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Pharmaceutical Excipients of Marine and Animal origin: A Review

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Abstract: This article gives an overview of natural, marine and animal derived compounds which are used as excipients in pharmaceutical preparations. Pharmaceutical excipients are inactive substances, used to formulate dosage forms and play a multi role in pharmaceutical formulations. The use of marine and animal derived excipients to deliver active pharmaceutical ingredients have been limited by the development of synthetic materials. However, advantages offered by these excipients are being cheap, freely available and biocompatible. Marine polysaccharides are abundant in sea and have a low extraction cost. Marine and animal excipients have a diverse pharmaceutical application such as fillers, binders, film coating agents, colorants, flavoring agents, encapsulating agents and lubricating agents. Even though they produce diverse pharmaceutical application, their use is limited due to consumer's religious beliefs and some toxicity problems.

Key words: Marine excipients, animal excipients, lactose, gelatin, alginate, chitosan.

1. Introduction

The present modern world prefers natural products than the synthetic additives. Increased interest towards these natural products promotes researches based on natural products. All living organisms produce biodegradable polymers which are almost renewable. Most natural compounds are made of carbohydrates and few from proteins, therefore they are cheap, environmental friendly, biocompatible, freely available, and nontoxic. These characteristic promotes the wide use of natural products in food and pharmaceutical industry [1].

Pharmaceutical industry is one of the most important industries in the world. It manufactures a variety of dosage forms such as tablets, capsules, solutions, syrups, suspensions, ointments, gels, creams, vaccines and injections. A dosage form contains both active pharmaceutical ingredient and excipients. Active pharmaceutical ingredient is any component that provides pharmacological activity. Excipients are inactive substances, used as a medium or vehicle to give medicament. Excipients have the ability to modify solubility, stability, bioavailability of the active ingredients [2]. Excipients include fillers,

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disintegrants, lubricants, colorants, antioxidants, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, solubilisers, permeation enhancers, flavoring and aromatic substances, as well as outer covering of the medicinal products, e.g. gelatin capsules [3].

Pharmaceutical excipients are of various origin: animal (e.g. lactose, gelatin, stearic acid, bees wax, honey musk, lanoline), plant (e.g. starches, sugars, cellulose, arginates), mineral (e.g. talc, calcium phosphate, silicon dioxide) and by synthesis (e.g. povidone, polysorbates, polyethylene glycol) [4]. Marine organisms have a large biodiversity and growing interest in many study areas. These marine compounds possess simple extraction and purification processes [5]. Marine polysaccharides are widely used in food, cosmetic and pharmaceutical industries. Marine algae are the important source of marine polysaccharides, but they can also be obtained from marine animal sources [6].

Excipients should have a good safety and quality profile in order to use in drug formulations. Marine and animal derived compounds have some added advantages compared to synthetic polymers, i.e. they are cheap, chemically inert, bio degradable, environmental friendly and easily available [7].

Excipients of animal origin should documented on their viral safety and TSE (Transmitting Animal Spongiform Encephalopathy) risks. The use of gelatin as a shell material in soft gelatin capsules has a risk of spreading bovine spongiform encephalopathy [8]. Safety concerns from animal derived excipients have also included prion-related diseases, so extracted excipients are further refined and tested to reduce the risk of contaminants. Religious beliefs can restrict certain animal products [9]. Therefore, dietary restrictions can extend to excipients [10].

2. Pharmaceutical Excipients of Marine Origin

2.1 Agar

Agar is a marine biomaterial present in the cell wall of red algae *Gelidium amansii*, family Gelidaceae. Agar mainly consists two polysaccharides, linear agarose and heterogeneous agaropectin (Fig. 1) [11]. Agar is used as suspending agent, emulsifying agent, gelling agent in suppositories, surgical lubricant, tablet disintegrant and medium for bacterial culture [12].

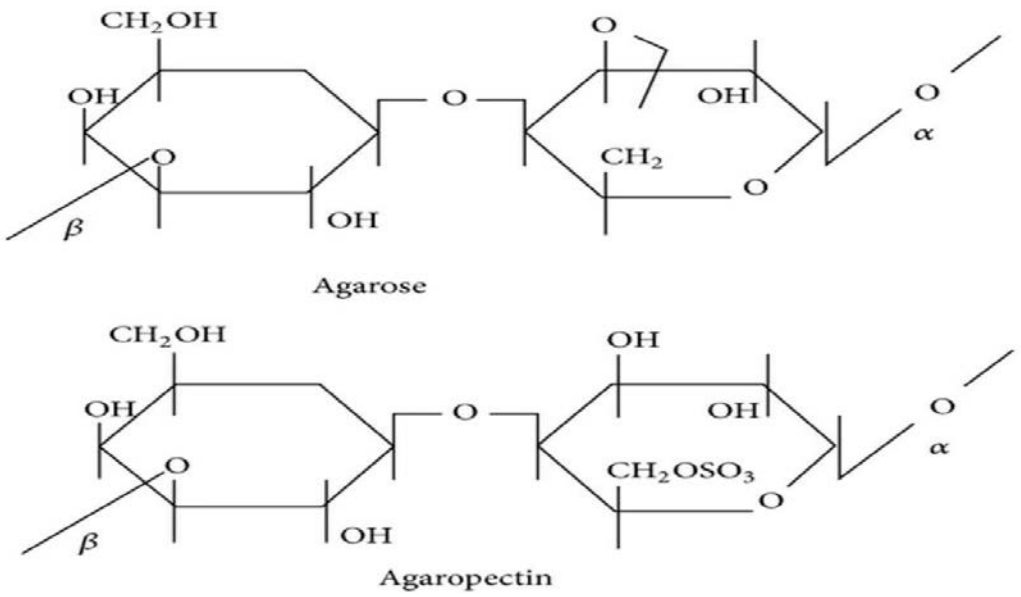

Fig. 1 Structure of Agar composed of agarose and agaropectin

A successful *in vivo* study showed that agar beads are suitable vehicle for sustained release preparations. Agar beads containing sulfamethoxazole drug showed a sustained drug supply to the plasma due to sustained absorption [13]. The dissolution profile of hypnotic drug, phenobarbitone sodium incorporated with agar beads indicated that agar beads may be useful for the preparation of sustained release formulations [14]. Roxithromycin orodispersible tablets prepared with modified agar showed good friability, least disintegration time and were stable for six months [15].

2.2 Alginate

Alginate is a marine polysaccharide obtained from brown seaweeds *Laminaria hyperborea*, *L.digitata* and *Ascophyllum nodosum*. Alginic acid is a linear polymer mainly composed of D-mannuronic acid and L-glucuronic acid [16] (Fig. 2) [17]. The seaweed is extracted with a dilute alkaline solution which solubilizes the alginic acid present. The alginic acid extracted is later converted to salt form sodium alginate which is the major form currently used [18].

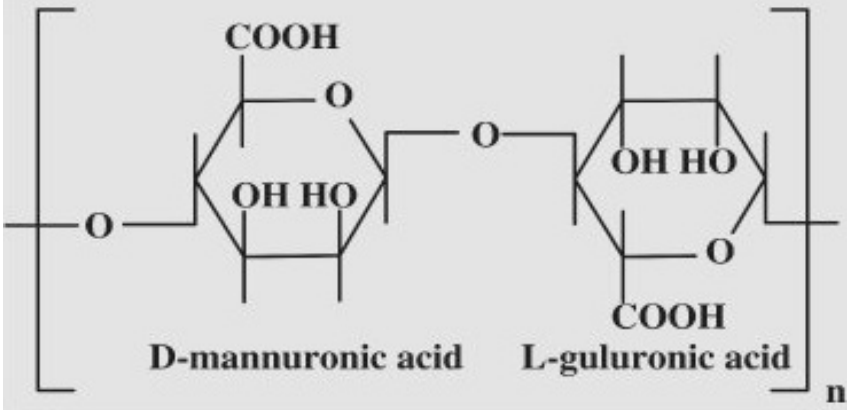

Fig. 2 Structure of Alginic acid from mannuronic and guluronic acid monomers

Alginates have a wide application as rate-controlling excipient in drug delivery systems, as an excipient in pharmaceutical preparations for local application and as a matrix for biomolecules [18]. Sodium alginate is widely used as a thickening, gel forming, suspending and stabilizing agent in pharmaceutical preparations. It is also used as bioadhesive microspheres, nanoparticles and microencapsulating agent in nano drug delivery systems. The carboxyl groups present in alginate are charged at pH value higher than 3-4, making them soluble at neutral and alkaline conditions. Alginate is stable at stomach pH therefore it is used as a carrier molecule to formulate gastro resistant tablets [6]. Prolonged release press-coated ibuprofen tablets were prepared using sodium alginate as a coating material to control the drug release. Changing the chemical structure of alginate and degree of viscosity have influenced the release rate of the ibuprofen active agent [19].

2.3 Carrageenan

Carrageenan is a marine, high molecular weight sulfated polysaccharide made of galactose and 3,6-anhydrogalactose units. It is obtained from red algae of the *Kappaphycus* and *Eucheuma*. Carrageenans are classified according to their degree of sulfation as, Kappa (κ), Lambda (λ) and Iota (ι) (Fig. 3) [20]. Kappa carrageenans mainly used as gelling agent and Lambda carrageenans are non-gelling agent used as binder and thickener in formulations. Carrageenan can also be used as a substitute for gelatin in soft and hard gel capsules [21].

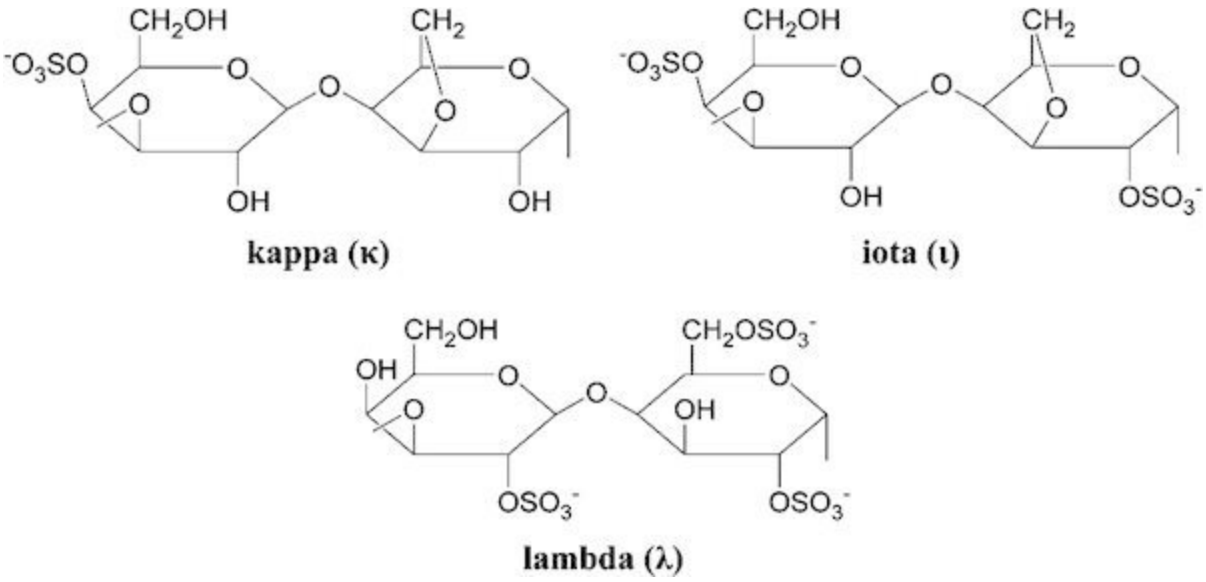

Fig. 3 Structures of kappa, iota and lambda Carageenan

Studies showed that carrageenan can be used as a suitable excipient in controlled release preparations. The controlled release tablets prepared with all three types of carrageenan showed good compactibility and good consolidation behavior [22]. Specially κ and ι carrageenan are useful excipients in oral extended-release tablets [23]. Carrageenan has a strong gelling characteristic with a negative charge, which made it a suitable gelling and viscosity enhancing agent for controlled release and prolonged retention [24]. In another study K-carrageenan was used as a substitute to replace the standard extrusion aid, microcrystalline cellulose in pellets formation. The pellets produced with K-carrageenan were of high quality which indicates K-carrageenan can be used as a novel extrusion aid [25].

2.4 Fucoidan

Fucoidan is a sulfated polysaccharide found in many species of brown algae such as *Fucus vesiculosus* and *Sargassum stenophyllum.* Fucoidan polymer is mainly composed of fucose and sulfate (Fig. 4) [26] but also has other monosaccharides, mannose, galactose, glucose and xylose [27]. Fucoidan based drug carriers, such as nanoparticles, microparticles and hydrogels have been successfully developed [6]. Chitosan/fucoidan micro complex-hydrogel was produced for the control release of heparin binding growth factors. The formulated hydrogel did not show any bleeding complications at the injection sites and the drug release was extremely good [28]. In another study, chitosan/fucoidan multilayer nanocapsules showed a great potential to act as a carrier for control release of bioactive compounds [29].

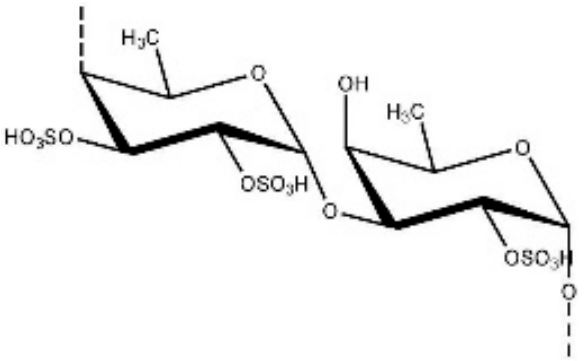

Fig. 4 Structure of Fucoidan

2.5 Chitosan

Chitosan is a cationic linear biopolymer (Fig. 5) [30] derived by deacetylation of chitin, an amino polysaccharide natural biopolymer found in the exoskeletons of arthropods and crustacean. It is used as a filler or diluent and as a binder in direct compression tablets. Chitosan has a lowest bulk and tapped density that cause excellent flow as well as compression and compaction during tablet processing [31]. Chitosan also used as wetting agent, coating agent, microspheres and micro capsules in drug delivery systems.

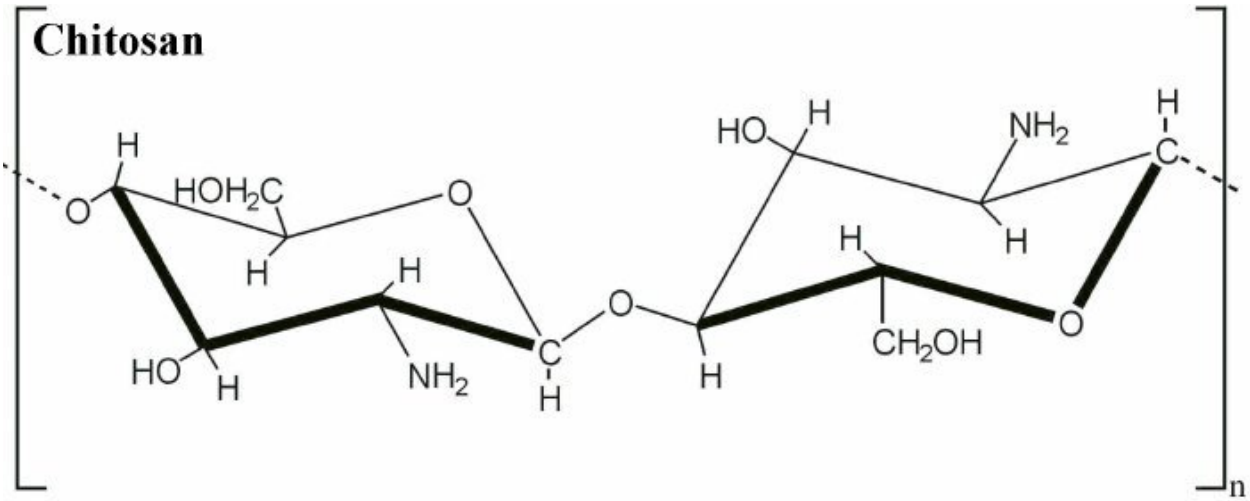

Fig. 5 Structure of Chitosan bipolymer

Addition of 50% chitosan in direct compression tablets showed quick disintegration. In a concentration more than 5%, chitosan showed excellent binding property than corn starch and microcrystalline cellulose [32]. Chitosan is a good excipient for development of controlled release dosage forms due to its polymeric cationic character and gelling and film forming properties [33]. Sustained release gels of indomethacine, papaverine hydrochloride and lidocaine prepared with dried chitosan showed zero order kinetics and low preparation cost compared to commercial products [32]. Grinding of poorly soluble drugs, such as griseofulvin or prednisolone with chitosan showed an enhanced dissolution rate and reduced crystal size

in the formulation [33]. Enhance the absorption of nasal and oral drugs, biodegradable polymer for implants and carrier to vaccine delivery [34].

3. Pharmaceutical Excipients of Animal Origin

3.1 Lactose

Lactose is a disaccharide (Fig. 6) [35] produced as a byproduct of dairy industry and is a major component of whey. For many decades, lactose is the widely used filler in tablet manufacturing. Lactose has a very good compressibility which makes it more suitable for a tablet filler. The purest form of α-lactose is widely used in pharmaceutical industry as an excipient [36]. Lactose has different roles in dosage formulation types. It is used as a filler, diluent or bulking agent in tablets and capsules, as a sweetener in liquid formulation and as a carrier for dry powder inhalation products [37].

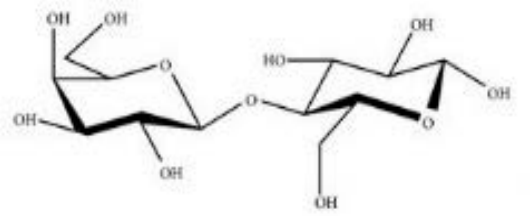

Fig. 6 Structure of disaccharide carbohydrate lactose

Main pharmaceutical use of lactose is as an excipient because of its cost effectiveness, low hygroscopicity, low sweetness, compatibility with active ingredients and other excipients availability, bland taste, high chemical and physical stability, and acceptable water solubility. These properties make it the most suitable pharmaceutical excipient for dosage formulations, where it is estimated to cover about 70% of all such formulations [38].

3.2 Gelatin

Gelatin is a soluble protein (Fig. 7) [39] derived by partial hydrolysis of collagen, the main fibrous protein constituent in bones, cartilages and skins. The properties of the gelatin are influenced by the source, age of the animal, and type of collagen. The growing trend to replace synthetic agents with natural ones have increased the use of gelatin in pharmaceutical industry. The main sources of gelatin are pig skin, bovine hide and pork and cattle bones. Gelatin is insoluble in cold water, soluble in hot water, insoluble in most immiscible solvents and in volatile and fixed oils.

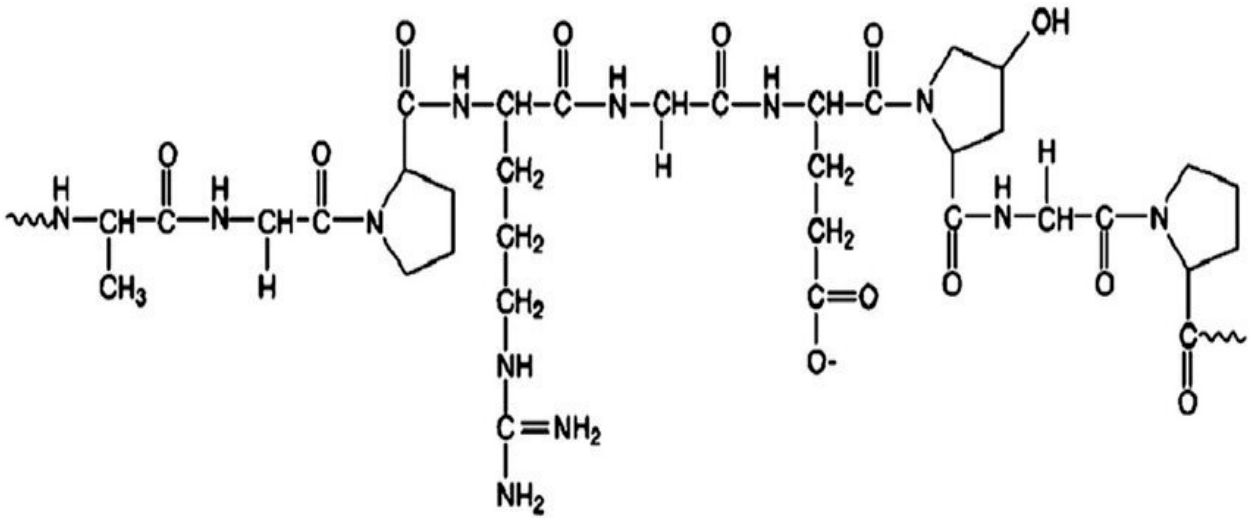

Fig. 7 Structure of gelatin

Gelatin is used as an emulsifier, binder, foaming agent, colloid stabilizer, biodegradable film-forming material and micro-encapsulating agent in pharmaceutical industry [40]. Glycerinated gelatin is a combination of gelatin and glycerin, which is used as a vehicle to manufacture suppositories. Gelatin is also used as a shaping material in capsule manufacturing. Both hard and soft gelatin capsule's outer covering are made from gelatin. Currently gelatin is included in greater than 1100 drugs registered in the Russian Federation. Of these nearly 71% are capsules and 24%, tablets. Gelatin is also used to produce lozenges, lyophilizates, pastes and powders [41].

3.3 Stearic acid

Stearic acid is a saturated fatty acid with 18 carbon chain, obtained from fats and oils of animal or vegetable by extraction process. Cocoa and flaxseed contain substantial amount of stearic acid [42]. Magnesium stearate is a magnesium salt of stearic acid, which contains two stearic acids and one magnesium. Stearic acid is commonly used as solubilizing agent, emulsifying agent, tablet and capsule lubricant in dosage formulations. Magnesium stearate is the most common lubricant used in the tablet formulations. In tablet manufacturing, a small amount of magnesium stearate will be added to the final homogenous blend. This will coat the powder blend particle surface and limit the penetration of lubricant within the particle matrix. A very minute percentage of steaeric acid and magnesium stearate, typically represents 0.25 - 1.5 % of tablet weight [43].

3.4 Bees wax

Beeswax is a natural product obtained from *Apis mellifer*. The three main types of beeswax products are yellow, white, and beeswax absolute. Yellow beeswax is the crude product obtained from the honeycomb, white beeswax is bleached or filtered yellow beeswax, and beeswax absolute is yellow beeswax treated with alcohol. Beeswax consists mainly esters of higher fatty acids and alcohol. Apart from esters, it contains small quantities of hydrocarbons, free acids and others [44]. Beeswax is separated

from propolis, a resinous material harvested from beehives. Chopped propolis is mixed with de-ionized water and the temperature is adjusted to about 100^{o}C without boiling for one to four minutes. Samples cooled down to room temperature thus the upper layer provide the beeswax, which later extracted [45].

Bees wax is used as a filming agent and modified release agent in pharmaceutical products. Nanotechnological approach was used to investigate the application of natural lipids in preparation of nanostructures lipid carriers. Nanostructures lipid carrier was composed of copaiba oil and beeswax combination and lidocaine used as a model drug. This lipid formulation significantly reduced the cytotoxicity of lidocaine and did not affect the cell viability also showed a sustained *in vitro* drug releasing profile for 24 hours [46]. Beeswax also used in many ointments and creams.

3.5 Honey

Honey is a natural sweet, saccharine substance and viscous fluid produced by hive bee, *Apis mellifera.* Purified honey BP is prepared by melting honey at a moderate temperature, skimming off any impurities which collect on standing, and diluting with water to a weight of 1.35- 1.36 g/ml at 20 ^{o}C. Honey is used as a sweetener to enhance the flavor and viscous of over the counter cough liquids and linctuses. Honey contain many compounds other than sweeteners, including minerals, proteins, and various antioxidants [47]. Honey is also a hydrophilic binder, where increase in honey binder concentration decreased the drug release profile of mefenamic acid tablets, i.e. sustained release behavior was obtained [48].

3.6 Lanolin

Lanolin is a smelly pale yellow natural oil also known as wool wax or wool grease, is secreted by the sebaceous glands of sheep. It has good emollient or soothing properties and widely used as a base for ointments and creams in pharmaceutical and cosmetic industries. Mixing lanoline with vegetable oils or soft paraffin will enhance it's penetrating ability towards the subcutaneous route, thus it is used as a carrier to deliver pharmaceutical drugs subcutaneously. Lanoline is mainly made up of mixture of esters and fatty alcohols, with a small percentage of these alcohols in their free state and combined with a mixture of fatty acids, namely palmic acid and myristic acid [49].

A novel nanoscale-dispersed eye ointment for the treatment of dry eye was successfully formulated using a mixture semisolid excipients lanoline and petroleum. This semisolid excipient was coupled with medium chain triglycerides as a liquid lipid. The nanodispersion was formed by dispersing both phases in polyvinyl pyrrolidone solution. The developed formulation has no cytotoxicity and stable when stored for six months at 4 ^{o}C [50].

3.7 Carmine

Carmine is an authorized food additive used in many foods and pharmaceuticals. This natural coloring matter is extracted from the dried bodies of female insect *Dactylopius coccus* from order Hemiptera and class Arthropoda. Carminic acid (Fig. 8) [51] is a substance found in high concentration in cochineal insects, which deters predation by other insects. It is extracted from the insect’s body and eggs and is mixed with ammonium, potassium, sodium or calcium salts to make carmine dye. A deep crimson dye is extracted from the female cochineal insects, which comes from carminic acid. A brilliant purple, water

soluble coloring matter, which is a C-glycoside, anthraquinine derivative. The pharmaceutical industry uses carmine dye to color pills and ointments [52]. Carmine is found in millions of pink and red medicinal pills, syrups and cosmetics [53].

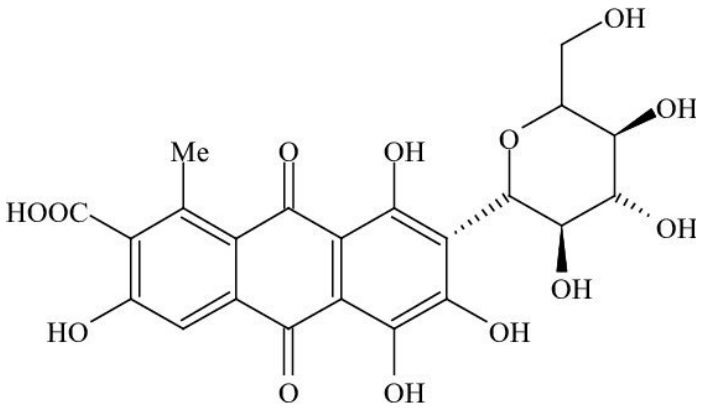

Fig. 9 Structure of carminic acid

3.8 Shellac

Shellac is a resinous natural polymer excretion of the insect *Laccifer lacca* belonging to family Coccidae. It is produced in Burma, Assam and India. The insects live on the juices of plants which are members of the Leguminosae, Euphorbiaceae, Moraceae, Dipterocarpaceae, Rhamnaceae and Sapindaceae. Shellac is chemically similar to synthetic polymers, thus it is considered as natural plastic. It is used widely in the food and pharmaceutical industry, due to its film forming and acid resistance property.

Shellac has alkaline properties therefore shellac-coated pills may be used for a timed enteric or colonic release. Shellac wax was used as a oleogelator to prepare oleogels and oleogel-based emulsions. Shellac gels showed good thermo-reversibility, hysteresis, thixotropy, shear thinning and partial structure recovery. The stability of prepared gel was over 18 weeks and have temperature dependent melting behavior desirable for oral applications [54]. An environmental friendly coating was successfully prepared by modifying the natural shellac with1,3-propanediamine by using ethanol as a solvent. This modified shellac coating showed an improved anticorrosive performance than the natural shellac coating [55].

Shellac is a nonpoisonous natural polymer but using shellac as an enteric coating material has declined due to its poor solubility in intestine, less stability, batch-to-batch variation and need of organic solvent.

4. Conclusion

Marine and animal derived excipients have been widely used in pharmaceutical industry with a wide range of functional diversity. Only those excipients which meet FDA standards can be in cooperated into the medicines and foods. Some of the marine (alginate) and animal excipients (lactose and gelatin) are

extremely important in drug manufacturing and rarely synthetic substances have been discovered to replace them. We cannot exclude these natural excipients in development of novel dosage formulations.

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