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Review Article

Phytosomes: An Emerging Nanotechnology For Improved Bioavailability of Phytomedicines – A Review

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ABSTRACT

Novel complexation technique named as `phytosome' plays an important role to facilitate absorption and improve bioavailability. The delivery of phytomedicine is always challenging due to poor aqueous solubility, poor permeation, low systemic availability and extensive first pass metabolism. Drug molecules from natural sources and dietary soy phospholipids are complexed and generated cell like structures called phytosomes. Phytosome act as a bridge between novel delivery system and conventional delivery system and has effectively enhanced the bioavailability of many popular herbal extracts including milk thistle, *Ginko biloba*, grape seed, green tea, hawthorn, Ginseng etc and can be developed for various therapeutic uses or as dietary supplements. Current review highlights recent information, on commercial preparation of phytosomes as well as the various other novel approaches for delivery of herbal constituents.

Key-words: Nanotechnology; Phytosome; Bioavailability; Dosage forms.

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INTRODUCTION

The therapeutic effectiveness of any drug obtained from plant, animals or synthetic, depends upon the ability of the dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacological response [1]. Consequently a number of vesicular drug delivery systems such as liposomes, niosomes, transferosomes and pharmacosomes were developed. Advances have since been made in the area of vesicular drug delivery, leading to development of systems that allow drug targeting, and the sustained or controlled release of conventional medicines. Since ancient times the therapeutic uses of traditional medicines and phyto-medicines have proved very popular for health maintenance by various means [3]. The advancement in the field of herbal drug delivery started recently with the aim to manage human diseases efficiently. Plants are endowed with a multitude of medicinal and health giving substances, most of them are secondary metabolites, prominent among these are being the flavanoids. To date, more than 4000 naturally occurring flavanoids have been identified from plant source having diverse biological activities [2]. The usage of phytomedicine has been increased due to their better therapeutic activity and less side effects as compared to the allopathic medicines.

The use of nanotechnology i.e phytosomes for treatment, identification, monitoring and managing biological systems have recently been referred to as nanomedicine. In herbal formulation the nano-based formulation has a great number of advantage for phytosomes, including improvement of solubility and bioavailability, safeguard from toxicity, enhancement of pharmacological activity, improvement of stability, increase in tissue macrophages distribution, sustained delivery protection from physical and chemical degradation [4] . Phytochemical and pharmacological investigation have been done extensively and well established. Phytomedicines shows impressive *in-vitro* activity but less *in-vivo* efficacy due to their poor water solubility, lipophilicity and inappropriate molecular size resulting in poor absorption and hence poor systemic availability.

THE PHYTOSOME TECHNOLOGY:

Phytosome is a newly introduced patented technology developed by M/S Indena S.p.A of Italy [9]. (Indena is the world's leading company in the identification, development and production of active principles derived from plants, for use in the pharmaceutical, health-food and personal care industries). Phytosomes are cell-like structures which result from the stoichiometric reaction of the phospholipids [8]. Some commonly used synthetic phospholipids are dioleoyl-phosphatidyl-choline (DOPC), dioleoyl-phosphatidyl-ethanolamine (DOPE), distearoyl-phosphatidyl-choline (DSPC), distearoyl-phosphatidyl-ethanolamine (DSPE).Among all these phospholipids, phosphatidylcholine classes of phospholipids are very important in the drug delivery technology. Phosphatidylcholine is the principal molecular building block of cell membranes miscible both in water and oil environments and excellently absorbed when taken by mouth.

Most of the biologically active constituents of plants are polar or water soluble molecules. However, water soluble phytoconstituents like flavanoids, tannins, glycosidic aglycones etc, are poorly absorbed either due to their large molecular size which cannot be absorbed by passive diffusion or due to their poor lipid solubility thus limiting their ability to pass across the lipid rich biological membranes, resulting in poor bioavailability when taken orally or applied topically [5]. Often isolation and purification of individual components from whole herbal extract lead to partial or total loss of therapeutic activity, the natural synergy become lost which is due to chemically related constituents in herbal extracts [6] . The chemical complexity of the crude or partially purified extract seems to be essential for the bioavailability of the active constituents. Standardization was developed to solve this problem but the standardized extract showed poor bioavailability which limited their utility [8]. The patented technology developed to incorporate standardized plant extract or water soluble phytoconstituents into phospholipids to produce

lipid compatible molecular complexes are called as phytosomes [often referred as herbosomes] and highly improve their bioavailability [7].

BENEFITS OF PHYTOSOMES [10-17]

1. It enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability.
2. Their low solubility in aqueous media allows the formation of stable emulsions or creams.
3. Enhanced ability of phytosomes to cross cell membranes and enter cells.
4. Phytosome technology protects herbal extracts from destruction by digestive secretions and gut bacteria.
5. Phytosomes are superior to liposomes in skin care products.
6. Less dose requirement is due to absorption of chief constituents.
7. No compromise of nutrient safety.
8. No problem of drug entrapment.
9. Entrapment efficiency is high and predetermined because drug itself is in conjugation with lipids forming the vesicles.
10. Phytosomes shows better stability profile because chemical bonds are formed between phosphatidylcholine molecules and phytocconstituents.
11. Pharmacologically assured delivery to the tissues.
12. The structure of phytosome makes it suitable for cosmetic application.
13. Phosphatidylcholine used in the phytosome process besides acting as a carrier also nourishes the skin, because it is essential part of cell membrane.
14. Significantly greater clinical benefit.
15. They have been used to deliver liver-protecting flavonoids, because they can be made easily bioavailable by phytosomes.

PHYSICAL PROPERTIES OF PHYTOSOMES [18 – 20]

Phytosome has lipophilic substances with a clear melting point. Average size of phytosome range is 50 nm to a few hundred μm. They are easily soluble in non-polar solvents, insoluble in water and moderately soluble in fats and unstable in alcohol. Liposomal like structures of micellar shape are formed when phytosome are treated with water.

CHEMICAL PROPERTIES OF PHYTOSOMES

On the basis of their physicochemical and spectroscopic data, it has been shown that, the phospholipids-substrate interaction is due to the formation of hydrogen bond between the polar heads of phospholipids (i.e. phosphate and ammonium groups) and the polar functional groups of substrate, In phytosomes the active principle is anchored to the polar head of phospholipids, becoming an integral part of the membrane [19].

CHARACTERIZATION AND EVALUATION OF PHYTOSOMES

The behavior of phytosomes in both physical and biological systems is governed by factors such as the physical size, membrane permeability, percentage of entrapped solutes, and chemical composition as well as the quantity and purity of the starting materials. Therefore, phytosomes can be characterized in terms of their physical attributes i.e. shape, size, distribution, percentage, drug captured, entrapped volume, percentage drug released and chemical composition [18].

Different characterization techniques used for phytosomes:

i) Visualization

Visualization of phytosomes can be achieved using transmission electron microscopy (TEM) and by scanning electron microscopy (SEM) [21].

ii) Vesicle size and Zeta potential

The particle size and zeta potential can be determined by dynamic light scattering (DLS) using a computerized inspection system and photon correlation spectroscopy (PCS) [22].

iii) Entrapment efficiency

The entrapment efficiency of a drug by phytosomes can be measured by the ultracentrifugation technique [23].

iv) Transition temperature

The transition temperature of the vesicular lipid systems can be determined by differential scanning calorimetry [24].

v) Surface tension activity measurement

The surface tension activity of the drug in aqueous solution can be measured by the ring method in a DuNouy ring tensiometer [25].

vi) Vesicle stability

The stability of vesicles can be determined by assessing the size and structure of the vesicles overtime. The mean size is measured by DLS and structural changes are monitored by TEM [10].

vii) Drug content

The amount of drug can be quantified by a modified high performance liquid chromatographic method or by a suitable spectroscopic method [11].

viii) Spectroscopic evaluations

To confirm the formation of a complex or to study the reciprocal interaction between the phytoconstituent and the phospholipids, the following spectroscopic methods are used [12].

ix) 1H-NMR

The NMR spectra of (+)-catechin and its stoichiometric complex with distearoyl phosphatidylcholine have been studied by Bombardelli *et al.* [26]. In nonpolar solvents, there is a marked change of the 1H-NMR signal originating from the atoms involved in the formation of the complex, without any summation of the signal peculiar to the individual molecules. The signals from the protons belonging to the flavonoids are to be broadened that the proton cannot be relieved. In phospholipids, there is broadening of all the signals while the singlet corresponding to the N-(CH3)3 of choline undergo an uplift shift. Heating the sample to 60˚ results in the appearance of some new broad bands, which correspond mainly to the resonance of the flavonoid moiety.

x) 13C-NMR

In the 13C-NMR spectrum of (+)-catechin and its stoichiometric complex with distearoyl phosphatidylcholine, particularly when recorded in C6D6 at room temperature, all the flavonoid carbons are clearly invisible. The signals corresponding to the glycerol and choline portion of the lipid (between

60–80 ppm) are broadened and some are shifted, while most of the resonances of the fatty acid chains retain their original sharp line shape. After heating to 60°, all the signals belonging to the flavonoid moieties reappear, although they are still very broad and partially overlapping.

xi) FTIR

The formation of the complex can be also be confirmed by IR spectroscopy by comparing the spectrum of the complex with the spectrum of the individual components and their mechanical mixtures. FTIR spectroscopy is also a useful tool for the control of the stability of phytosomes when micro-dispersed in water or when incorporated in very simple cosmetic gels. From a practical point of view, the stability can be confirmed by comparing the spectrum of the complex in solid form (phytosomes) with the spectrum of its micro-dispersion in water after lyophilization, at different times. In the case of simple formulations, it is necessary to subtract the spectrum of the excipients (blank) from the spectrum of the cosmetic form at different times, comparing the remaining spectrum of the complex itself.

xii) In vitro and in vivo evaluations

Models of *in-vitro* and *in-vivo* evaluations are selected on the basis of the expected therapeutic activity of the biologically active phytoconstituents present in the phytosomes [12]. For example, *in vitro* antihepatotoxic activity can be assessed by the antioxidant and free radical scavenging activity of the phytosomes. For assessing antihepatotoxic activity *in-vivo,* the effect of prepared phytosomes on animals against thioacetamide-, paracetamol or alcohol- induced hepatoxicity can be examined [27-28]. Skin sensitization and tolerability studies of glycyrrhetinic acid-Phytosome® ointment, a commercial product, describe the *in vivo* safety evaluation methodology [29].

DIFFERENCE BETWEEN PHYTOSOMES AND LIPOSOMES [6, 8, 30]

PHYTOSOME	LIPOSOME
In phytosomes active chemical constituents molecules are anchored through chemical bonds to the polar head of phopholipid.	In liposomes, the active principle is dissolved in the medium of activity or in the layers of the membrane. No chemical bonds are formed.
In phytosomes, phosphatidylcholine and the individual plant compound form a 1:1 or 2:1 complex depending on the substance	In liposomes, hundreds and thousands of phosphatidylcholine molecules surround the water soluble molecule.
It has much better bioavailability and absorption	Its bioavailability and absorption is lesser than phytosome.

MECHANISM OF PHYTOSOME FORMATION

The phytoactive components of herbal extracts are well suited to direct binding to phosphatidylcholine from soy. Phosphatidyl choline is a bifunctional compound, the phosphatidyl moiety being lipophilic and the choline moiety being hydrophilic in nature. Phospholipids are small lipid molecules in which the glycerol is bound to only two fatty acids, instead of three as in triglycerides, with the remaining site is occupied by a phosphate group [32]. Specifically, the choline head of the phosphatidylcholine molecule binds to phytoconstituents while the fat soluble phosphatidyl portion, comprising the body and tail, then envelopes the choline-bound material. This results in small

microspheres or the production of cells known as phytosomes [33]. Thus, phytosomes are also considered as a phytolipid delivery system [15]. The phytosome process produces small cells which protect the valuable components of the herbal extract from the destruction by digestive secretions and gut bacteria [29]. They improve transition of constituents from the water phase to the lipid friendly environment of the enterocyte cell membrane and from there into the cell, finally reaching the circulation [31].

PREPARATION METHODS:

Phytosomes are prepared by reacting 3–2 moles (preferably with one mole) of a natural or synthetic phospholipid, such as phosphatidylcholine, phosphatidylethanolamine or phosphatidyiserine, with one mole of phytoconstituents either alone or in the natural mixture in an aprotic solvent, such as dioxane or acetone, in a 1:2 or 1:1 ratio [16]. The optimum ratio of phospholipid to phytoconstituent is 1:1 [17]. The complex thus formed can be isolated by precipitation with an aliphatic hydrocarbon or lyophilization or spray drying [34]. Some liposomal drug complexes operate in the presence of water or buffer solution where the phytosomes interact with a solvent with a reduced dielectric constant. Complexation of extracts or specific active ingredients with dietary phospholipids is generally prepared by solvent evaporation/anti-solvent precipitation techniques using alcoholic or organic solvents but supercritical fluids have been used in recent years, as well [35].

i) Solvent evaporation technique

In solvent evaporation technique, generally both the drug and the phospholipids are placed in the same flask containing a suitable solvent/solvent system (i.e. tetrahydrofuran and ethanol). The reaction is allowed to be performed at suitable fixed temperature for a fixed duration of time to get maximum yield and drug entrapment [36 - 37]. Marsupsin–phospholipid complex has been formulated using mechanical dispersion oriented liquid antisolvent precipitation process [38]. In diethyl ether the phospholipids were dissolved by sonication and marsupsin dissolved in distilled water. Then the drug solution was added dropwise to the phospholipid solution with sonication. The resultant formulation showed 44% entrapment of marsupsin with 20% cumulative drug release.

ii) Co-solvent lyophilization method

In another recent work Jain et al. [39] have prepared a rutin–phospholipid complex by an anhydrous co-solvent lyophilization method in which the drug and the phospholipids were dissolved in methanol but in different vessels. Both the solutions were stirred mechanically till all the solvents are evaporated out. The photomicrography represented the rutin–phospholipid complex in amorphous state when compared to rutin which is crystalline. A 1:3 molar ratio of drug to phospholipid provided superior experimental results. The range for complexation of a specific plant active molecule or a group of structurally similar plant actives with phospholipids performed are from 0.5:1 to 3:1. In most of the research works a stoichiometric ratio of 1:1 has been considered most suitable for formulating a complex. Different solvents with low dielectric permittivity have been utilized by different researchers as the reaction medium for formulating phytosomes. Protic solvent like ethanol replaced the Aprotic solvents like methylene chloride, Ethyl acetate, dioxane etc. for preparing complexes. Yue et al. [40] and Zhang et al. [41] have used tetrahydrofuran as the reaction solution. Maiti et al. [42 -43] and Habbu et al. [44] have used dichloromethane as solvent and n-hexane as the medium for precipitation of the complex. Most of the recent work has been done using absolute ethanol as the reaction medium [45]. In addition to the solvent system, different researchers have used phospholipids from different sources. The common criterion for selection was the ratio of phosphatidyl group lied in them. Soylecithin, phosphatidylserine, and 1, 2- distearoyl-Sn-glycero-3- phosphatidylcholine are some of the phospholipids used.

Phospholipids of the soybean oil have been used because of the higher content of phosphatidylcholine in them, which offers compatibility and similarity with the Mammalian plasma membrane [46 - 47].

Table 1: COMMERCIAL PRODUCTS OF PHYTOSOMES AVAILABLE [48 - 55]

Sl.no	Phytosomes trade name	Phytoconstituents complex	Indications
1.	Silybin phytosome	Silybin from *Silibium marianum*	Hepatoprotective, Antioxidant.
2.	Grape seed (Leucoselect) phytosome	Procyanidins from *Vitis vinifera*	Antioxidant, Anticancer
3.	Ginseng phytosome	Ginsenosides from *Panax ginseng*	Immunomodulator
4.	Hawthorn phytosome	Flavonoids from *Crataegus species*	Antihypertensive, Cardioprotective
5.	Sericoside phytosome	Sericoside from *Terminalia sericea*	Skin improver, Anti-Wrinkles
6.	Ginko select phytosome	Flavonoids from *Ginko biloba*	Anti aging,Protects Brain and Vascular liling
7.	Olea select phytosome	Polyphenols from *Olea europea*	Anti–hyperlipidemic, Anti-inflammatory
8.	Green select phytosome	Epigallocatechin from *Thea sinensis*	Anti-cancer, Antioxidant
9.	Echinacea phytosome	Echinacosides from *Echinacea angustifolia*	Immunomodulatory, Nutraceuticals.
10.	Bilberry (Mertoselect) phytosome	Anthocyanosides from *Vaccinium myritillus*	Antioxidant, Improvement of Capillary Tone.
11.	Palmetto (Sabalselect) phytosome	Fattyacids, alcohols and sterols from *Serenoa repens*	Anti-oxidant, Benign Prostatic hyperplasia
12.	Visnadine (Visnadax) phytosome,	Visnadine from *Ammi visnaga*	Circulation Improver, Vasokinetic
13.	Centella phytosome	Terpens from *Centella asitica*	Brain tonic, Vein and Skin Disorder
14.	Glycyrrhiza phytosome	18-β glycyrrhetinic acid from *Glycyrrhiza glabra*	Anti-inflammatory, Soothing
15.	Melilotus (Lymphaselect) phytosome	Triterpens from *Melilotus officinalis*	Hypotensive, Indicated in Insomnia
16.	Curcumin (Merivaselect) phytosomes	Polyphenol from *Curcuma longa*	Cancer Chemo preventive Agent
17.	Mertoselect phytosome	Polyphenols, Antcinoside from *Vaccinium myrtilus*	Antioxidant
18.	PA2 phytosome	Proanthocyanidin A2 from horse *Chestnut bark*	Anti-Wrinkles, UV protectant.
19.	Escin β sitosterol phytosome	Escin β-sitosterol from horse *Chestnut fruit*	Anti-odema.
20.	Ximilene and ximen oil phytosome	Ximilene and ximen oil from *Santalum album*	Skin Smoothner, Micro Circulation Improver
21.	Ruscogenin phytosome	Steroid saponins from *Ruscus aculeatus*	Anti-inflammatory, Improve Skin circulation
22.	Zanthalene phytosome	Zanthalene from *Zanthoxylum bungeanum*	Anti-Irritant, Anti-Itching, Soothing.
23.	Curbilene phytosome	Curbilene from *Curcurbita pepo* seeds	Skin care, Matting Agent.
24.	Esculoside phytosome	Esculoside from *Aesculus hippocastannum*	Vasoactiv, Anti-cellulite, Microcirculation improver

FORMULATION WITH PHYTOSOMES®COMPLEX [51]

i) Soft gelatin capsule:

Soft gelatin capsules represent an ideal solution to formulate Phytosome®complexes. The Phytosome® complex can be dispersed in oily vehicles to obtain suspensions to be filled in soft gelatin capsules. Vegetable or semi-synthetic oils can be used to this purpose. Indena recommend a granulometry of 100% <200 µm to best perform capsule production. According to Indena experience, not all the Phytosome® complexes behave in the same way when dispersed in oily vehicles and when the oily suspension is filled in the soft gelatin capsules; for this reasons preliminary feasibility trials should be performed to select the most suitable vehicle.

Table 2: Soft gelatin capsule formulation with Phytosome®complex

Composition	Amount
Ginkgoselect® Phytosome	180mg
Soybean oil	250mg
Soy lecithin	q.s
Glycerylmonostearate	q.s

ii) Hard gelatin capsules:

The Phytosome® complex can be formulated in hard gelatin capsules as well. A direct volumetric filling process (without pre compression) can be applied, even if the apparently low density of the Phytosome® complex seems to limit the maximum amount of powder that can be filled into a capsule (usually not more than 300 mg for a size 0 capsule). With a piston tamp capsule filling process; however, it is possible to increase the amount of powder which can be filled in a capsule, but pre compression might affect the disintegration time. Indena recommend to carefully monitoring the related parameters during product/process development. A preliminary dry granulation process is advisable to define the best manufacturing process.

Table 3: Hard gelatin capsule formulation with Phytosome® Complex: Dry granulation process

Composition	Amount
Ginkgoselect®Phytosome	180mg
Dicalcium Phosphate dehydrate	196mg
Silicified microcrystalline cellulose	47mg
Croscarmellose sodium	23mg
Talc	2mg
Magnesium stearate	2mg

iii) Tablets

Dry granulation represents the ideal manufacturing process to obtain tablets with higher unitary doses and with suitable technological and biopharmaceutical properties. However, due to the limited flowability, potential stickiness and low apparent density of the Phytosome® complex, a direct compression process can be applied only for low unitary doses; note that whenever a direct compression process is applied, the Phytosome® complex should be diluted with 60-70% of excipients to optimize its technological properties and to obtain tablets with appropriate technological and biopharmaceutical characteristics. On the other hand, wet granulation should be avoided due to the negative effect of water and heat (granulation/drying) on the stability of the phospholipid complex.

Table 4: Tablet formulation with Phytosome® complex: Dry granulation process

Composition	Amount
Leucoselect®Phytosome	100mg
Soy polysaccharides	138mg
Corn starch	100mg
Silicon dioxide	6mg
Talc	3mg
Magnesium stearate	3mg

iv) Topical dosage form

The Phytosome® complex can be formulated topically as well. The ideal process to incorporate the Phytosome® complex in emulsion is to disperse the phospholipidic complex in a small amount of the lipidic phase and add it to the already created emulsion at low temperatures (not higher than 40°C). The Phytosome® complexes are dispersible in the main lipidic solvents employed in topical formulations. In case of formulations containing a limited amount of lipids, the Phytosome® complex might also by dispersed into the watery phase, and again added to the final formulation at temperature lower than 40°C.

Table 5: O/W emulsion with Phytosome® complex

Composition	Amount
Escin/ß-Sytosterol Phytosome®	1.50g
Glycyrrhetinic acid Phytosome ®	1.50g
Isopropyl miristate	5g
Hydrogenated lanolin	5g
Cetyl palmitate	3g
Polysorbate 20	2.20g
Polyacrylamide (and) C13-14 isoparaffin and laureth-7	2g
Phenoxyethanol	1g
Dimethicone 350 cps	0.50g
Imidazolidinyl urea	0.30g
Tocopherol	0.20g
Preservatives	0.30g
Disodium edentate	0.10g
Ascorbyl palmitate	0.10g
Purified water	q.s to 100g

BIOAVAILABILITY OF PHYTOSOMES

Recent research shows improved absorption and bioavailability with phytosomes as compared to the conventional means.

Mazumder A et al., (2016) studied on sinigrin phytosomes, Since its efficacy has not been explored on wound healing, they examined the effect of sinigrin on HaCaT cells. Sinigrin was efficiently formulated into the phytosome with an average particle size of 153±39nm, zeta potential of 10.09±0.98mV and complex efficiency of 69.5±5%. The formation of the sinigrin-phytosome complex was confirmed by DSC and FTIR analysis. They found that the sinigrin-phytosome complex significantly exhibited wound healing effects when compared to sinigrin alone. After 42h, the phytosome complex completely healed the wound, whereas sinigrin alone showed only 71% wound closure [56]

Li F et al., (2015) prepared the Echinacoside phytosomes to develop a new oral dosage form to enhance its intestinal absorption and improve bioavailability. Compared with the physical mixture Echinacoside(ECH) alone, the *n*-octanol/water partition coefficient (*P*) determination results showed that the lipophilicity of ECH was significantly enhanced by formation of Phytosomes. Accordingly, the intestinal absorption rate (K_a) was improved to 2.82-fold and the effective permeability coefficient (P_{eff}) increased to 3.39-fold. Compared with Echinacoside alone the relative bioavailability of ECH was increased significantly after formulation into phytosome ($p < 0.05$). This might be mainly due to an improvement of the absorption of Phytosome. [57]

Mukerjee *et al.*, (2008) developed a novel hesperetin phytosome by complexing hesperetin with hydrogenated phosphatidyl choline. This complex was then evaluated for antioxidant activity in CCl4 intoxicated rats along with pharmacokinetic studies. It was found that the phytosome had asustained release property for over 24 h and enhanced antioxidant activity. Pharmacokinetic study revealed that the phytosome had higher relative bioavailability than that of parent molecule at the same dose level. [58]

CONCLUSION

This review is an attempt to present a concise authenticated profile of phytosomes as a novel drug delivery system. Thorough study of literature proves that the phytosomes are novel formulations which offer improved bioavailability of hydrophilic flavanoids and other similar compounds through skin or gastrointestinal tract. As far as potential of phytosome technology is concerned, it has great future since its formulation technology is simple with the characterization methodologies and analytical techniques are well established and therefore easily upgraded to a commercial scale.

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