didodecyldimethylammonium bromide (DMAB) as stabilizer. Results of our characteristic studies showed nanometric particle size achievement (115.53 ± 5.24 nm and 104.47 ± 6.04 nm) for 0.1% and 0.25% w/v DMAB NP formulations, respectively. NP formulations utilizing 0.25% DMAB concentration demonstrated improved zeta potential (29.52 ± 2.36 mV), polydispersity (0.08 ± 0.02) and percent drug entrapment (69.09 ± 0.29) when compared to 0.1% DMAB formulation (22.99 ± 2.59 mV, 0.15 ± 0.01 and 66.03 ± 0.77, respectively). These findings demonstrate successful formulation of DMAB based niacin loaded polymeric NPs. Further studies are warranted for the optimization of niacin loaded NP formulation.

INTRODUCTION
Niacin is one of the few known compounds shown to increase blood levels of high-density lipoprotein while beneficially altering low-density lipoprotein and triglyceride (TG) levels [1]. As such, niacin has become an attractive option for the treatment of dyslipidemia and atherosclerotic disease. Niacin exerts its anti-lipidemic effects through alterations in key enzymatic pathways responsible for TG synthesis as well as VLDL and LDL degradation [2]. Recently, the G-protein coupled receptors (GPR) 109A and GPR109B have been identified in adipose tissue and immune cells as niacin receptors. These receptors are thought to play a role in niacin induced lipid alterations. Activation of GPR109A and GPR109B can increase release of arachidonic acid and prostaglandin synthesis, subsequently resulting in increased activation of vasodilatory prostaglandin receptors, thus inducing the niacin flush [3]. However, many patients are discouraged from taking niacin due to the flushing effects felt from increased dosages. Interestingly, the flushing effect of niacin has been shown to be reduced by concomitant administration of NSAIDs as well as reformulated delivery systems that prolong or extend systemic niacin release [2]. The purpose of this study was to develop and characterize PLGA-based niacin loaded NPs that could be used as an alternative delivery method to offset or reduce the adverse flushing effect of niacin.

EXPERIMENTAL METHODS
NP synthesis was achieved through an emulsion-diffusion-evaporation process. An organic phase consisting of 50 mg PLGA and 45 mg nicotinic acid dissolved in 3 mL ethyl acetate was added to 6 mL of aqueous phase containing 0.1% w/v or 0.25% w/v DMAB stabilizer. The resultant mixture was probe sonicated for 5 minutes at 20 kHz to create the primary emulsion. NP diffusion was facilitated by the addition of 25 mL high-performance liquid chromatography (HPLC) grade H₂O then stirred for 2 hours at 750 rpm to ensure complete organic phase evaporation. Following evaporation, solutions were centrifuged at 12,000 rpm for 5 minutes. NP containing supernatant was then collected and analyzed for size, zeta potential, polydispersity, and percent of drug entrapped. The mean NP size, zeta potential, and polydispersity index (PDI) was measured using a NICOMP Zetasizer (Particle Sizing Systems, Port Richey, FL, USA). A solution consisting of 100 μL of NP solution combined with 300 μL acetonitrile was used to assess the percentage of drug entrapment under ultra-violet spectrometry at 260 nm (Eppendorf BioPhotometer, Hauppauge, NY, USA). Blank NP solution was used for control purposes. A standard calibration curve was created with a stock solution consisting of niacin dissolved in HPLC grade H₂O at varying concentrations ranging from 0.1 mg/mL to 2 mg/mL before NP entrapment studies. Data is presented as mean ± standard deviation (SD). A Student’s t-test was used to compare 0.1% and 0.25% DMAB formulations.

RESULTS AND DISCUSSION
Niacin entrapped PLGA-NPs were formulated using two differing concentrations of DMAB as stabilizer (0.1% and 0.25% w/v). No significant difference in mean particle size was noted between formulations. The absolute value of zeta potential gives an indication of the potential stability of NP systems [4]. Our results show that stability was
significantly higher in NPs formulated with 0.25% DMAB, showing a zeta potential of 29.52 ± 2.36 mV. Similarly, a significant decrease in the polydispersity of NPs formulated at 0.25% DMAB was noticed (Table 1). The increased zeta potential is most likely reflective of the direct increase in DMAB concentrations as DMAB is more cationic in nature which can impart a positive charge on the NP surface [5]. Higher concentrations of DMAB would facilitate a higher degree of DMAB incorporation into the NP outer shell. As the concentration of DMAB increased in NPs, a subsequent rise in positive charge would be expected based on the cationic properties of DMAB. Correspondingly, the increased distribution of stabilizer on the particle surface could enhance NP dispersion during sonication, giving rise to smaller particles with a more uniform shape and improved PDI value [6].

<table>
<thead>
<tr>
<th>DMAB (% w/v)</th>
<th>Particle size (nm)</th>
<th>Zeta potential (mV)</th>
<th>PDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>115.53 ± 5.24</td>
<td>22.99 ± 2.59</td>
<td>0.15 ± 0.01</td>
</tr>
<tr>
<td>0.25</td>
<td>104.47 ± 6.04</td>
<td>29.52 ± 2.36'</td>
<td>0.08 ± 0.02'</td>
</tr>
</tbody>
</table>

All values reported as mean ± SD (n = 3).

PDI is the polydispersity index.

' P < 0.05 compared to 0.1% DMAB formulation.

Interestingly, when compared to 0.1% DMAB formulation, a significant increase in both the amount of drug entrapped and entrapment efficiency was noticed in formulations containing 0.25% DMAB stabilizer (Table 2). It is important to note that drug solubility has one of the most critical impacts on encapsulation efficiency [7]. It is possible that DMAB functions to alter the solubility of niacin in the aqueous continuous phase resulting in the increased drug entrapment noticed in our study. Also, particle charge alterations brought forth by increased inclusion of DMAB into NPs could facilitate ionic interactions between the drug and polymer shell, resulting in increased drug incorporation within the NP [8].

<table>
<thead>
<tr>
<th>DMAB (% w/v)</th>
<th>Amount entrapped (mg)</th>
<th>% EE</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>29.72 ± 0.35</td>
<td>66.03 ± 0.77</td>
</tr>
<tr>
<td>0.25</td>
<td>31.09 ± 0.13&quot;</td>
<td>69.09 ± 0.29&quot;</td>
</tr>
</tbody>
</table>

All values reported as mean ± SD (n = 3).

Amount entrapped per 20 mg celecoxib.

EE is the entrapment efficiency.

" P < 0.01 compared to 0.1% DMAB formulation.

CONCLUSION

In this study, we utilized a solvent diffusion evaporation process for the development of niacin loaded PLGA-NPs. Characteristic studies demonstrated effective formulation of niacin loaded NPs with high stability and drug entrapment. Our results show that the use of DMAB as stabilizer in NP synthesis can alter total drug stability and drug entrapment in the presence of changing concentrations of DMAB. Further studies are warranted to elucidate optimum niacin NP formulations.

REFERENCES


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