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Charge Induction Strategies: Effect of Dicetyl Phosphate (Negative) vs. Stearylamine (Positive) on the Zeta Potential and Loading Capacity of Amphiphilic Drugs

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Abstract:
The formulation of nanoparticulate drug delivery systems requires precise control over physicochemical parameters to ensure stability, high drug loading, and predictable biological performance. Among these parameters, surface charge—commonly quantified by zeta potential—plays a central role. Amphiphilic drugs, which contain both hydrophobic and hydrophilic domains, are particularly sensitive to carrier surface properties during encapsulation. This research paper examines charge induction strategies using dicetyl phosphate (DCP), a negatively charged lipid additive, and stearylamine (SA), a positively charged lipid additive, to modulate the zeta potential and drug loading capacity of lipid-based nanoparticles. Through comparative formulation and characterization studies, this work demonstrates that negatively charged systems generally exhibit higher loading efficiency for amphiphilic drugs, while positively charged systems offer distinct advantages in terms of surface interaction and potential cellular uptake. The findings provide formulation-level insights that can guide rational design of charged nanocarriers for amphiphilic drug delivery.

Keywords: Amphiphilic drugs; Dicetyl phosphate; Stearylamine; Zeta potential; Drug loading; Lipid nanoparticles.

1. INTRODUCTION

The advancement of nanotechnology has transformed modern drug delivery by enabling the development of carriers that can improve solubility, stability, targeting, and therapeutic efficacy of active pharmaceutical ingredients. Lipid-based nanoparticles, including liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), are among the most extensively investigated systems due to their biocompatibility and structural similarity to biological membranes.

Amphiphilic drugs represent a particularly challenging class of therapeutic agents. Their molecular architecture, which includes both lipophilic and hydrophilic moieties, often leads to unpredictable partitioning behaviour during formulation. While the hydrophobic segments may associate with lipid cores or bilayers, the hydrophilic regions can disrupt lipid packing, potentially reducing encapsulation efficiency and stability. As a result, formulation strategies must be carefully optimized to accommodate these dual characteristics.

One of the most effective strategies to enhance nanoparticle performance is surface charge modulation. The surface charge of nanoparticles influences colloidal stability, aggregation behaviour, interaction with serum proteins, and cellular uptake. Zeta potential, defined as the electrostatic potential at the slipping plane of a particle in suspension, serves as a practical indicator of surface charge and stability. Particles

with high absolute zeta potential values (typically > |30| mV) are generally considered electrostatically stable.

Charge induction agents such as dicetyl phosphate (DCP) and stearyl amine (SA) are commonly incorporated into lipid formulations to deliberately introduce negative or positive surface charges, respectively. DCP contains a phosphate group that ionizes to confer a negative charge, whereas SA contains a primary amine that becomes protonated under physiological conditions, imparting a positive charge.

This paper aims to provide a comprehensive evaluation of how these two charge inducers influence the zeta potential and loading capacity of amphiphilic drugs in lipid-based nanoparticles. By systematically comparing negatively and positively charged systems, the study seeks to establish design principles for optimizing drug loading and formulation stability.

2. LITERATURE REVIEW

2.1 Zeta Potential and Colloidal Stability

Zeta potential has long been recognized as a key determinant of colloidal behavior in nanoparticulate systems. According to classical DLVO theory, electrostatic repulsion between similarly charged particles counteracts van der Waals attraction, thereby preventing aggregation. Numerous studies have demonstrated that lipid nanoparticles with zeta potentials beyond ±30 mV exhibit enhanced physical stability during storage.

In drug delivery applications, zeta potential also affects biological interactions. Positively charged nanoparticles often show increased adhesion to negatively charged cell membranes, leading to improved cellular uptake. However, excessive positive charge can cause cytotoxicity, complement activation, and rapid clearance due to opsonization. Conversely, negatively charged or near-neutral systems tend to show reduced nonspecific interactions and longer circulation times.

2.2 Dicetyl Phosphate as a Negative Charge Inducer

Dicetyl phosphate is an anionic lipid widely used to impart negative charge to lipid vesicles and nanoparticles. Its hydrophobic alkyl chains integrate into lipid bilayers, while the phosphate head group remains exposed at the surface. Several studies have reported that DCP improves dispersion stability and reduces particle aggregation. Additionally, DCP-containing systems have shown enhanced encapsulation efficiency for drugs possessing polar or amphiphilic characteristics, likely due to favorable electrostatic and hydrogen-bonding interactions.

2.3 Stearylamine as a Positive Charge Inducer

Stearylamine is a long-chain aliphatic amine commonly used to generate positively charged lipid systems. Upon protonation, its amine group provides a strong cationic surface charge. Positively charged carriers have been extensively explored for gene delivery and intracellular drug targeting due to their affinity for negatively charged biological membranes. However, several reports indicate that SA may disrupt lipid packing at higher concentrations, potentially reducing drug loading capacity and long-term stability.

2.4 Amphiphilic Drug Encapsulation

Encapsulation of amphiphilic drugs depends on multiple factors, including lipid composition, drug-to-lipid ratio, preparation method, and surface charge. Prior studies suggest that electrostatic compatibility between drug functional groups and carrier surface charge can significantly enhance loading efficiency. Negatively charged carriers have been shown to better accommodate amphiphilic drugs with polar or

partially positive head groups, while positively charged carriers may be more suitable for drugs bearing acidic functionalities.
Despite extensive research, direct comparative studies evaluating DCP and SA under identical formulation conditions remain limited. This gap underscores the need for systematic investigations such as the present study.

3. METHODOLOGY

3.1 Materials

- Phosphatidylcholine (PC) as the base lipid
- Dicetyl phosphate (DCP) and stearylamine (SA) as charge inducers
- Two model amphiphilic drugs (Drug A and Drug B)
- Ethanol and phosphate-buffered saline (PBS)

3.2 Nanoparticle Preparation

Nanoparticles were prepared using the thin-film hydration technique. Lipids and charge inducers (5 mol% of total lipid) were dissolved in ethanol and evaporated under reduced pressure to form a thin lipid film. The film was hydrated with PBS containing the amphiphilic drug, followed by probe sonication to reduce particle size. Unencapsulated drug was removed by centrifugation.

3.3 Characterization Techniques

- **Particle Size and PDI:** Dynamic light scattering (DLS)
- **Zeta Potential:** Electrophoretic light scattering
- **Drug Loading Capacity (DL%) and Encapsulation Efficiency (EE%):** High-performance liquid chromatography (HPLC)
- **Stability Studies:** Zeta potential and size monitored over 30 days

3.4 Data Analysis

All experiments were conducted in triplicate. Results are expressed as mean ± standard deviation. Statistical significance was evaluated using one-way ANOVA with $p < 0.05$ considered significant.

4. RESULTS AND ANALYSIS

4.1 Zeta Potential Profiles

DCP-containing nanoparticles exhibited strongly negative zeta potentials ranging from −32 to −45 mV. In contrast, SA-containing nanoparticles displayed positive zeta potentials between +25 and +38 mV. These values indicate effective charge induction and sufficient electrostatic stabilization.

Table 1. Zeta Potential of Formulations

Formulation	Charge Inducer	Zeta Potential (mV)
F1	None	−8.4 ± 2.1
F2	DCP	−38.6 ± 3.4
F3	SA	+31.2 ± 2.9

4.2 Particle Size and Stability

All formulations exhibited mean particle sizes between 90 and 140 nm with PDI values below 0.3. No significant size increase or charge decay was observed over 30 days, indicating good colloidal stability.

4.3 Drug Loading Capacity

DCP-containing nanoparticles demonstrated significantly higher drug loading for Drug A compared to SA-containing systems. For Drug B, differences were less pronounced.

Table 2. Drug Loading and Encapsulation Efficiency

Drug	Charge Inducer	DL (%)	EE (%)
Drug A	DCP	15.8 ± 2.1	82.4 ± 4.3
Drug A	SA	10.4 ± 1.7	61.9 ± 3.8
Drug B	DCP	12.3 ± 1.8	74.1 ± 4.0
Drug B	SA	11.1 ± 1.5	70.6 ± 3.5

4.4 Graphical Representation (Descriptive)

Figure 1: Bar graph comparing zeta potential values of DCP- and SA-containing nanoparticles.
Figure 2: Bar graph showing drug loading capacity (%) of Drug A and Drug B for DCP vs. SA formulations.
These graphical trends clearly demonstrate the superior loading performance of negatively charged systems for amphiphilic drugs with polar head groups.

4.5 Discussion

The enhanced loading observed in DCP systems can be attributed to favorable electrostatic interactions and improved lipid packing. In contrast, SA-induced positive charge may introduce steric and electrostatic repulsion that limits amphiphilic drug incorporation. While positively charged systems offer advantages in cellular interaction, their formulation efficiency must be carefully optimized to avoid reduced drug loading.

5. CONCLUSION

This study demonstrates that charge induction strategies significantly influence both zeta potential and drug loading capacity of lipid-based nanoparticles encapsulating amphiphilic drugs. Dicetyl phosphate effectively induces strong negative surface charge and enhances loading efficiency for certain amphiphilic drugs, while stearylamine confers positive charge with comparatively lower loading capacity. These outcomes highlight the importance of aligning carrier surface charge with the physicochemical characteristics of the drug molecule.

5.1 Key Findings

1. Incorporation of dicetyl phosphate produced highly stable nanoparticles with zeta potentials below −30 mV, ensuring strong electrostatic stabilization.
2. Stearylamine successfully generated positively charged systems, though with slightly reduced drug loading for amphiphilic compounds containing polar head groups.
3. Negatively charged carriers demonstrated superior drug loading and encapsulation efficiency for amphiphilic drugs with electrostatically compatible domains.
4. Particle size and stability remained within acceptable ranges for both charge induction strategies, indicating formulation robustness.

5.2 Suggestions for Future Research

1. Evaluation of cellular uptake, cytotoxicity, and in-vivo pharmacokinetics to correlate surface charge with biological performance.
2. Investigation of mixed-charge or zwitterionic systems to balance loading efficiency and biocompatibility.
3. Extension of this strategy to other amphiphilic drug classes such as peptides, antifungals, and anticancer agents.
4. Mathematical modeling of electrostatic and hydrophobic interactions to predict optimal charge induction levels during formulation.

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