INTERNATIONAL JOURNAL OF PHARMACEUTICAL AND CHEMICAL SCIENCES

Review Article

Comparative Study of Carriers Used in Proniosomes

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ABSTRACT

Niosomes are nonionic surfactant vesicles that have potential applications in the delivery of hydrophobic or amphiphilic drugs. But it has certain drawbacks like physical stability such as aggregation, fusion and leaking, and has shown some inconvenience in transportation, distribution and storage. A novel drug delivery system, Proniosomes, a dry formulation minimizes all such problems related to niosomes. These proniosomes are used to produce niosomes within minutes by the addition of hot water followed by agitation and such proniosome-derived niosomes are as good as or even better than conventional niosomes. Proniosomes can be prepared using suitable carrier among the different carriers such as maltodextrin, sorbitol,lactose,mannitol,magnesium aluminum silicate,microcrystalline cellulose. The present study involves comparison of such carriers and criteria for selection of suitable carrier for the preparation of the proniosomes.

Keywords: Niosomes, Proniosomes, Carrier, Maltodextrin, Lactose, Sorbitol, Mannitol.

INTRODUCTION

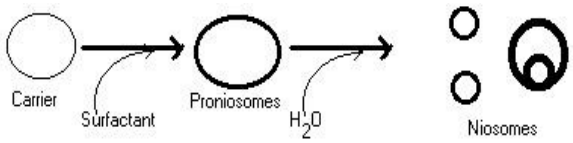
The carrier when used in the proniosomes preparation permits the flexibility in the ratio of surfactant and other components that incorporated. In addition to this, it increases the surface area and hence efficient loading. The carriers should be safe and non-toxic, free flowing, poor solubility in the loaded mixture solution and good water solubility for ease of hydration. Commonly used carriers are maltodextrin, sorbitol monopalmitate, lactose monohydrate, spray dried lactose, glucose monohydrate and sucrose stearates. Of these carriers sorbitol, glucose monohydrate and lactose monohydrate is difficult to coat with the loading mixture solution due to their solubility in this solution and upon application; the samples became viscous slurries. Whereas, when maltodextrin used as the carrier in the proniosomes preparation, it permitted flexibility in the ratio of surfactant and other components, which is incorporated. Hence, it considered as an efficient carrier for proniosomal formation.

Niosomes: Niosomes are synthetic microscopic vesicles consisting of an aqueous core enclosed in a bilayer consisting of cholesterol and one or more nonionic surfactants. They are made of biocompatible, biodegradable, non-toxic, non-immunogenic and non-carcinogenic agents which form closed spherical structures (self assembly vesicles) upon hydration. With high resistance to hydrolytic degradation, niosomes are capable of entrapping many kinds of soluble drugs while exhibiting greater vesicle stability and longer shelf life. Vesicles are colloidal particles in which a concentric bilayer made-up of amphiphilic molecules surrounds an aqueous compartment. They are useful vehicles for a drug delivery of both hydrophobic drugs, which associate with the lipid bilayer and hydrophilic drugs, which are encapsulated in the interior aqueous compartment. In general, vesicles made of natural or synthetic phospholipids are called liposomes whereas those made of non-ionic surfactants (e.g., alkyl ethers and alkyl esters) and cholesterol constitutes a non-ionic surfactant vesicular system called niosomes.

Although niosomes as drug carriers have shown advantages such as being Less expensive and chemically stable, they are associated with problems related to physical

stability such as fusion, aggregation, sedimentation and leakage on storage. Proniosomes, a dry formulation minimizes all such problems related to niosomes.

Proniosome: Proniosomes are water-soluble carrier particles that are coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media. The resulting niosomes are very similar to conventional niosomes and more uniform in size. The additional convenience of the transportation, distribution, storage, and dosing would make 'dry niosomes' a promising industrial product.Proniosome-derived niosomes are as good as or even better than conventional niosomes:



Commonly used materials for proniosomes preparation

1. Surfactants: Span20, Span40, Span60, Span80, Span85, Tween20, Tween40, Tween80
2. Stabilizers: Cholesterol, lecithin
3. Carriers: Maltodextrin, sorbitol, mannitol, magnesium aluminum silicate, microcrystalline cellulose, spray dried lactose, glucose monohydrate and sucrose stearates

Selection of the carrier in the proniosomal formulation requires more attention as it affects some factors like flexibility in surfactant and other component ratio, surface area, efficient loading, etc.

Brief review of various carriers are as follows

MALTODEXTRIN: It is a mixture of glucose, disaccharides and polysaccharides, obtained by the partial hydrolysis of starch. Maltodextrin is a flavorless, easily digested carbohydrate made from cornstarch. The starch is cooked, and then acid and/or enzymes (a process similar to that used by the body to digest carbohydrates) are used to break the starch into smaller chains (3-20 chains in maltodextrin). These chains are composed of several dextrose molecules held together by very weak hydrogen bonds. A maltodextrin is a short chain of molecularly linked dextrose (glucose) molecules, and is manufactured by regulating the hydrolysis of starch. Typical commercial maltodextrins contain as few as three and as many as nineteen linked dextrose units. While the singular term "maltodextrin" is permitted in an ingredient statement, the term "maltodextrin" can be applied to any starch hydrolysis product that contains fewer than 20 dextrose (glucose) units linked together. This means that the term "maltodextrin" stands for a family of products, not a single distinct ingredient.

Characters: A white or almost white, slightly hygroscopic powder or granules, freely soluble in water.

Description: It is a White powder or granular white powder, available in a variety of particle sizes and DE* values. Non-sweet, nutritive saccharide polymers composed of D-glucose units linked primarily by alpha-1-4 bonds. The higher the DE, the greater the extent of starch hydrolysis and can be used for sweetness moderation. Maltodextrin with a DE of 5 is the least sweet, and is approximately 1/10 as sweet as sucrose. Maltodextrin with a DE of 18 is approximately 1/4 as sweet as sucrose.

- DE = dextrose equivalents, a quantitative measure of the degree of starch polymer hydrolysis.

Appearance: Maltodextrins are obtained by the partial hydrolysis of starch whereby the basic polymeric structure is retained. Maltodextrins are water soluble, non-sweet products that are supplied as spray-dried powders. Maltodextrins are defined by the FDA as products having a DE less than 20.

They are generally recognized as safe (GRAS) food ingredients. Maltodextrins are excellent solids builders for standard and low-fat products. They are effective spray-drying aids for flavors, fruit juices, and other hard-to-dry products. They also have a neutral taste.

Characteristic and Application

- Maltodextrins are easily dispersed into water or other aqueous-based systems and are commonly used in consumer products such as dry mixes.
- Maltodextrins are used as crystallization inhibitor. Added in candies and half-soft sweets, it can prevent sweets appearing sand and extend the shelf life. Debasing and eliminating the smell of mutton, stabilizing the alimentation elements, keeping the character and flavor and increasing the quality.
- Maltodextrins are used as source of carbohydrate in high-energy drink, especially for athletes. They also are easily digestible carbohydrates for nutritional beverages, which fits athletes training to increase sugar content in musculature and enhance physical strength and eliminate fatigue
- Maltodextrins are used as carrier for spray-drying of active substances.
- Maltodextrins are used as diluents in single unit dosage preparations such as sachets. Because of their inherent polymeric nature maltodextrins also make excellent binders for direct compression. Since it has weak sweetness, they're widely used in food processing such as sweets, ice cream, jam, cakes etc., and the flavour of other materials in the products can be improved
- Maltodextrins are used as coating agent in pharmaceutical industries.
- Maltodextrins are used as binder since they have a rather high viscosity in solution and good binding properties. If proper amount of maltodextrin powder is added to solid granules or ball candies or white-sugar rice cakes, molding rate is increased and work efficiency is improved.
- Maltodextrins are used as stabilizers since they belong to large numerator saccharide, high viscidity and high foam stability. Therefore, it can be used as foam stabilizer in beer making and gas liquor making.
- In Confectionary industry used to increase flexibility, lower sweetness, prevent granulation and melting, change taste, improve institutional framework and prolong storage life of sweets. Its good fluidity and transparency not only attach on the surface but also penetrate the paper, raising the fibers' cohesive force, meanwhile improving appearances and physical properties. This sweetener reduces the incidence of toothache, blood pressure, obesity, diabetes etc.
- In Beverage industry used as a raw material, maltodextrin will increase natural smell, after reasonable mixing, reduce nutritional loss, lower sweetness, improve dissolubility, reduce costs and further increase economic profits.
- In Other industries maltodextrin has good stability on emulsification, so can be used as a coverer and absorbent in cosmetics for increasing luster and skin elasticity. It can also be used in the production of solvents and powdered insecticides.

Table 1: Specifications of maltodextrin

Appearance	White powder with low yellow shadow, no fixed shape
Smell	Special smell of malt - dextrin, no other exceptional smells
Taste	Minimal or low sweetness, no other taste
Moisture	6 % (max.)

De – equivalent	10 – 20 %
pH	4.5 - 6.5
Sulfated ash	0.6% (max.)
Total plate count	1500 / g
Pathogenic bacteria	Not confirmed

Sorbitol: It is also known as glucitol, Sorbogem and Sorbo, is a sugar alcohol that the human body metabolizes slowly. It can be obtained by reduction of glucose, changing the aldehyde group to a hydroxyl group. Sorbitol is found in apples, pears, peaches, and prunes.It is synthesized by sorbitol-6-phosphate dehydrogenase, and converted to fructose by succinate dehydrogenase and sorbitol dehydrogenase Succinate dehydrogenase is an enzyme complex that participates in the citric acid cycle
Sorbitol is a sugar substitute. It may be listed under the inactive ingredients listed for some foods and products. Sorbitol is referred to as a nutritive sweetener because it provides dietary energy: 2.6 kilocalories (11 kilojoules)per gram vers us the average 4 kilocalories (17 kilojoules) for carbohydrates. It is often used in diet foods (including diet drinks and ice cream), mints, cough syrups, and sugar-freechewing gum. It also occurs naturally in many stone fruits and berries from trees of the genus Sorbus.

Characteristics and applications

- Sorbitol can be used as a non-stimulant laxative via an oral suspension or enema.
- Sorbitol exerts its laxative effect by drawing water into the large intestine, thereby stimulating bowel movements
- Sorbitol has been determined safe for use by the elderly, although it is not recommended without consultation with a clinician. Sorbitol is found in some dried fruits and may contribute to the laxative effects of prunes.
- Sorbitol is used in bacterial culture media to distinguish the pathogenic *Escherichia coli* O157:H7 from most other strains of *E. coli*, as it is usually incapable of fermenting sorbitol, but 93% of known *E. coli* strains are capable of doing so.
- Sorbitol, combined with kayexalate, helps the body rid itself of excess potassium ions in a hyperkalaemic state. The kayexalate exchanges sodium ions for potassium ions in the bowel, while sorbitol helps to eliminate it. The FDA has discouraged this combination when in 2010 it issued a warning of increased risk for GI necrosis.
- Sorbitol often is used in modern cosmetics as a humectant and thickener. Sorbitol often is used in mouthwash and toothpaste. Some transparent gels can be made only with sorbitol, as it has a refractive index sufficiently high for transparent formulations. It is also used frequently in almost all "sugar free" chewing gum.
- Sorbitol is used as a cryoprotectant additive (mixed with sucrose and sodium polyphosphates) in the manufacture of surimi, a highly refined fish paste most commonly produced from Alaska pollock (*Theragra chalcogramma*). It is also used as a humectant in some cigarettes. Sorbitol sometimes is used as a sweetener and humectant in cookies and other foods that are not identified as "dietary" items.
- Sorbitol also may aggravate irritable bowel syndrome and similar gastrointestinal conditions, resulting in severe abdominal pain for those affected, even from small amounts ingested.
- Ingesting large amounts of sorbitol can lead to abdominal pain, flatulence, and mild to severe diarrhea. Sorbitol ingestion of

20 grams (0.7 oz) per day as sugar-free gum has led to severe diarrhea leading to unintended weight loss of 11 kilograms (24 lb) in eight months, in a woman originally weighing 52 kilograms (110 lb); another patient required hospitalization after habitually consuming 30 grams (1 oz) per day.

Table 2: Specifications of Sorbitol

Appearance	White powder with low yellow shadow, no fixed shape
Smell	no other exceptional smells
Taste	Sweet taste
Moisture	3% (max.)
pH	4.5 - 6.5
Density	1.489 g/cm³
Melting point	95 °C, 368 K, 203 °F
Boiling point	296 °C, 569 K, 565 °F

Mannitol: It is a white, crystalline organic compound with the. This polyol is used as an osmotic diuretic agent and a weak renal vasodilator. It was originally isolated from the secretions of the flowering ash, called manna after their resemblance to the Biblical food, and is also referred to as **mannite** and **manna sugar**. In plants, it is used to induce osmotic stress. Mannitol is a sugar alcohol; that is, it is derived from a sugar by reduction, with a molecular weight of 182.17 g/mol, and a density of 1.52 g/mL. Other sugar alcohols include xylitol and sorbitol. Mannitol and sorbitol are isomers, the only difference being the orientation of the hydroxyl group on carbon. Mannitol and sorbitol are isomers. Both are ($C_6H_8(OH)_6$). The difference is the second carbon atom in the chain is chiral like, leading to physically different molecules.

Characteristics and applications

- Mannitol is used clinically in osmotherapy to reduce acutely raised intracranial pressure until more definitive treatment can be applied, e.g., after head trauma. It is also used to treat patients with oliguric renal failure.
- Mannitol can also be used as a facilitating agent for the transportation of pharmaceuticals directly into the brain.
- Mannitol is commonly used in the circuit prime of a heart lung machine during cardiopulmonary bypass. The presence of mannitol preserves renal function during the times of low blood flow and pressure, while the patient is on bypass. The solution prevents the swelling of endothelial cells in the kidney, which may have otherwise reduced blood flow to this area and resulted in cell damage.
- Mannitol is also the basis of Bronchitol which was developed by the Australian pharmaceutical company Pharmaxis as a treatment for cystic fibrosis and bronchiectasis.
- Mannitol is also the first drug of choice for the treatment of acute glaucoma in veterinary medicine. It is administered as a 20% solution IV. It dehydrates the vitreous humor and, thus, lowers the intraocular pressure. However, it requires an intact blood-ocular barrier to work.[12]
  Mannitol is the primary ingredient of Mannitol Salt Agar, a bacterial growth medium, and is used in others. In oral doses larger than 20 g, mannitol acts as an osmotic laxative, and is sometimes sold as a laxative for children.
- Mannitol does not stimulate an increase in blood glucose, and is therefore used as a sweetener for people with diabetes, and in chewing gums.
- Mannitol is contraindicated in patients with anuria and congestive heart failure.

Table 3: Specifications of Mannitol

Appearance	White and crystalline powder.
Smell	no other exceptional smells
Taste	Sweet taste
Solubility	22g mannitol /100ml water
Density	1.52 g/ml
Melting point	165°-169°C

Boiling point	295°C

Lactose: Lactose is a disaccharide sugar that is found most notably in milk and is formed from galactose and glucose. Lactose makes up around 2~8% of milk (by weight), although the amount varies among species and individuals. It is extracted from sweet or sour whey. The name comes from *lac* or *lactis*, the Latin word for milk, plus the -ose ending used to name sugars.

Characteristics and applications

- Food industry applications, both of pure lactose and lactose-containing dairy by-products, have markedly increased since the 1960s. For example, its bland flavour has lent to its use as a carrier and stabiliser of aromas and pharmaceutical products. Purified lactose can also be purchased, as high calorie diet additive.
- Lactose is little fermented by baker's yeast and during brewing, which may be used to advantage. It is thus sometimes used to sweeten stout beer as it is non-fermentable in beer; the resulting beer is usually called a milk stout or a cream stout.
- Another major use of lactose is in the pharmaceutical industry. Lactose is added to pills as a filler because of its physical properties (i.e., compressibility) and low price.

Table 4: Specifications of Lactose

Appearance	White,Solid
Smell	no other exceptional smells
Taste	Sweet taste
Solubility	21.6g /100ml
Density	1.489 g/cm³
Melting point	202.8°C
Boiling point	668.9 °C

COMPARE STUDY OF DEVELOPED PRONIOSOMES

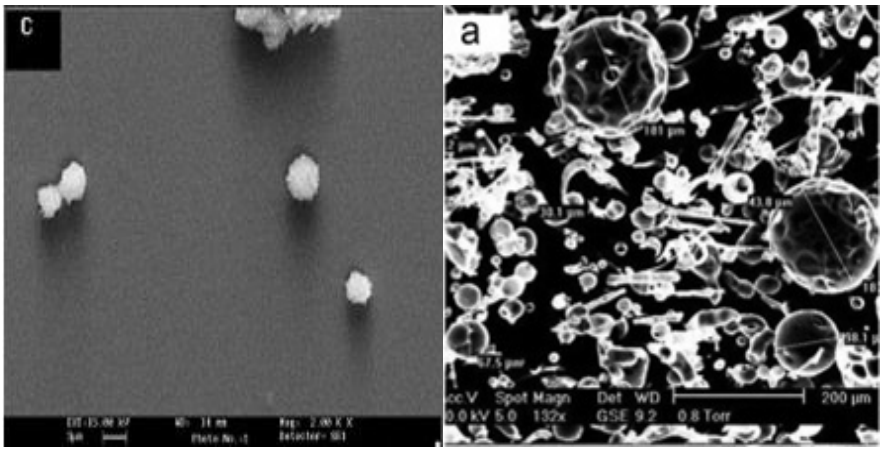
- **Almira I. Blazek-Welsh et** al developed proniosomes. They found **sorbitol** carrier based preparation was tedious and the dissolved sorbitol interfered with the encapsulation of one model drug. A slurry method has been developed to produce proniosomes using **maltodextrin** as the carrier. The flexibility of the proniosome preparation method would allow for the optimization of drug encapsulation in the final formulation based on the type and amount of maltodextrin. This formulation of proniosomes is a practical and simple method of producing niosomes at the point of use for drug delivery. [1] Because the sorbitol carrier is soluble in the organic solvent, it is necessary to repeat the process until the desired surfactant loading has been achieved. The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar vesicles to form as the carrier dissolves. It was observed, however, that certain solutes were affected by the presence of dissolved carrier. Although conventional niosome suspensions would include only the multilamellar surfactant particles in buffer, a typical formulation derived from sorbitol based proniosomes would consist of multilamellar surfactant particles in buffer and dissolved sorbitol. The residual sorbitol concentration in the formulation reported to affect entrapment efficiency. Specifically, dissolved sorbitol could **decrease entrapment efficiency** to less than one half of that observed without sorbitol. It was difficult to coat sorbitol particles because sorbitol is soluble in chloroform and other organic solvents. If the surfactant solution was applied too quickly, the sorbitol particles would degrade and the sample became viscous slurry. To avoid this constraint, several methods of making proniosomes

were attempted, but most proved to be time consuming and had narrowly constrained limits on acceptable production conditions. In this article, experiments are described in which **maltodextrin** was evaluated as an alternative to **sorbitol** as the carrier material in the proniosome preparations.[1] The objective in developing proniosomes was to devise a method of producing a nonionic surfactant based dosage at the point of use to avoid problems of physical and chemical stability found in storage of some surfactant-based dosage forms. By creating a dry formulation, issues related to hydrolysis of the active ingredient or surfactants are avoided; by forming the suspension as needed, precipitation and aggregation are avoided. Although the sorbitol-based proniosomes accomplished these objectives, the effect of the carrier on entrapment efficiency remained problematic. Significant concentrations of sorbitol altered the distribution of one model compound. However, making proniosomes with a reduced amount of sorbitol was a tedious process and began to compromise the advantages of proniosomes related to minimizing film thickness. The use of **maltodextrin** as the carrier in the proniosome preparation permitted flexibility in the amounts of surfactant and other components, which greatly enhances the potential application of proniosomes in a scaled-up production environment.[1] Although maltodextrin is a polysaccharide, it has minimal solubility in organic solvents tested here. Thus, it was possible to coat the maltodextrin particles by simply adding surfactant in organic solvent to dry maltodextrin and evaporating the solvent. An analogous process with sorbitol results in a solid, surfactant/sorbitol cake. Because the maltodextrin particle morphology is preserved, hollow blown maltodextrin particles can be used for a significant gain in surface area. The higher surface area results in a thinner surfactant coating, which makes the rehydration process more efficient. For drugs where maltodextrin is found to affect encapsulation efficiency, the maltodextrin can be minimized by producing proniosomes with greater surfactant loading. **Conclusion**: Maltodextrin-based proniosomes are a potentially scalable method for producing niosomes for delivery of hydrophobic or amphiphilic drugs. [1]

- **T. Sudhamani et al** prepared ibuprofen loaded maltodextrin based proniosome and they concluded that the use of maltodextrin as the carrier in the proniosome reparation permitted flexibility in the amounts of surfactants and other components, which greatly enhances the potential application of proniosomes in a scaled-up production environment.[2]
- **Chandra et al** prepared proniosome based drug delivery system of piroxicam and they found that preparing proniosomes on maltodextrin was comparatively easy as compared to sorbitol. Maltodextrin is a polysaccharide; it has minimal solubility in organic solvents. Thus, it is possible to coat maltodextrin particles by simply adding surfactant in organic solvent to dry maltodextrin and evaporating the solvent. The maltodextrin particle morphology is preserved (Figure C), circular maltodextrin particles can be used for a significant gain in surface area. The higher surface area results in a thinner surfactant coating, which makes the rehydration process more efficient. The use of maltodextrin as the carrier in the proniosome preparation permitted flexibility in the ratio of surfactant and other

components which can be incorporated.[3] Maltodextrin is a polysaccharide; it has minimal solubility in organic solvents. Thus, it is possible to coat maltodextrin particles by simply adding surfactant in organic solvent to dry maltodextrin and evaporating the solvent. The maltodextrin particle morphology is preserved (Figure C), circular maltodextrin particles can be used for a significant gain in surface area. The higher surface area results in a thinner surfactant coating, which makes the rehydration process more efficient. The use of maltodextrin as the carrier in the proniosome preparation permitted flexibility in the ratio of surfactant and other components which can be incorporated.[3] Coating sorbitol results in a solid cake like mass (below Figure E). It was necessary that the sorbitol bed be completely dry before further additions are made and making proniosomes with a reduced amount of sorbitol was not only tedious but lead to niosomes with larger vesicle size. Addition of water leads to swelling of bilayers as well as vesicles due to interaction of water with polar groups of surfactant. In presence of excess of water there was complete hydration leading to formation of niosomes. Niosomes formed from conventional proniosomes, maltodextrin based and sorbitol based proniosomes are shown in (Figure B, D and F) respectively.[3]

- **Karthik Y Janga et al** prepared zaleplon based proniosomes and they concluded that among the different carriers that include maltodextrin, sorbitol, mannitol, lactose, magnesium aluminum silicate, microcrystalline cellulose, it is preferred to use spray dried mannitol because it possess high porosity and surface area that enables the formulator for the easy adjustment of amount of carrier required to support the lipid and also to prepare proniosomes with high surfactant to carrier mass ratio.[4]
- **Solanki et al** prepared proniosomes by the slurry method using maltodextrin as a carrier. Scanning electron microscopy (SEM) of uncoated maltodextrin powder (Figure a) shows the highly porous surface, which would provide more surface area to be coated with surfactant mixture.[5]



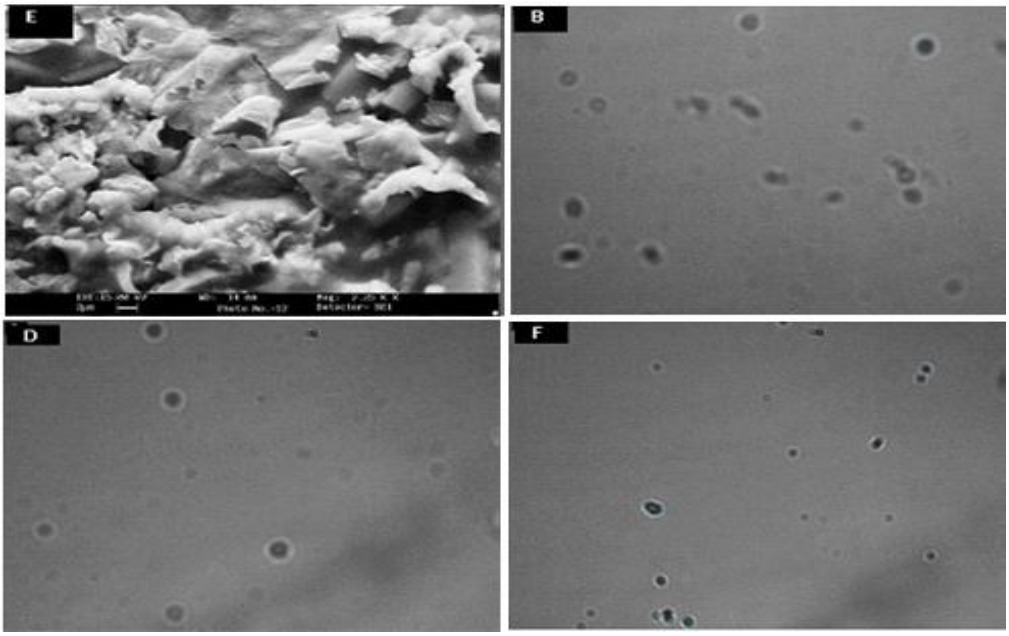


Fig 1: (A,B,C,D,E,F)

Table 5: Some of the proniosomal formulations using different carriers are

S. No.	Drug	Hydrophilic or Lipophilic	Category	Result(s)	carrier
1	Ibuprofen	Lipophilic	NSAIDS	Proniosomes derived niosomes are superior in their ability to release the drug at a constant rate.	Maltodextrin
2	Aceclofenac	Lipophilic	NSAIDS	The polynomial equation and contour plots developed by using central composite design allowed to prepare Proniosomes with optimum characteristic.	Maltodextrin
3	Piroxicam	Lipophilic	NSAIDS	Span 60 based lecithin vesicle showed significant decrease in paw swelling. There is a increased drug delivery from lipid vesicles.	Maltodextrin and Sorbitol
4	Indomethacin	Lipophilic	NSAIDS	The release rate of the drug from the vesicle was in the controlled manner.	Maltodextrin
5	Captopril	Hydrophilic	Antihypertensive	Prolonged release of captopril	Sorbitol
6	Celecoxib	Lipophilic	Cyclooxygenase - inhibitor	Enhanced bioavailability of celecoxib	Sorbitol
7	Cromolyn Sodium	Hydrophilic	Antiasthmaatic and antiallergic	High nebulisation efficiency percentage and good physical stability were observed.	Spray dried lactose

CONCLUSION

The merits and demerits of various carriers used in the preparation of proniosomes are

studied. Among all the carriers maltodextrin was found to provide more entrapment efficiency of drug, Scanning electron microscopy (SEM) of uncoated maltodextrin powder showed the highly porous surface, which would provide more surface area to be coated with surfactant mixture. Further, maltodextrin found to be safe and non-toxic, free flowing, poor solubility in the loaded mixture solution and good water solubility for ease of hydration.

The use of maltodextrin as the carrier in the proniosome preparation permitted flexibility in the amounts of surfactant and other components, which greatly enhances the potential application of proniosomes in a scaled-up production environment. Preparing proniosomes with maltodextrin is comparatively easy as compared to other carriers.

REFERENCES

1. Almira I. Blazek-Welsh and David G. Rhodes Maltodextrin-Based Proniosomes. AAPS Pharmsci. 2001;3(1).
2. T.Sudhamani, V. Ganesan, N. Priyadarsini and M. Radhakrishnan. Formulation and evaluation of Ibuprofen loaded maltodextrin based Proniosome. International Journal of Biopharmaceutics. 2010;1(2):75-81.
3. Chandra and PK. Sharma. Proniosome based drug delivery system of piroxicam African Journal of Pharmacy and Pharmacology. 2008;2(9):184-190.
4. Karthik Y Janga, Raju Jukanti and Ashok Velpula. Bioavailability adjustment of zaleplon via proliposomes. European journal of Pharmaceutics and Biopharmaceutics.
5. Ajay Solankia, Jolly Parikha and Rajesh Parikh. Preparation, Characterization, Optimization, and Stability Studies of Aceclofenac Proniosomes. Iranian Journal of Pharmaceutical Research. 2008;7(4):237-246.
6. Ankur Gupta, Sunil Kumar Prajapati, M Balamurugan, Mamta Singh and Daksh Bhatia. Design and Development of a Proniosomal Transdermal Drug Delivery System for Captopril. Tropical Journal of Pharmaceutical Research. 2007;6(2):687-693.
7. Mohamed Nasr. In Vitro and In Vivo Evaluation of Proniosomes Containing Celecoxib for Oral Administration. AAPS PharmSciTech. 2010;11(1).DOI: 10.1208/s12249-009-9364-5.
8. Abd alber and El-Leithy HM. International journal of pharmaceutics. 2008;357:189-198.