Review Article

Nanosponges:A review

Ishan Mohd*,Satinder Kakar,Ramandeep Singh

Himachal Institute of Pharmacy,Paonta Sahib,H.P., India..

Abstract

Cosmeceuticals are cosmetic products with biologically active ingredients purporting to have medical or drug-like benefits. A cosmeceutical is an ingredient with medicinal properties that manifests beneficial topical actions and provides protection against degenerative skin conditions. The word "Cosmeceuticals" was popularized by Albert M. Kligman in the late 1970s.Polyherbal extracts are mentioned which can be incorporated in nanosponges.

Keywords: Nanosponge,polyherbal,extract

1. INTRODUCTION

Cosmetics - Cosmeceuticals are cosmetic products with biologically active ingredients purporting to have medical or drug-like benefits.

Consumers are always interested in maintaining a youthful appearance, and as the global population's median age increases, this market is increasingly expanding. According to the United States Food and Drug Administration (FDA), the Food, Drugs, and Cosmetics Act; a product can be a drug, a cosmetic, or a combination of both, but the term "cosmeceutical" has no meaning under the law".

Moisturizers, sunscreen, pigment lightener and other formulations have been renovated to improvised forms by addition of drug like ingredients for better results. Cosmeceuticals contribute majorly to the cosmetic industry. Although the effects may be small, these products however improve the skin feel and appearance with continued use over a period of time; thus there lies great opportunity to explore this avenue.[1,2]

Commonly used substances included in cosmeceutical formulations are described as follows:

- Moisturizing Agents
- Sunscreen Agents
- Skin Lightening Agent
- Lotions
- Hand creams

Skin.

Skin is the outermost tissue of the body and the largest organ in terms of both weight and surface area. It has an area of approximately 16, 000 cm^2 for an adult and represents about 8% of the body weight. A skin has a very complex structure that consists of many components. Cells, fibers and other components make up several different layers that give skin a multi-layered structure. Veins, capillaries and nerves form vast networks inside this structure. In addition, hairs stick out from the insideof skin. Numerous fine hair furrows are scattered over the surface of skin.

*Correspondence
Ishan Mohd.
Himachal Institute of Pharmacy,Paonta Sahib,H.P., India..
E-Mail: ishanmohammad07@gmail.com

Skin Layers

Skin layers consist of different layers – the epidermis, the dermis and subcutaneous layer. There is a very clear wavy boundary between these layers. The thickness of the skin layers differs quite a bit depending on gender, age, individual, body regions, etc. It has been found that males tend to have thicker skin layers than females. On the other hand, while several studies on the relation between age and the thickness of the skin layers have been reported, a clear relationship has not yet been found. Conditions of skin such as water-retention also differ depending on region, age and individual.

TOPICAL DRUG DELIVERY SYSTEM

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and maintain the desired drug concentration. Many novel drug delivery systems have been developed e.g. Transdermal, Intrauterine, Intravaginal, and Implants etc. Drug delivery systems are methods which are used to ensure that drugs get into the body and reach the area where they are needed. Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes.

Topical Route of Drug Administration

Although the intact skin is much less permeable than other tissues many substances do penetrate

The skin to some degree, at relatively slow rates the penetration of the drugs and other substances through skin depends on; the physiochemical properties of the penetrant, the state of the skin and the nature of the vehicle. Drugs applied topically, mainly for local action, include anti-septic, anti-fungal, anti-inflammatory agents as well as skin emollients for protective effects. While this route can also be used for systemic drug delivery. Topically applied drug may diffuse through the skin by hair follicles, sweat glands or sebaceous glands but permeation through the multiple lipid bilayers of stratum corneum is the dominant pathway through the rate is very slow.

Topical preparations meant for systemic or local effect are classified as:

- Solids – Dusting powder
- Semi-solids – Creams, Gel, Ointments, Paste andother
- Liquids – Solution, Emulsion, Liniments,
- Suspension, Soaps, Shakes, Lotion, Paints and other.

DRUG PROFILE-
KOJIC ACID

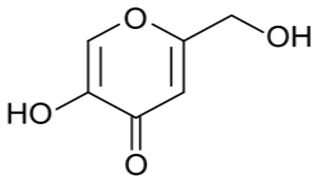
Kojic acid is a chelation agent produced by several species of fungi, especially Aspergillusoryzae, which has the Japanese common name koji. Kojic acid is a by-product in the fermentation process of malting rice, for use in the manufacturing of sake, the Japanese rice wine.It is a mild inhibitor of the formation of pigment in plant and animal tissues, and is used in food and cosmetics to preserve or change colors of substances. It forms a bright red complex with ferric ions.

Uses

Kojic acid may be used on cut fruits to prevent oxidative browning, in sea food to preserve pink and red colors, and in cosmetics to lighten skin. As an example of the latter, it is used to treat skin diseases like melasma.

Mechanism of action of kojic acid

Kojic acid inhibits many animal and plant enzymes. Primarily, it suppresses enzymes that remove oxygen from certain amino acids, polyphenols and xanthine's. Some of these chemicals are used in making the dark skin pigment called melanin. Kojic acid competes with, and blocks, the natural enzymes that direct melanin production. But the competition is reversible, so the acid cannot permanently disrupt these important body functions. As a result, kojic acid applied to your skin blocks new melanin production, eventually lightening your skin.



IUPAC name: 5-Hydroxy-2-(hydroxymethyl)-4H-pyran-4-one

Other names: Kojic acid, 5-Hydroxy-2-(hydroxymethyl)-4-pyrone, 2-Hydroxymethyl-5-hydroxy-γ-pyrone

Table1:. Physico chemical properties

Molecular formula	$C_6H_6O_4$
Molar mass	142.11g/mol
Melting point	152-155°C
Solubility in water	Slight
Appearance	White

Table 2: Applications of kojic acid

Field	Functions
Medical	Antibacterial Antifungal Pain killer
Food	Flavour enhancers Antioxidant Maltol and ethyl maltol
Agriculture	Anti melanosis Insecticide activator
Cosmetics	Whitening agent Ultra violet filter Tyrosinase inhibitor Radical scavenging activity Radio protective agent
Chemistry	Reagent for iron determination Synthesis of 2-methyl-4-pyrone Iron chelator Kojic acid-chitosan conjugates

NEEM (AZADIRACHTA INDICA)

Since antiquity neem has been renowned for healing. The earliest Sanskrit medical writings refer to the benefits of its fruits, seeds, oil, leaves, roots, and bark. Each of these has long been used in the Indian Ayurveda and Unani systems of medicine. Thus, over thousands of years, millions of Asians have used neem medicinally. In addition, in places where the tree has been introduced in recent times, such as tropical America and Africa, it has also established a reputation as a useful cure for various ailments[3-5]

Fig 1:Neem (Azadirachta Indica)

Biochemical composition

The chemical constituents are found in the leaves of neem as nimbin, nimbanene, 6-desacetylnimbinene, nimbandiol, nimbolide, ascorbic acid, n-hexacosanol and amino acid, 7-desacetyl-7-benzoylaz-adiradione, 7-desacetyl-7-benzoylgedunin, 17-hydroxyazadiradione and nimbiol.

Table 3: Physicochemical properties of neem

Botanical name	**Azadirachta indica**
Family	**Meliaceae**
Molecular formula	**$C_{35}H_{44}O_{16}$**
Physical description	**green crystalline powder & reddish brown wood**
Properties	**Anti-inflammatory, Anti-microbial, antioxidant**
Solubility in water	**Less soluble**

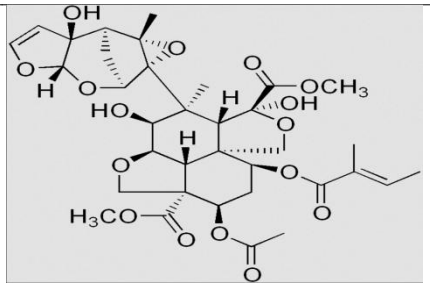


Fig 2:. Chemical structure of Neem

USES - As medicine and traditional uses, Preliminary medical research, as cosmetic, for various pharmacological purposes such as antioxidant, antimicrobial, antirheumatic activity.

Aloe Vera (Aloe barbadensis miller)

Aloe vera has been used for medicinal purposes in several cultures for millennia: Greece, Egypt, India, Mexico, Japan and China. Egyptian queens Nefertiti and Cleopatra used it as part of their regular beauty regimes. Alexander the Great, and Christopher Columbus used it to treat soldiers' wounds[6-8].

Fig 3:Neem (Azadirachta Indica)

Biochemical composition- Aloe vera contains 75 potentially active constituents: vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids and amino acids.

Anti-inflammatory action: Aloe vera inhibits the cyclooxygenase pathway and reduces prostaglandin E2 production from arachidonic acid. Recently, the novel anti-inflammatory compound called C-glucosyl chromone was isolated from gel extracts

Table 4: physicochemical properties of neem

Botanical name	***Aloe barbadensis miller***
Family	**Liliaceae**
Molecular formula	**$C_{16}H_{13}NO_3$**
Physical description	**triangular, fleshy leaves with serrated edges**
Properties	**Anti-inflammatory, Anti- microbial, antioxidant, anti-aging, skin protection.**

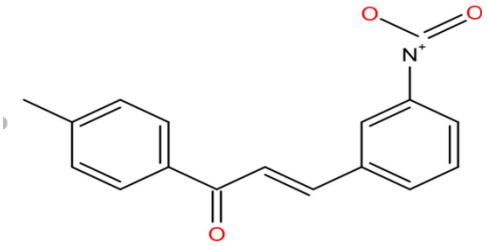
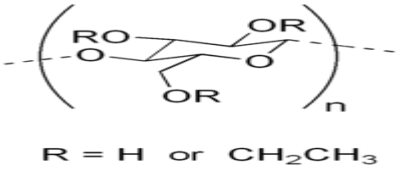


Fig 4:Chemical structure of Aloe vera

USES - As medicine and traditional uses, Preliminary medical research, as cosmetic, for various pharmacological purposes such as to treat burns, the skin condition psoriasis and even acne.

ETHYLCELLULOSE

Ethylcellulose is a free-flowing, white to light tan powder used in the pharmaceutical and food manufacturing industries. It is prepared from wood pulp or cotton by treatment with alkali and ethylation of the alkali cellulose with ethyl chloride. Ethylcellulose is used in pharmaceutical industry as a coating agent, flavoring fixative, tablet binder and filler, film-former, and as a viscosity-increasing agent. Ethyl cellulose is also used in the food industry as an emulsifier (E462).



R = H or CH_2CH_3

Appearance: white or yellowish-white powder or granular powder, odorless or almost odorless.

Solubility: practically insoluble in water, soluble in methylene chloride and in a mixture of 20 g of alcohol and 80 g of toluene, slightly soluble in ethyl acetate and in methanol, practically insoluble in glycerol (85 per cent) and in propylene glycol. The solutions may show a slight opalescence.

POLYVINYL ALCOHOL

Poly (vinyl alcohol) (PVOH, PVA, or PVAl) is a water-soluble synthetic polymer. It has the idealized formula [CH2CH (OH)]n. It is used in papermaking, textiles, and a variety of coatings. It is white (colorless) and odorless. It is sometimes supplied as beads or as solutions in water.

Polyvinyl alcohol

Structure and properties

PVA is an atactic material that exhibits crystallinity. In terms of microstructure, it is composed mainly of 1, 3-diol linkages [-CH2-CH(OH)-CH2-CH(OH)-] but a few percent of 1,2-diols [-CH2-CH(OH)-CH(OH)-CH2-] occur, depending on the conditions for the

polymerization of the vinyl ester precursor. Polyvinyl alcohol has excellent film forming, emulsifying and adhesive properties. It is also resistant to oil, grease and solvents. It has high tensile strength and flexibility, as well as high oxygen and aroma barrier properties. However, these properties are dependent on humidity, in other words, with higher humidity more water is absorbed. The water, which acts as a plasticizer, will then reduce its tensile strength, but increase its elongation and tear strength.

NANOSPONGES

Nano sponge plays a vital role in targeting drug delivery in a controlled manner. Nano sponge delivery system can control target drugs to a specific body site and have an enormous impact on the health care system. Targeting drug delivery is the major problem which is being faced by the researchers. Target drug administration with improvement in therapeutic efficacy, reduction in side effects and optimized dosing regimen, leads in the area of therapeutics.

The nano sponge is a tiny sponge about the size of a virus with a 'backbone' (a scaffold structure) of naturally degradable polyester. The long length polyester strands are mixed in solution with small molecules called cross-linkers that have an affinity for certain portions of the polyester. They 'cross link' segments of the polyester to form a spherical shape that has many pockets (or cavities) where drugs can be stored.

Advantages

1. Targeted site-specific drug delivery.
2. Can be used to mask unpleasant flavors and to convert liquid substances to solids
3. Less harmful side effects (since smaller quantities of the drug have contact with healthy tissue).
4. Nano sponge particles are soluble in water, so the hydrophobic drugs can be encapsulated within the Nano sponge, after mixing with a chemical called an adjuvant reagent.
5. Particles can be made smaller or larger by varying the proportion of cross-linker to polymer.

DISADVANTAGES

1) Nano sponge includes only small molecules.
2) Depend only upon loading capacities[9,10]

Materials used for preparation of nanosponges

There are some important components that can be used for the preparation of nano sponges which can be summarized as follows:

Table 5:Chemicals Used For the Preparation of Nano sponges

Polymer	Hyper cross linked Polystyrenes, Cyclodextrins and its derivatives like Methyl β-Cyclodextrin, Alkyloxy-carbonyl Cyclodextrins, 2-Hydroxy Propyl β-CyclodextrinsandCopolymers like Poly (valerolactone – allylvalerolactone) & Poly (valerolactone-oxepanedione) and Ethyl Cellulose & Poly vinyl acetate.
Cross-linkers	Diphenyl Carbonate, Di-aryl carbonates, Di-isocyanates, Pyromelliticanhydride,Carbonyldi-imidazoles, Epi-chloridrine, Glutraldehyde, Carboxylic acid di-anhydrides, 2, 2- bis (acrylamido), Acetic acid and
	Dichloromethane

Table 6: Examples of Drugs formulated as nanosponges

Drug	**Nano-vehicle**	**Therapeutic indication**
Econazole nitrate	Ethyl Cellulose Polyvinyl alcohol	Antifungal
Paclitaxel	β-Cyclodextrin	Cancer
Tamoxifen	β-Cyclodextrin	Breast cancer
Resveratrol	β-Cyclodextrin	Inflammation Cardiovascular diseases Dermatitis Gonorrhea Fever Hyperlipidemia
Dexamethasone	β-Cyclodextrin	Brain tumor
Temozolamide	Poly (valerolactone allylvalerolactone) Poly (valerolactone-allylvalerolactone-oxepanedione)	Brain tumor

Preparation of Nanosponge

Formulation of Nanosponges of Kojic acid and {Azadirachta Indica} Neem)

Nanosponges were prepared by Quasi emulsion solvent diffusion technique which requires two immiscible phases, internal and external phase with a surfactant which aids formation of an emulsion by reducing the interfacial tension.

Method of preparation of Nanosponges

The required amount of Drug (kojic acid and {Azadirachta Indica} Neem)) and ethyl cellulose were weighed accurately and dissolved in 20ml of DCM: Methanol (1:1) under sonication, this constitutes the internal phase. The surfactant PVA was weighed accurately and dissolved in distilled water at 60˚ C, which is the external phase. The external phase was allowed to cool to attain room temperature. The internal phase was taken in a burette and added drop wise to the external phase. During addition the emulsion was stirred using a Remixer at 1000 rpm. Mixing was continued for about 2hrs to achieve complete diffusion of the external phase. The nanosponges formed were filtered and dried in hot air oven at 40˚ C for a period of 12 hrs.

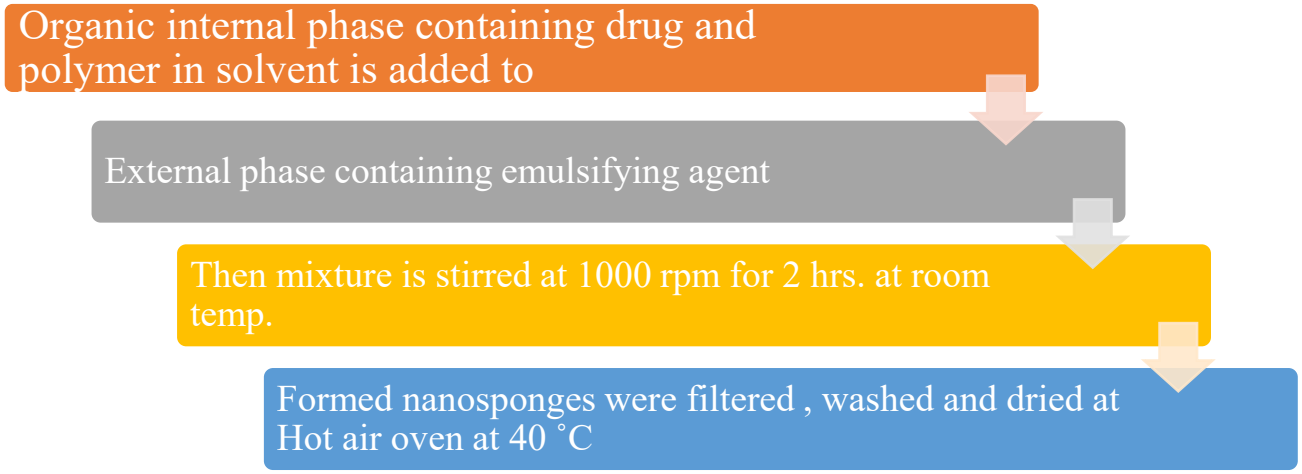


Fig 5:Flow chart of method of preparation

SYNTHESIS OF NANOSPONGES

1. Solvent method

Dissolve the polymer in suitable solvent. Then add this to excess quantity of cross- linker. Reflux the mixture for 48 hours at a temperature of 10ºC. Then allow this solution to cool at room temperature. Add this to excess quantity of bi distilled water and filter the product. Then purify by prolonged soxhlet extraction with ethanol. Dry the product and grind in mechanical mill to get homogenous powder.

2. Ultarsound-Assisted synthesis

Nanosponges can be obtained by reacting polymers with cross-linkers in the absence of solvent and under sonication. The nanosponges obtained by this method will be spherical and uniform in size. Mix the polymer and the cross-linker in a particular molar ratio in a flask. Place the flask in an ultrasound bath filled with water and heat it to 90°C. Sonicate the mixture for 5hours. Then allow the mixture to cool and break the product roughly. Wash the product with water to remove the non-reacted polymer and subsequently purify by prolonged soxhlet extraction with ethanol. Dry the obtained product under vacuum and store at 25°C.

3. Emulsion Solvent Diffusion Method

Nanosponges can be prepared by using ethyl cellulose (EC) and polyvinyl alcohol (PVA). Ethyl cellulose is dissolved in dichloromethane. Add this mixture into aqueous solution of polyvinyl alcohol. Stir the mixture at 1000 rpm for 2 hours in a magnetic stirrer. Then filter the product and dry it in an oven at 40oC for 24 hours.

4. From Hyper Cross- Linked B- Cyclodextrins

Here, β- cyclodextrin (β- CD) can be used as carrier for drug delivery. Nanosponges can be obtained by reacting cyclodextrin with a cross- linker. Nanosponges can be synthesized in neutral or acid forms. The average diameter of a Nanosponge is below 1 µm but fractions below 500 nm can be selected.

EVALUATION OF NANOSPONGES

1. Particle Size Determination

The particle size can be determined by dynamic light scattering using 90 plus particle sizer equipped with MAS OPTION particle sizing software. From this the mean diameter and polydispersity index can be determined.

2. Zeta Potential

Zeta potential is a measure of surface charge. It can be measured by using additional electrode in the particle size equipment.

3. Microscopy Studies

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the microscopic aspects of the nano sponges. The morphology of nanosponges can be determined by SEM analysis.

4. Production Yield

The production yield (PY) can be determined by calculating initial weight of raw materials and final weight of nanosponges.

$$\text{Production Yield} = \frac{\text{Practical mass of Nano sponge.}}{\text{Theoretical mass (polymer + drug).}} \times 100$$

5. Loading Efficiency

The loading efficiency of nano sponges can be determined by the quantitative estimation of drug. Loaded into nano sponges by UV spectrophotometer & HPLC methods[55].

6. Compatibility Studies

The drug should be compatible with the polymers which are used for the preparation of Nano sponge. The compatibility of drug with adjuvants can be determined by Fourier Transform Infra-red Spectroscopy (FT-IR). Crystalline characteristics can be studied by powder X-ray diffraction (XRD) and Differential Scanning Calorimetry (DSC).

7. Solubility studies

The most widely used approach to study inclusion complexation is the phase solubility method described by Higuchi and Connors, which examines the effect of a Nano sponge, on the solubility of drug. Phase solubility diagrams indicate the degree of complexation.

Conclusion - From the above study it is concluded that Nano sponges System are based on nano, polymer-based spheres that can suspend or entrap a wide variety of substances, and then be incorporated into a formulated product such as a gel, lotions, cream, ointments. This technology offers entrapment of ingredients and thus reduced side effects improved stability, increases elegance and enhanced formulation flexibility.

In the present study the formulated nano sponge loaded with kojic acid and Neem is incorporated into the gel. Among all the formulation Starting from kojic acid and neem -aloe vera extract is considered as the best drug content nano sponge with greater percentage drug release. The characterization by SEM finally concluded the appearance as a “Nano sponge”.[11-14]

References

1. Grace R. Cosmeceuticals: Functional food for the skin. Natural Foods Merchandiser 2002; XXIII: 92-96.
2. Singhal mukul, khanna surabhi, Nasa atul, Cosmeceuticals for the skin Asian Journal of Pharmaceutical and Clinical Research, 4 (2), 2019 1-6.
3. Draelos ZD. The effect of ceramide-containing skin care products on eczema resolution duration. Cutis. Jan 2018; 81(1):87-91.
4. Dhureja H, Cosmeceuticals: an emerging concept, Indian Jr. Pharmacol. 2015, 37 970, 155-159.
5. Huczko A, Lange H. Fullerenes: experimental evidence for a null risk of skin irritation and allergy. Fullerene Sci Technol 7:935-9 (1999).
6. Isa, Masako and Eric Mark Kramer, "Adopting the Caucasian 'Look': Reorganizing the Minority Face", in the Emerging Monoculture: Assimilation and the "Model Minority", Eric Mark Kramer (ed.), Westport, CT: Praeger, 41-74, 2020.
7. Shilimkar Vaibhav1 and K. Lakshaman, Tyrosinase Enzyme Inhibitory Activity of selected Indian Herbs, International Journal of Research in Pharmaceutical and Biomedical Sciences, Vol. 3 (3)2016.
8. Jenny A, Merima P, Alberto F, Francesco T. Role of β-cyclodextrin nanosponges in propylene photooxidation. Carbohydrate Polymers. 86: 2011; 127-135.
9. E.K. Patel, R.J. Oswal. Nanosponge and Microsponges: A Novel Drug Delivery System. IJRPC. 2(2): 2012; 237-244.
10. Ajay Vishwakarma, Preetam Nikam, Rajendra Mogal Nanosponges; A Beneficiation for Novel Drug Delivery International Journal of Pharm Tech Research, Vol.6, No.1, 11-20, 2014.
11. Mohan Kumar V, Veena N M, Manjula B P, Formulation And Evaluation Of Microsponges For Topical Drug Delivery Of Mupirocin, International Journal of PharmTech Research 2013, 5(3), 1434-1440.
12. Archana K. Gaikwad, Transdermal drug delivery system: Formulation aspects and evaluation, Comprehensive Journal of Pharmaceutical Sciences Vol. 1(1), pp. 1 - 10, Feb. 2013.
13. Yerram Chandramouli, Firoz, Preparation and evaluation of microsponge loaded controlled release topical gel of acyclovir sodium, International Journal of Biopharmaceutics, 2012; 3(2): 96-102.
14. Bathini Sree, Tejaswi, Formulation and in vitro Evaluation of Clarithromycin floating microspheres for eradication of helicobacter pylori.