

## A Novel Drug Delivery System: Niosomes Review

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**Abstract:** Drug targeting is a kind of mechanism in which the drug is administered in the body in such a way that the drug interacts at a cellular or subcellular level with the target tissue to achieve a desired therapeutic response at a desired location without unwanted interactions at other sites. This can be done by modern methods such as niosomes, which target the drug delivery system. Niosomes are the type of non-ionic surfactant vesicles which are a new approach to liposomes that is biodegradable, non-toxic, more durable and cheaper. Their liposome-like structure and therefore they can represent alternate vesicular structures in relation to liposomes. The niosomes appear to load various types of drugs. This review article describes niosome structure, benefits, drawbacks, niosome preparation methods and pharmaceutical NSV characterisation.

**Keywords:** Niosome, Cholesterol, Hydrophilic and Lipophilic drugs, Surfactant, Targeted delivery Bioavailability Improvement, Factors, Applications.

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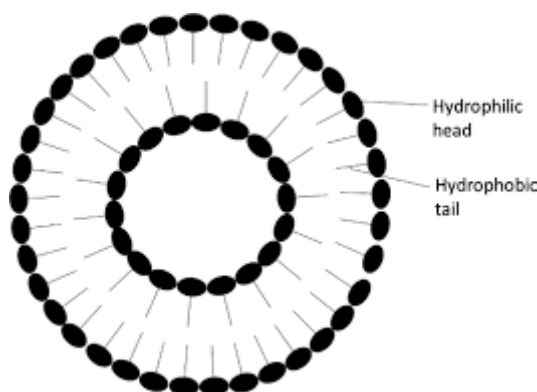
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### I. Introduction

Paul Ehrlich initiated the targeted delivery development in 1909 when he envisaged a mechanism for the delivery of drugs that would directly target diseased cell. Drug targeting can be characterized as the ability to direct a therapeutic agent directly to the intended site of action with little or no non-target tissue involvement.<sup>1</sup> In niosome, amphiphile vesicles are a non-ionic surfactant like Span-60 that is normally stabilized by adding cholesterol and a small amount of anionic surfactant or dicetyl phosphate. The first non-ionic surfactant vesicles report came from L'Oreal's cosmetic applications. Researchers and academics broadly accept the concept of incorporating the drug into niosome for better targeting of the drug at the appropriate tissue destination. Niosomes such as targeting, ophthalmic, topical, parental, etc. can be used for various types of drug delivery.<sup>2</sup> Niosomes are microscopic lamellar structures of the size range between 10 to 1000 nm. The niosome is made up of surfactants that are non-immunogenic, biodegradable and biocompatible. Niosomes are better than liposomes and their higher surfactant chemical stability than phospholipids that are easily hydrolyzed by the ester bond and cost-effective.<sup>3</sup>

### II. Structure Of Niosome

An ordinary niosome vesicle would comprise of a vesicle shaping amphiphile for example a non-ionic surfactant, for example, Span-60, which is generally balanced out by the expansion of cholesterol and a modest quantity of anionic surfactant, for example, dicetyl phosphate, which likewise helps in balancing out the vesicle.<sup>4,5</sup>



**ADVANTAGES OF NIOSOME** <sup>6,7</sup>

- 1 Niosomes may contain an assortment of medication states of mind, for example, hydrophilic, lipophilic and amphiphilic drugs.
- 2 The medication can discharge in the way that is continued/controlled.
- 3 No extraordinary conditions are required for surfactant taking care of and preparing.
- 4 Poorly dissolvable medications have expanded bioavailability for oral use.
- 5 Surfactants have biodegradable, biocompatible, non-poisonous and non-immunogenic reactions.
- 6 Drug protection against metabolism of the enzyme.
- 7 Niosomes helps in improving the stability of loaded drug.
- 8 They can increase drug permeation through the body.

**DISADVANTAGES OF NIOSOMES** <sup>8</sup>

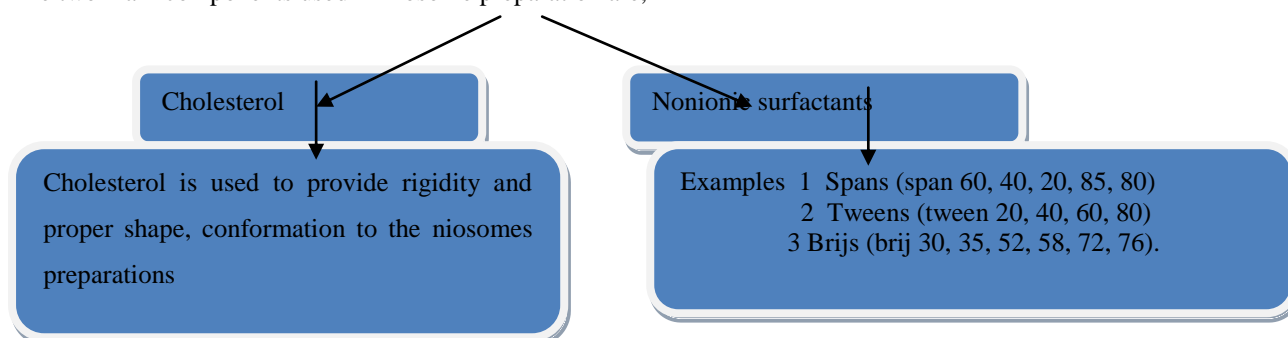
- 1 Physical instableness.
- 2 Aggregation
- 3 Fusion
- 4 Leakage of clogged drug

**Comparison between Niosomes and Liposomes** <sup>9</sup>

LIPOSOMES	NIOSOMES
More Expensive	Less Expensive
Require special methods for the final preparation and handling of the formulations.	For such formulations it doesn't require any special methods.
Phospholipids can be chargeable and neutral.	Uncharged non-ionic surfactant.

**COMPOSITION OF NIOSOMES** <sup>10,11,12</sup>

The two main components used in niosome preparation are,



**TYPES OF NIOSOMES**

The various types of niosomes are as:

- i) Multi lamellar vesicles (MLV),
- ii) Large unilamellar vesicles (LUV),
- iii) Small unilamellar vesicles (SUV).

Parameters	Multi lamellar Vesicles	Small Unilamellar Vesicles	Large Unilamellar Vesicles
Vesicle Size	Greater than 0.05µm	0.025 – 0.05µm	Greater than 0.10µm
Method of Preparation	Hand Shaking Method	Sonication Extrusion Method Solvent Dilution Technique	Reverse Phase evaporation Method

## FORMULATION AND EVALUATION OF NIOSOMES

### Method of preparation

**A. Passive Trapping Techniques-** This category includes most of the methods used in niosome preparation in which the drug is added during the niosome preparation, i.e. during its development.

#### 1. Sonication -

Drug solution mixture in buffer, surfactant and cholesterol.

↓  
Sonicated at 60 ° C for 3 minutes with a titanium sonicator to yield niosomes. <sup>13</sup>

#### 2. Ether Injection Method –

Niosomes gradually dissolve in diethyl ether in a surfactant solution to keep warm water at 60° C

↓  
Mixture in ether is inserted into an aqueous substance solution via a 14-gage needle

↓  
Vaporization of the ether occurs in single-layer vesicles

↓  
The vesicle diameter between 50 and 1000 nm depends on the conditions used. <sup>14,15</sup>

**3. Reverse Phase Evaporation Technique –** Cholesterol and surfactant (ratio 1:1) dissolves in the organic solvent mixture (ether and chloroform), removing the aqueous product solution and containing water in the oil emulsion; two stages are acoustic at 4-5°C. The emulsion is dried at 40 ° C in a rotary evaporator to create a semi-solid gel of large vesicles. Small amounts of phosphate buffered saline (PBS) are applied to the clear gel and sonicate again. Viscous niosomal suspension is further diluted with phosphate-buffered saline, and placed into a water bath for 10 minutes to form niosomes. <sup>16</sup>

#### 4. The “Bubble” Method-

The bubbling machine contains a round flask with three columns in the water bath to regulate the temperature.

↓  
The water-cool reflux is put in the first neck and the thermometer is inserted through the third neck in the second neck and nitrogen source.

↓  
Cholesterol and surfactant are spread in the buffer at 70 ° C (pH 7.4) Dispersion mixture with high shear homogenizer for 15 seconds

↓  
"Bubbled" with nitrogen gas at 70 ° C <sup>17</sup>

#### 5. Hand Shaking Method (Thin Film Hydration Technique/Rotary Evaporator) –

The combining products-cholesterol and surfactant and inducer of charge

↓  
The Dissolves in a round bottom flask in a volatile organic solvent (chloroform, diethyl ether or methanol).

↓  
Use of a rotary evaporator to evaporate organic solvent at 20 ° C room temperature

↓  
A thin layer of firm mixture is formed

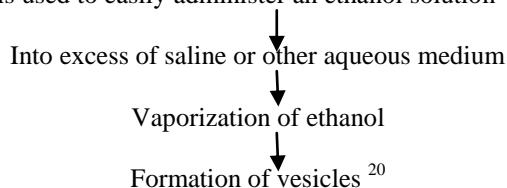
↓  
With gentle agitation, the dry surfactant film can be rehydrated with an aqueous phase at 0-60°C

↓  
Formation of niosomes. <sup>18</sup>

**6. Multiple Membrane Extrusion Method -** Mixing surfactant, cholesterol and dicetyl phosphate in chloroform by rotary evaporator forms thin film. The film hydrates with membranes of aqueous polycarbonate material. Solution and subsequent suspension extrude through polycarbonate membrane for up to 8 passages in row. It is a good way to control the number of niosomes. <sup>19</sup>

### 7. Ethanol Injection Method-

A fine needle is used to easily administer an ethanol solution with surfactant.

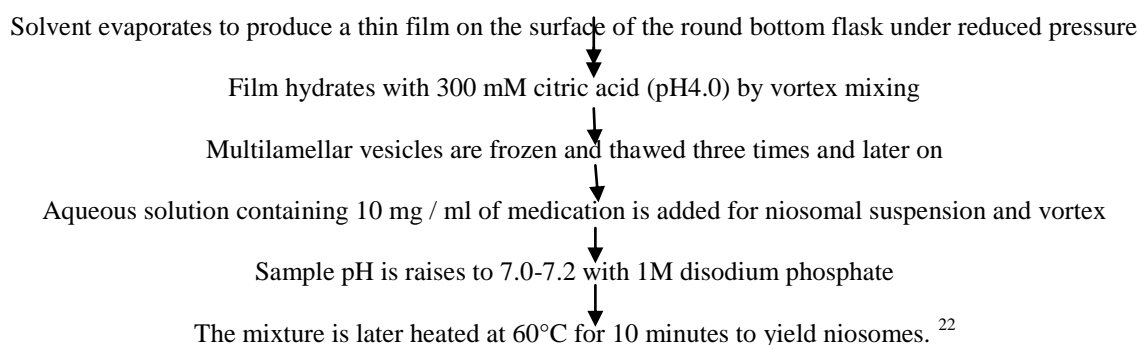


**8. Micro Fluidization** – The theory used in this technique is the submerged jet concept in which two fluidized streams communicate with each other at ultra high velocity and within the contact chamber in the micro channels. Thin liquid layer impingements are organized together with common front such as the energy supply stays the same in the region of niosome formation, the formation with niosome vesicles of greater uniformity, smaller size and improved reproducibility. <sup>21</sup>

**B. Active Trapping Techniques** - It involves the drug loading during niosome development. The niosomes are primed and the drug is then filled with a pH gradient or gradient of ions to promote drug penetration into niosomes. Various benefits of niosome shape include 100% entrapment, high drug lipid levels, lack of leakage, cost-effectiveness, and labile drug suitability.

#### 1. Trans Membrane pH Gradient Drug Uptake Process-

In remote loading process surfactants and cholesterol are dissolved in organic solvent (chloroform)



#### C. Miscellaneous Methods –

**1. Emulsion Method:** This is a simple method of producing a niosome in which oil is prepared from an organic surfactant solution, cholesterol, and aqueous solution of the product in water (o / w) emulsion. <sup>23</sup>

**2. Heating Method:** This approach is one-step, modular and non-toxic as well as patent-based. A suitable aqueous solution such as purified water buffer, etc. where mixtures of non-ionic surfactants, cholesterol and/or load-inducing compounds are applied to glycerol in the presence of polyol. The mixture is heated until the vesicles have formed (at low shear forces). <sup>24</sup>

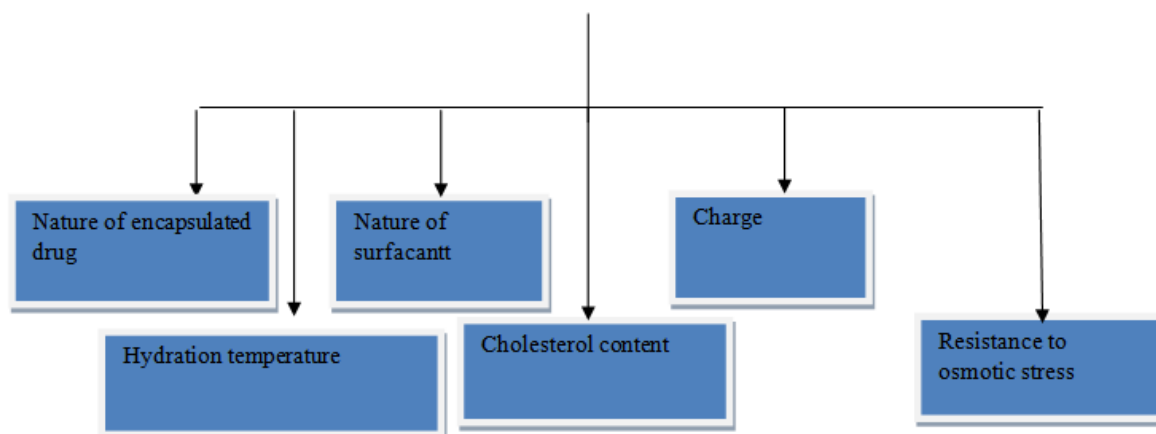
**3. Formation of Niosomes from Proniosomes:** Proniosome is a dry solution in which a thin film of dried surfactant coats single water-soluble molecule. The niosomes are identified with brief agitation by the introduction of aqueous phase at  $T > T_m$ . T is the temperature and  $T_m$  is the mean temperature of the phase transition. <sup>25</sup>

Carrier + surfactant = proniosomes,

Proniosomes + water = niosomes.

**4. Lipid Injection Method:** This method does not require an expensive organic phase. The dissolved drug is first melted with a mixture of lipids and surfactant and then inserted into a strongly agitated heated water system. Pharmaceutical dissolves in liquid lipid and the mixture is injected into surfactant-containing agitate, heat-aqueous phase.

## FACTORS INFLUENCING NIOSOMAL FORMULATION: 26-30



**1 Nature of Surfactant:** An increase in the HLB value of surfactants results in an increase in the mean size of niosomes due to a reduction in surface-free energy with an increase in the hydrophobicity of surfactants. The niosome bilayers can exist either as a liquid state or in a gel state. It depends on the temperature, surfactant type and cholesterol. In the gel state, alkyl chains are well ordered, while in the liquid state they are disordered. The efficiency of trapping is influenced by the surfactant's solid, liquid phase transition temperature (TC).

Eg: Span 60 with a higher TC shows improved trapping.

For niosomal preparations, the HLB value of surfactants ranging from 14 to 17 is not suitable. Reduction of the HLB value of surfactants from 8.6 to 1.7 reduces the efficiency of trapping and the highest efficiency of trapping is found at the HLB value of 8.6.

**2. Nature of Encapsulated Drug:** The niosomal bilayer's charge and rigidity are strongly influenced by the encapsulated drug's physical chemical properties. Drug capture occurs by communicating with the surfactant head groups resulting in increased charge and causing mutual repulsion of the surfactant bilayer, thus increasing the vesicle size. The drug's HLB determines the degree of trapping.

**3. Hydration Temperature:** The niosome's size and shape are affected by the hydration temperature. The temperature of hydration should be above the temperature of the liquid phase transition. Temperature change affects surfactant assembly into vesicles and alteration of the shape of the vesicle. The modification is also due to the hydration time and volume of the hydration medium. Improper selection of the medium volume of hydration temperature, time and hydration may result in fragile niosomes / drug leakage problems.

**4. Cholesterol Content:** Cholesterol incorporation improves the efficiency of trapping and the hydro-dynamic diameter of niosomes. In two cases, cholesterol acts:

- Increases the liquid state bilayer chain order.
- Decreases the order of the chain of bilayer gel state.

An increase in concentration of cholesterol results in an improvement in the rigidity of the bilayers and a decrease in the rate of release of encapsulated content. Medicine

**5. Charge:** The presence of charge leads to an increase in inter-lamellar distance in multi-lamellar vesicle structure between successive bilayers and greater overall trapped volume.

**6. Resistance to Osmotic Stress:** Hypertonic solution addition induces vesicle diameter reduction. During hypotonic solution, vesicle eluting fluid inhibition results during slow release followed initially by faster release due to mechanical loosening of vesicle structure under osmotic stress.

## SEPARATION OF UNENTRAPPED DRUG 31-33

The expulsion of untrapped solute from the vesicles can be practiced by different strategies, which include: -

1) **Dialysis:** Through dialysis tubing against phosphate buffer or regular solution of saline or glucose, the aqueous niosomal dispersion is dialysed.

2) **Gel Filtration:** The untrapped drug is removed by gel filtration of niosomal dispersion through a column of SephadexG-50 and elution with phosphate-buffered saline or normal saline.

3) **Centrifugation:** The niosomal suspension is centrifuged and the supernatant is removed. The pellet is cleaned and then resuspended in order to obtain a drug-free niosomal suspension.

## CHARACTERIZATION OF NIOSOMES 34-40

**1. Bilayer Rigidity and Homogeneity:** Niosomes' biodistribution and biodegradation are determined by the bilayer's rigidity. In homogeneity, dispersion can occur within niosome frameworks as well as between

niosomes and can be defined by. PNMR, Differential Calorimetry Scanning (DSC) and Fourier Red Spectroscopy Transform-Infra (FT-IR) techniques.

2. **Size and Shape:** Different methods are used to calculate the mean diameter, such as the process of laser light scattering, as well as electron microscopy, molecular sieve chromatography, photon correlation microscopy, optical microscopy.

3. **Stability Study:** Niosomal formulations are subject to stability studies by processing for a duration of three months at 4 ° C, 25 ° C and 37 ° C in a thermostatic oven. After a month, the drug quality of all formulations is tested by entrapping efficiency the parameter of output.

4. **Scanning Electron Microscopy:** In a scanning electron microscope (SEM) (JSM 6100 JEOL, Tokyo, Japan) the niosomes were detected. We were mounted directly onto the SEM sample stub using double-sided sticking tape and coated under a reduced pressure of 0.001 mmHg with 200 nm thick gold film. At sufficient magnification, photographs were taken.

5. **Vesicle Charge:** The surface charge of the vesicle can play a significant role in the actions of in vivo and in vitro niosomes. Charged niosomes are more stable than unchanged vesicles against aggregation and fusion. To obtain an approximation of the surface potential, microelectrophoresis can be used to calculate the zeta potential of individual niosomes. The use of pH-sensitive fluorophores is an alternative approach. More recently, for calculating the zeta potential of niosomes, dynamic light scattering was used.

6. **Niosomal Drug Loading and Encapsulation Efficiency:** The niosomal aqueous suspension was ultracentrifuged, supernatant was removed and sediment washed twice with distilled water to remove the adsorbent material to assess drug loading and encapsulation capacity.

- The entrapment efficiency (EE) was then calculated using formula:

$$\text{Entrapment efficiency} = \frac{\text{amount of drug in niosomes}}{\text{amount of drug}} \times 100$$

7. **In-vitro Release:** In-vitro release rate study carried out by the use of

1. Dialysis Tubing.
2. Reverse dialysis.
3. Franz diffusion cell.

a. **Dialysis Tubing:** A dialysis bag is washed with distilled water. The prepared vesicle suspension is piped into a bag consisting of the dialysis of the tubing and sealed after. Then the bag containing the vesicles is put in a 250 ml beaker with a steady shaking at 25 ° C in 200 ml of buffer solution. The buffer is an analysis of the drug content of a suitable system of research at different time intervals.

b. **Reverse Dialysis:** A number of small dialysis is put in proniosomes as containing 1ml of the dissolution medium. The proniosomes are then transferred to the process of dissolution. Direct proniosome dilution is possible with this approach and it is not possible to quantify the rapid release using this method.

c. **Franz Diffusion Cell:** Using Franz diffusion cell, the study of in vitro diffusion can be performed. Proniosomes are placed in a Franz diffusion cell's donor chamber filled with cellophane membrane. The proniosomes are then dialyzed at room temperature against an acceptable dissolution medium; the samples are removed from the medium at suitable intervals and tested for drug content using specific methods such as U.V spectroscopy, HPLC, etc.

## APPLICATIONS OF NIOSOMES

Niosomal drug delivery for their action against various diseases is potentially applicable to many pharmacological agents. Few of its treatment applications are as follows:

### Targeting of bioactive agents

#### 1. To reticulo-endothelial system (RES)

Preferentially the vesicles occupy RES cells. It is known as opsonins due to circulating serum factors, which mark them for clearance. However, such localized accumulation of drugs has been exploited in the treatment of animal tumors known to metastasize the liver and spleen and in parasitic hepatic infestation.<sup>41</sup>

#### 2. To organs other than reticulo-endothelial system (RES)

The carrier mechanism can be guided to specific sites in the body by the use of antibodies. Immunoglobulins tend to have lipid surface affection and thus provide a convenient means of targeting the drug carrier. Many cells have the intrinsic ability to recognize and bind specific carbohydrate determinants and this property can be used to direct the carrier system to specific cells.<sup>42,43</sup>

### Neoplasia

The anthracyclic antibiotic doxorubicin shows a dose-dependent irreversible cardio-toxic effect, with broad spectrum anti-tumor activity. The drug's half-life increased by its niosomal drug trapping, as well as prolonging

its circulation and altering its metabolism. If the mice with S-180 tumor are treated with niosomal delivery of this drug, the lifespan of the mice increased and the incidence of sarcoma proliferation decreased.<sup>44</sup>

Niosomal methotrexate when intravenously administered to S-180 tumor-bearing mice results in complete tumor regression, higher plasma rates and slower removal.<sup>45,46</sup>

#### ***Delivery of peptide drugs***

In an in-vitro intestinal loop model, niosomal trapped oral delivery of 9-desglycinamide, 8arginine vasopressin was examined and reported significantly increased peptide stability.<sup>47</sup>

#### ***Immunological applications of niosomes***

Niosomes have been used to study the essence of the immune response caused by antigens. In terms of immunological selectivity, low toxicity and stability, niosomes have been identified as potent adjuvant.<sup>48</sup>

#### ***Niosome as a carrier for Hemoglobin***

Niosomal suspension has a visible spectrum that can be superimposed on free hemoglobin in order to be used as a hemoglobin carrier. Vesicles are also oxygen-permeable and the curve of hemoglobin-dissociation can be changed similarly to non-encapsulated hemoglobin.<sup>49</sup>

#### ***Transdermal delivery of drugs by niosomes***

Transdermal drug delivery integrated in niosomes has achieved an improvement in penetration rate, as sluggish drug penetration through skin is the major drawback of transdermal delivery route for other dosage forms. The topical delivery of erythromycin from different formulations like niosomes has been tested on hairless mouse and tests, and confocal microscopy has found that non-ionic vesicles can be designed to target pilosebaceous glands.<sup>50</sup>

#### ***Other Applications***

##### **a) Sustained Release**

By niosomal encapsulation, drugs with low therapeutic index and higher water solubility may be retained in circulation, and continuous release action can be achieved by niosomes. Suggested function of liver as a methotrexate depot after the liver cells take up niosomes.<sup>51</sup>

##### **b) Localized Drug Action**

Niosomal dosage form is one of the approaches to achieving localized drug action due to the size of niosomes and their low penetrability via epithelium and connective tissue, the drug located at the site of administration. It results in an increase in the drug's efficacy and potency, and also decreases its systemic toxic effects, e.g. Mononuclear cells consume antimonials encapsulated inside niosomes, resulting in product localization, increased potency and therefore decreased in both dose and toxicity.<sup>52,53</sup>

### **III. Conclusion**

One of the examples of great progress of drug delivery technology is the neosomal drug delivery system. Scientists and academics generally accept the concept of drug absorption into the niosomes and targeting the niosomes to the particular site. They represent alternative vesicular systems that also have different advantages over liposomes such as cost, stability, etc. Niosomes are a promising technology for the delivery of drugs, and much work must be encouraged in this to satiate all the promise in this innovative drug delivery system.

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