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Recent Advances in the Use of Animal-Sourced Gelatine as Natural Polymers for Food, Cosmetics and Pharmaceutical Applications

(Kemajuan Terkini dalam Penggunaan Sumber Gelatin Haiwan sebagai Polimer Semula Jadi untuk Aplikasi Makanan, Kosmetik dan Farmaseutik)

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ABSTRACT

Gelatine is used as an excipient for various pharmaceutical dosage forms, such as capsule shells (both hard and soft), tablets, suspensions, emulsions and injections (e.g. plasma expanders). It is also broadly used in various industries such as food and cosmetics. Gelatine is a biopolymer obtained from discarded or unused materials of bovine, porcine, ovine, poultry and marine industrial farms. The discarded materials can be the skin, tendons, cartilages, bones and connective tissues. Gelatine sourced from animals is relatively easy and inexpensive to produce. The potential needs of gelatine cannot be overemphasised. Rising demands, health concerns and religious issues have heightened the need for alternative sources of gelatine. This review presents the various industrial uses of gelatine and the latest developments in producing gelatine from various sources.

Keywords: Cosmetics; food; gelatine, injections; pharmaceuticals; plasma expanders

ABSTRAK

Gelatin diguna sebagai eksipien (bahan tambahan) dalam pelbagai bentuk dos farmaseutik seperti kelongsong kapsul (keras dan lembut), tablet, ampaian (suspensi), emulsi dan suntikan (contoh: pengembang plasma). Ia juga diguna dalam pelbagai industri lain seperti industri makanan dan kosmetik. Gelatin adalah biopolimer yang diperoleh daripada bahan-bahan terbuang atau yang tidak diguna daripada haiwan ternakan termasuk lembu, porsin, ovin, unggas dan ikan. Bahan-bahan terbuang ini adalah seperti kulit, tendon, rawan, tulang dan tisu penghubung. Gelatin daripada sumber haiwan adalah agak mudah dan murah untuk dihasilkan. Potensi gelatin tidak dapat dinafikan. Permintaan yang semakin meningkat, masalah kesihatan dan isu-isu agama telah meningkatkan keperluan untuk sumber alternatif gelatin. Tinjauan ini membentangkan pelbagai kegunaan gelatin dalam industri dan perkembangan terkini dalam penghasilan gelatin daripada pelbagai sumber.

Kata kunci: Farmaseutik; gelatin; kosmetik; makanan; penambah plasma; sumber alternatif

Introduction

Discovery and development of new active pharmaceutical ingredients (APIs) and excipients have led to the continued interest in drug delivery research. Novel excipients are now being sought and used by pharmaceutical companies to develop new pharmaceutical formulations which can efficiently administer drugs into patients. Pharmaceutical formulation is defined as a composition or combination of an API along with excipients to finally produce a pharmaceutical dosage form. This dosage form is known as drug or medicine. An API is a component that provides or causes the necessary pharmacological effect of a particular drug. Various chemicals or biological entities can stand as APIs in drugs or medicines. Excipients, on the other hand, are usually inactive components of a formulation and are also known as additives. Excipients serve specific purposes such as binders, disintegrants, diluents, lubricants and colourants. They are even used as drug release modifiers to promote or aid the process of drug delivery (Bhattacharyya et al. 2006; Dangi et al. 2011; Organization 2015).

Agro-sourced polymer materials such as animal-sourced polysaccharides and proteins are now used extensively as excipients for pharmaceutical formulations and are produced in a carefully controlled environment. Polymers are macromolecules made up of covalently bonded monomers which may be linear, branched, or cross-linked with other chains. These are based on natural or synthetic polymers (Ige et al. 2012; Rastogi & Samyn 2015; Yadav et al. 2015). The common natural polymers are polysaccharides (chitosan, starch & alginates) and proteins (gelatine & silk)

Besides the pharmaceutical industry, these excipients are also utilised in various other industries which include food, nutraceuticals, cosmetics, beverages and agriculture. They are also employed in chemical engineering, forensic science and recreational applications. Figure 1 shows the

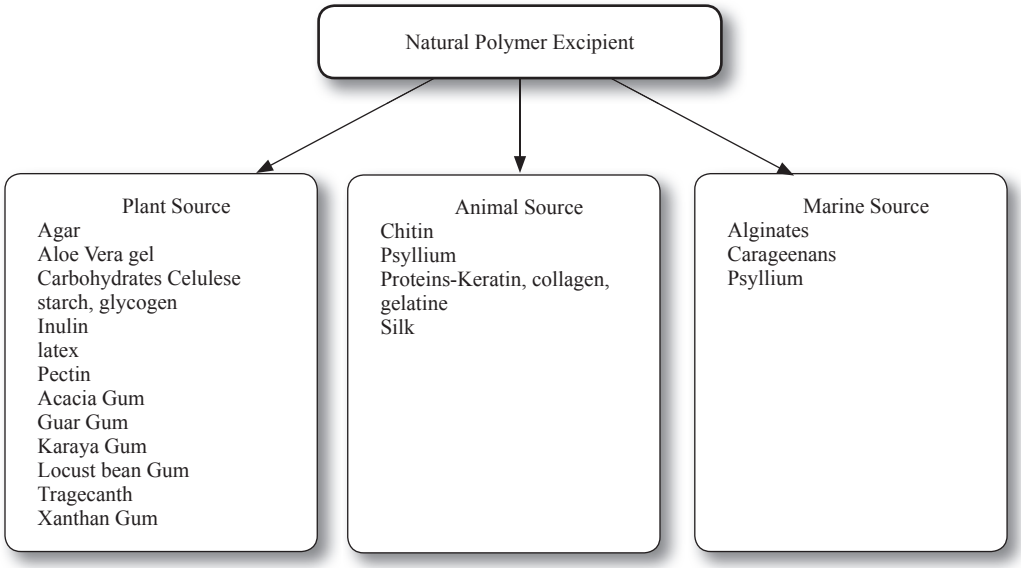


FIGURE 1. Classification of natural agro-sourced polymers

types of natural agro-sourced polymer materials which are commonly used as excipients.

Table 1 lists the materials which are effectively resourced to sustain the growing global need for safe and consumable excipients. These materials are given the specific term 'generally regarded as safe' or GRAS. Although excipients are costly additions, they are central to enhancing the final presentation of any pharmaceutical products. Thus, the drive for cheaper sources of these materials is important to positively influence the market price or economic development of the finished products. Basically, an increase in price of currently available excipients is due largely to acute shortage or undersupply of the appropriate raw materials. The overall pharmaceutical excipient demand is expected to grow at a stable rate of about 6.1% from 2016 to 2021, which is about USD8.1 billion in 2021 and estimated world excipient market volume to reach 728.4 kilo tons by 2020 (Markets 2016; Reports 2016; Research 2016a). There is even a confirmation of the global pharmaceutical excipient growth, indicating to reach USD9.3 billion by the end of 2020, growing at a CAGR of around 7.2% from 2014 to 2020 (Intelligence 2016). Whereas it was reported in a study, drug delivery technology is targeted to increase the efficiency of drug and proposing improved patient compliance of any types of drug formulations. Its market is anticipated to rise to USD1,504.7 billion by 2020 from USD 1,048.1 billion in 2015, with a steady growth rate at a CAGR of 7.5% from 2015 to 2020 (Markets 2015). Excipients used in injections or parenteral preparations alone are expected to rise at a strong pace through 2018. Examples of agro-sourced excipients used in parenteral formulations are lactose and gelatine (Dangi et al. 2011; Thassu et al. 2007; Walker 2015).

Gelatine is basically sourced from animal protein and utilised for various applications since 16th century during the late Ming and early Qing Dynasties in China. Commercial manufacturing of gelatine was introduced since the mid-17th century in Holland. By the late 18th century, which is during the Napoleonic era, claims were made about the food value of gelatine and this led to its manufacture in France. It is non-toxic, water soluble, biocompatible, inert excipient and an economical polypeptide source. Its functions as a valuable biologically active and irreplaceable auxiliary ingredient especially in parenteral products for the pharmaceutical and cosmeceutical industry are due to its viscosity, high mechanical strength at different concentrations. It is also believed to increase the number of red blood cells and haemoglobin thus, the promoting hematopoietic function (Liu et al. 2014; Nongxuan 2016). Gelatine is a mixture of heterogeneous high molecular weight protein derived from fibrous collagenous material such as bones, cartilages, connective tissues, skin, and tendons of animals (Ha et al. 2013)(Ha, 2013 #242). Gelatine production worldwide is worth about US$1.8 billion in 2013 and is estimated to rise even further by 2020 to about US$3.0 billion, with a growth rate at about 7.5% CAGR from 2014 to 2020 (Research 2014). Therefore, to sustain the usage, there is an urgent need for new alternative sources of gelatine, which are economical, abundantly and sustainably available for the potential growing demands in the various aforementioned industries.

Further extensive research is being carried out to date for the various manufacturing, refining gelatine production techniques and its applications from alternative sources (Gómez-Guillén et al. 2011; Ivanova et al. 2014; Mariod & Adam 2013; Mariod & Fadul 2015; Wray & Kaplan 2014). The results of these researchers could hopefully shed light on uses of alternatively sourced gelatine for its excipient or API usage (Gorgieva & Kokol 2011; Li et al. 2009; Malafaya et al. 2007; Nur Hanani et al. 2014; Paguirigan & Beebe 2006; Rose et al. 2014; Rottensteiner et al. 2014; Su & Wang 2015; Zhao et al. 2016).

Gelatine sourced from poultry by-products, for example, is an interesting option and is now extensively studied. Malaysia being a self-sufficient poultry meat production country shows an expanding output, which is

TABLE 1. Materials resourced from animal source as natural excipients and its applications

Types of natural excipients	Animal source	Type of material from natural source	Uses/applications
Beeswax	Honey bees	Honeycomb	emulsifiers, thickeners or stiffening or hardening agents and polishing agent, treatment for allergy, haemorrhoids, stimulate hair growth, antiseptic and anti-inflammatory properties, emollient properties and preventing and treating stretch marks, anti-ulcer agent, wax agent
Chitosan	Shrimp, crab, lobster and other shellfish	Exoskeleton or shell	Binding agent, coating/ film forming agent, controlled release/slow/sustain release agent, bioadhesive polymer agent, absorption/permeability enhancing properties thus used in ocular, nasal, buccal, gastrointestinal, peroral, vaginal, and transdermal drug delivery vehicles, diluent, disintegrant, mucoadhesive, tablet binder, viscosity increasing agent
Cochineal	Insect Dactylopius coccus family Dactylopiidae living on cacti	extracted from body and eggs and mixed with aluminium or calcium salts to form carmine dye	Colouring agent or colourants
Cantheride/ Cantharidin	Insect Hycleus lugens or blister beetle/ Lytta vesicatoria or Spanish fly	Body fluid of insect	Blistering agent
Honey	Honey bees	Honeycomb	Sweetening agent, antioxidant, anti-inflammatory, moisturizer, demulcent, antiseptic
Lactose	Cattle, Sheep, Goats	Milk	Binding agent, diluent, filler agent, dry powder inhaler carrier, disintegrant,
Lanolin/wool fat	Sheep	wax secreted by subaceous glands	Emulsifier or emulsifing agent, ointment base.
Lecithin	Chicken egg, soyabeen, peanut, sunflower, rapseed.	Egg yolk, corn or ground oil	Emollient, emulsifying agent, solubilizing agent, suppository base
Lard	Porcine	visceral fat deposit surrounding the kidneys and inside the loin	Ointment bases
Musk	Musk deer, Moschus moschiferus Linn. Family: Cervidae	dried secretion from preputial follicle	Perfumery agent
Spermaciti/ spermaceti	Whale of Physeter microcephalus Linn.	Head of sperms of whale	Emollient, stiffening agent, ointment/emulsion base
Suet/ tallow/ stearic acid	Sheep, cattle	Hard white fat around kidneys and loins	granulating agent, emulsifying agent, solubilizing agent, lubricant, softening agent
Shellac	tiny lac insect Laccifer lacca Kerr. (Kerria Lacca) Family Lacciferidae (Coccidae)	resinous protective secretion	Coating agent in tablets, micro-encapsulation, control release preparation, In cosmetics binding agent for lipstick, lacquers, nail polishes, eye shadows. In food for preparations of chocolates, lozenges, coffee beans
Gelatine	Bovine, Porcine, Ovine (sheep), Caprine (goat) and fish	Bones, skin, hide	Stabilizer, coating/film-forming agent, gelling agent, suspending agent, binding agent, viscosity-increasing agent, clarifying agent, suppository bases, vaginal drug delivery, regenerative joint cartilage, maintenance of skin health

in line with expectations for domestic demand growth. The chicken meat consumption rate is about 40 kg per year, per capita consumption. Hence, with the average growth of 1.5-2% in per capita consumption, it is projected that the poultry meat production will rise to 5-13.4% by 2017-2018 (Abdullah et al. 2016; Chowdhury et al. 2014; Poultry 2014; Site 2015). The tremendous growth in poultry production is due to the shifting of consumer preference

resulting in an increase in demand of poultry livestock and by-products (Rustad et al. 2011).

This review presents new alternative sources of agro-based gelatine that may be useful in fulfilling the current needs for downstream agro-based products.

Gelatinein Generic or Biosimilar Pharmaceutical Formulations

Pharmaceutical formulations are divided into originator or innovator products. Innovator drugs are newly-developed pharmaceutical formulations which are usually patented by the founding pharmaceutical companies or originators. Generic and/or biosimilar pharmaceutical formulations, on the other hand, are pharmaceutical products produced by non-originator companies from formulations with expired patents. Both generic and biosimilar should not differ from the referenced or original product 'approved before' and 'on market' and is expected to have substantially similar clinical results (in terms of safety profile and efficacy) (Wang 2011).

The use of entrepreneurial biotechnology and genetic engineering has made biological products to be sophisticatedly developed drugs. Biotechnological advancement has managed to introduce these products such as insulin, human growth protein somatostatin, hepatitis B vaccine and others to be introduced for human medical treatment. Manufacturing of these products into generic drugs is now rather difficult as the processes involved are highly specialised. Making a generic version of it is thought to be impossible, so much so that patenting the biotechnologically developed drug would be considered sufficient for research advancement. But now, as the patents have expired and with the progress of pharmaceutical development, copies of these biological products were found to be available. Thus, bringing forth a new type of class called biosimilar drugs. A biosimilar has an additional characteristic in which it is a biological product and is produced in or from a living system and is manufactured through processes that are reproducible, consistent, having the same safety, potency, and purity as the originator product.

The difference between formulations of a particular biosimilar product may be due to the presence of differing excipients added. Biosimilar products formulations should be 'highly or nearly similar' even though there are minor differences in the use of excipients or similar excipients from a different source (Niazi 2016; Roger 2006). The difficulty for developers of any biosimilar is that there is usually no direct access to originator companies' proprietary data. Therefore, the developer of a biosimilar, has to purchase the reference medicine from a pharmacy and then purify the drug substance, and engineer a process to produce the biosimilar that is, the development of a biosimilar requires the establishment of a new manufacturing process 'from scratch'.

Due to the complex production method of biological medicines, the active substance may differ slightly between the biological reference and the biosimilar medicine. 'Slight' differences can have a major impact (Prugnaud & Trouvin 2012; Sekhon & Saluja 2011). For example, in demonstrating the biosimilarity of two plasma expanders in which a new biosimilar is formulated using bovine gelatine while the referenced product uses a different gelatine source as well as different methods of processing as compared to conventional processes. The results showed slight differences in characteristics may be found in these products. The new product can still be regarded as a biosimilar to the referenced product as long as the differences are within acceptable range as designated in standard pharmacopoeias (Saw et al. 2012). A new drug or medicine and having/demonstrating similar or within acceptable range of pharmaceutical characteristics to the originator products are further compared through bioequivalent studies (Dunne et al. 2013).

The World Health Organization has defined a generic drug as a pharmaceutical product, usually intended to be interchangeable with an originator or innovator product that is manufactured without a licence from the originator or innovator company and marketed after the expiry date of the patent or other exclusive rights. Whereas US FDA has further defined generic drug as a drug product or pharmaceutical drug that is comparable or equivalent to a brand name product/reference listed drug product dosage form, strength, route of administration, quality, performance characteristics and intended use. Thus, it can be said that classifying any generic drug will depend on its 'active pharmaceutical ingredient or API' (as mentioned earlier) and is the main functional chemical that has or gives the desired biological effect.

A biopharmaceutical is also known as a biological medicinal products defined as any pharmaceutical drug product manufactured using biotechnology, in or extracted from or semi-synthesised from biological sources and different from chemically synthesized pharmaceuticals which includes vaccines, blood, blood components, allergenics, somatic cells, gene therapies, tissues, recombinant therapeutic protein and living cells used in cell therapy and composed of sugar, proteins or nucleic acid or complex combinations of these substances or may be living cells or tissues. It can further be explained as biological products or biopharmaceuticals, is a class of drugs based on proteins having a therapeutic effect. They are isolated from natural sources such as human, animal or microorganisms and are differentiated due to the presence of large molecule size API (MW $\geq$ 20,000 Daltons).

A biosimilar was known as a generic version of biological drugs or products, has an additional characteristic in which it is a biological product, and is produced in or from a living system, and is manufactured through processes that are reproducible and consistent. Whereas literature suggests that biosimilar is comparable but not identical to the reference product and neither a generic version of an originator product and does not ensure therapeutic equivalence. The difference between formulations of a particular biosimilar product may be due to the presence of differing added excipients. Biosimilar

products formulations should be 'highly or nearly similar' even though there are minor differences in the use of excipients or similar excipients from a different source.

These new products can be regarded as a pharmaceutical biotechnology product or biopharmaceutical proteins or amino acid sequence as the differences are within the acceptable range as designated in standard pharmacopoeias (Saw et al. 2012).

CHEMISTRY OF GELATINE

Gelatine is a naturally occurring, biocompatible protein polymer. It is a stable, heterogeneous mixture of amino acids having a structure, which is very favourable for different chemical modification such as for drug attachment. Gelatine is obtained by thermal denaturation of the protein collagen, which is the structural mainstay and the most common protein in the animal kingdom. Gelatine involves the mixture of heterogeneous high molecular weight proteins, which have gone through a separation or partial separation, or destruction of the rods and chains of the tertiary, secondary and primary structure of native collagens. Hydrogen bonds are destroyed by acid or alkaline treatment of skin, tendons, cartilages, bones and connective tissues from animal sources resulting in the loss of the triple-helix conformation (Figure 2) (Gorgieva & Kokol 2011; Mariod & Adam 2013). During the conversion of collagen to gelatine, random rearrangements of the chains give rise to mixtures of different molecular weight compounds – α-chains (one polymer chain), β-chains (two α-chains covalently cross-linked) and γ-chains (three covalently cross-linked α-chains) (Figure 2) (Totre et al. 2011). Gelatine consists of 85-92% protein, 2-4% mineral salts and 8-12% water. In solution form, gelatine has a unique protein behaviour in which it can be fabricated for its different industrial use by modifying its isoelectric points. The processes applied to obtain the gelatine are differentiated by Type A (acidic treatment) and Type B (alkaline treatment). The availability of these two distinct processes has facilitated to the robustness in the production of gelatine (Gorgieva & Kokol 2011; Totre et al. 2011)

DEMAND FOR GELATINE EXCIPIENTS

Production of gelatine in 2011 was nearly 373,300 tonnes in which porcine skin was the major source (42%) followed by bovine hide (29%) and bovine/porcine bones (27%) (Figure 3)(Research 2015). Gelatine production is expected to continue to grow at a steady rate of 3.8% from 2014 to 2020 and further by 5.3% from 2016 to 2024. The market for gelatine by 2020 would thus be worth at USD3.18 billion and is further expected to reach USD4.08 billion by 2024 as forecasted in the new report by Grand View Research, Inc. report, 'Global Gelatin Market Analysis and Segment Forecast to 2020' and 'Gelatin Market Size Expected To Reach $4.08 Billion By 2024' (Research 2016b). Gelatine use in relation to the gelatine market share for 2013 was highest in the food and beverages sector (28%), followed by nutraceuticals (25.8%) and pharmaceuticals (21%). Its use in the cosmetic industry was 5.5% (Figure 4). The use of gelatine in these industries is expected to increase further by 2020 to about 480,000 metric tonnes, driven

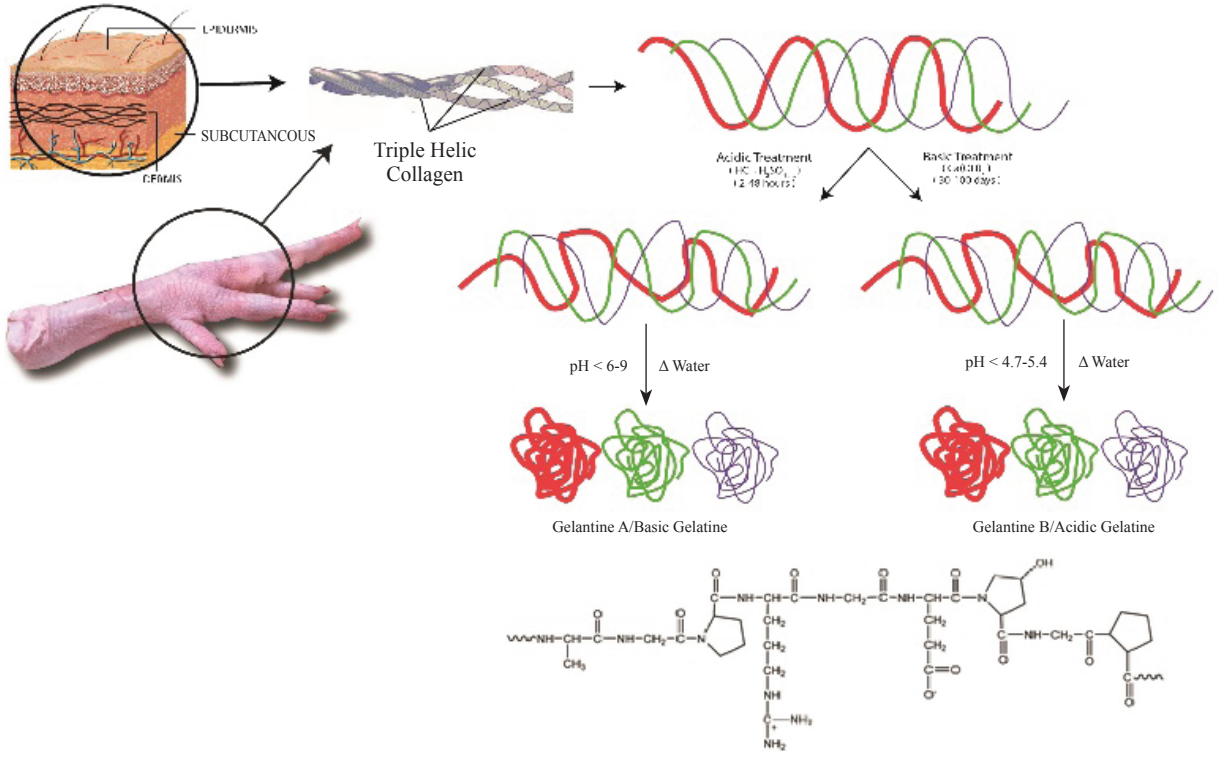


FIGURE 2. The conversion of triple helix of collagen to gelatine and its basic structure (Gorgieva & Kokol 2011)

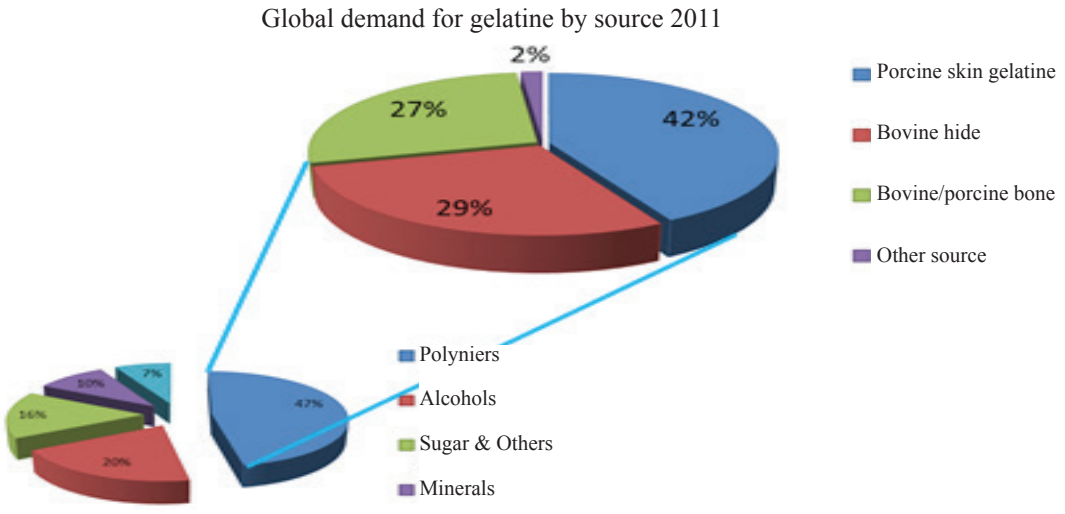


FIGURE 3. Global gelatine demand according to source/raw material in 2011 (Transparency Market Research 2015: Global Gelatin Market to Expand at 6.75% CAGR because of Greater Application Scope in Various End-use Industries http://www.transparencymarketresearch.com/pressrelease/gelatin.htm)

by increasing use of food, drugs and supplements in the pharmaceutical industry (Analysts 2016). Along with the advancements in drug delivery technology caused the evolvement of new excipients as novel dosage forms to fulfil specific functions which directly or indirectly influence the extent and or rate of drug release. This in return enrages the development of new and modified excipient source continue to emerge for better drug delivery performance (Mohamad et al. 2015).

Due to a tremendous increase in demand, there is an expectation of a drop in the supply of raw materials derived from the hides of bovine or porcine, which makes up to 90% of the gelatine source. This shortage of supply was notably cited due to the cost of complying with the new EU Sow Housing Regulations, inflated the cost of production and higher feed prices (Morrison 2012). Other factors that can negatively influence the supply of gelatine are recent weather conditions (lengthy dry spell) as well as stagnated bovine slaughtering and production growth in major gelatine producing countries such as India.

Moreover, prices in China have risen due to stricter production standards and regular inspections imposed after a number of capsules for pharmaceuticals were found to have been produced from scraps of leather containing excessive levels of chromium. Therefore, an exigent exploration into other sources of gelatine is needed. This may include studies into gelatine production from avian or even fish (Abdullah et al. 2016).

The development of alternative gelatine sources provides market opportunities for the industry. Demands in halal gelatine have created a strong influence in this sector. It is expected that the halal food and pharmaceutical industries would grow at about 12% of the total global trade in agro-food and pharmaceutical products (Alqudsi 2014; Sahilah et al. 2012; Shah & Yusof 2014). This growing market is basically due to the projected Muslims population of about 30% of the world's population by 2025 (Karim & Bhat 2008).

Different Types of Gelatine Raw Materials

Gelatine is basically sourced from different biopolymer raw materials such as indicated below:

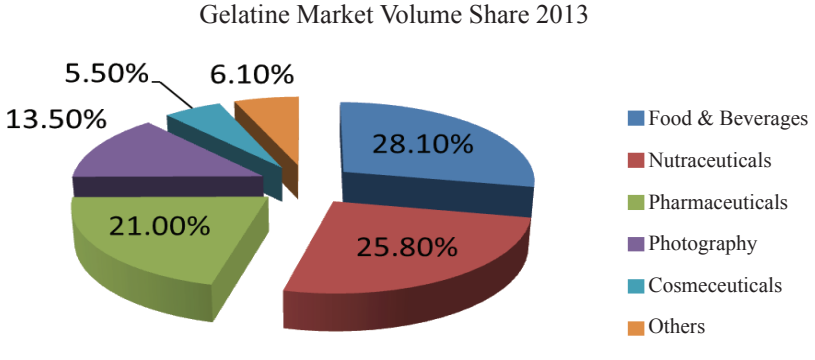


FIGURE 4. Global gelatine application in various industrial applications - 2013 (Grand View Research, Inc. 2014)

BOVINE

For decades, bovine edible products and by-products, which include organs, fat, skin, feet, bone, blood, abdominal and intestinal contents are mainly produced by slaughterhouses. The literature indicates about 66% of live weights, which are by-products such as skin, bone and feet are utilised as starting material for other industrial products such as gelatine.

Shortage of bovine-based raw materials for pharmaceuticals (which include gelatine) has been a great highlighted in countries such as India, due to religious concerns (Morrison 2012b, 2012c). India has a majority Hindu population (80%) where the religion reserves cows as holy, thus an increase in cow slaughter seems unlikely. Due to this since early 2000, there has been research undertaken throughout the world to find new developing sources due to shortage also in agricultural land, diseases and shift in human consumption for health reasons.

PORCINE

Porcine-based raw materials are one of the biggest sources of gelatine within the gelatine industry. However, due to the European Union's changes to pig farming laws in early 2013, the price of gelatine-based products is expected to increase by 5% because of shortages of porcine skin as well as bovine bones. This is because the farmers would have to spend more on housing the livestock (Morrison 2012a).

Besides religious concerns of the Hindu religion on bovine-based gelatine, Jew and Muslims are also very much uncomfortable about porcine-based gelatine. Jews, Muslims and Hindus represent ¾ of the world population, making the search for alternative gelatine source, which is acceptable to these religious populations, a pragmatic quest. The Halal market alone made about $700 billion in 2013 (Barry 2014).

OVINE AND CAPRINE

Ovine (sheep and goat) is considered as another mammalian source that can be used to obtain gelatine without any religious or even cultural barriers around the world. The global consumption in 2013 was estimated at 8.6 million tonnes whereby the per capita consumption was around 1.2 kg with the global population of 7.2 billion people. Its consumption is mainly concentrated in countries such as China, Australia, South Africa and New Zealand. The total world production of sheep and goat meat has increased from 11 billion pounds or about 500 thousand metric tonnes in 1965 to 18 billion pounds or about 8 million metric tonnes in 2011. China is the largest producer with 4.4 billion pounds or about 1 million metric tons, followed by the European Union (1.9 billion pounds or about 860 thousand metric tons), Australia (1.4 billion pounds or about 635 thousand metric tons) and New Zealand (1 billion pounds or about 453 thousand metric tons). Although world production has increased, demand has increased more than supply and this has resulted in record prices over the past 2 years. The World per capita lamb, mutton, and goat consumption has increased from 3.95 pounds in 1965 to 4.17 in 2007 (Brester 2012).

EQUINE

In China during the Tang Dynasty gelatine was sourced from the hide of *Equus asinus* L. also known as donkey because it was believed the efficacy of donkey hide is the best due to its quality such as hard, brittle and with shiny sections. The fragment is brown and translucent if held up to the light, having a slight odour and slightly sweet flavour. It is consumed as E Jiao herb, a common Chinese herb which has long been used as a blood tonic in traditional Chinease medicine practice such as to replenish vital energy (*qi*) and nourish blood (Liu et al. 2014). Official statistics from the People's Republic of China indicates that 90% of the country's ejiao products are made in Shandong Province which is about 5,000 tonnes. Even though, having constrains in donkey hide production due to the animal's low fertility rate and long rearing period, causes an annual price hike with a great demand for its' gelatine (ShanghaiDaily.com 2016).

POULTRY (CHICKEN)

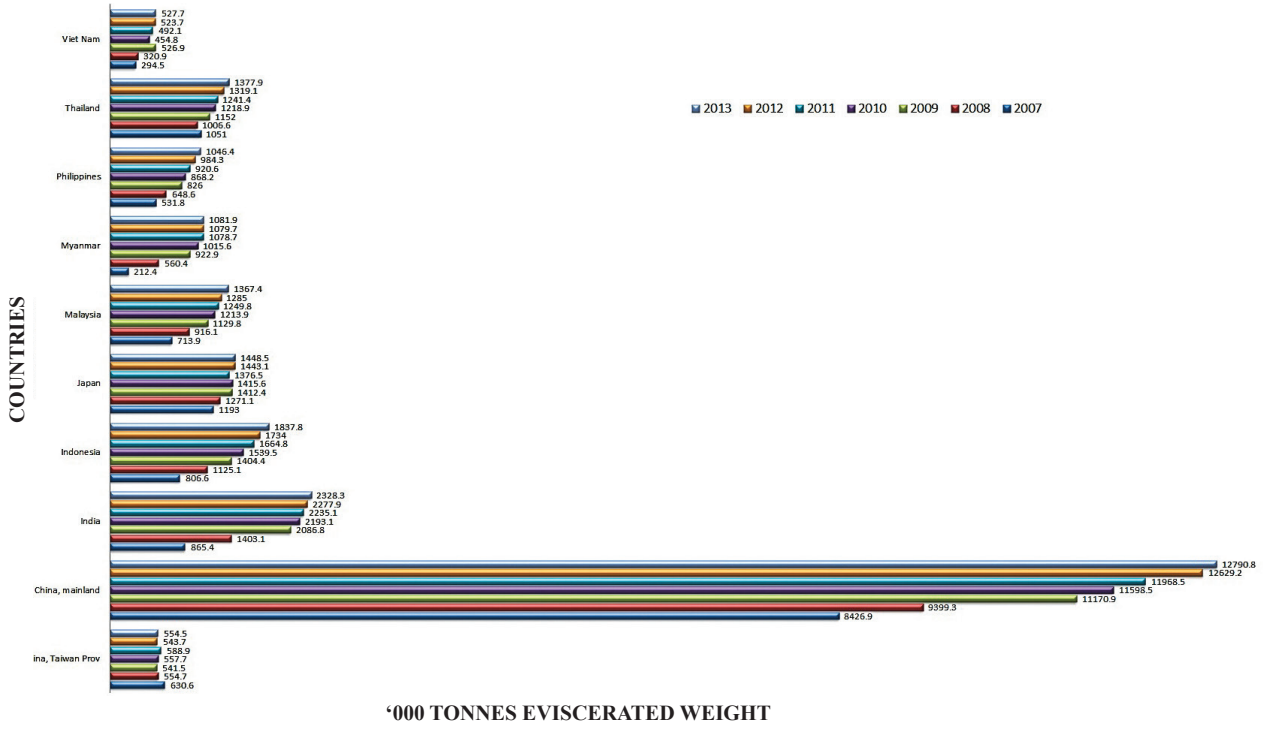
Over the years, there has been a shift in protein source consumption from the known mammalian source, also known as 'red meat' to be considered as healthier poultry, known as 'white meat' such as chicken or turkey. The total world poultry production has seen it growing and even undergoing various difficulties such as 'bird flu'. The estimated production growth in South East Asia is nearly 3-8% as in Table 2. The tremendous growth in poultry production is due to the switching of consumer preference resulting in an increase in demand. This increase of chicken meat consumption is due to the versatility of the meat and also socioeconomic factors such as relatively low cost in comparison to other types of meat, increase in household income, acceptance of chicken meat to most religions and perceptions that poultry meat is healthier than other types of meat (Jayaraman et al. 2013; Norimah et al. 2008; Zhang et al. 2010).

The processing of chicken would lead to enormous amounts of waste materials such as skin, bones and shank which could be used as an essential alternative source for gelatine production. Synergistically, it would effectively improve the waste management of poultry industry and enhance efficient environmental friendliness. This in return, will also help to overcome the increasing demand for gelatine usage worldwide and in-depth research of its physicochemical research which is being carried out due to the pricing and commitments of industrial farmers (Abdullah et al. 2016; Lasekan et al. 2013; Rafieian et al. 2013).

MARINE/FISH

The marine source is also one of the recently being researched as a possible contributor to gelatine alternative to mammalian gelatine, especially fish sourced. One of the major advantages of fish gelatine is that it can be accepted

TABLE 2. i Indigenous chicken meat production in Asia. Global Poultry Trends-Asia Accounts for a Third of Chicken Meat Output by http://www.thepoultrysite.com/articles/3533/.



by people from all religions and not associated with BSE outbreak. Some fish gelatines are available commercially, although they are not well-characterized. Fish gelatine represents less than 1% of total world gelatine output (Irwandi et al. 2009; Wang et al. 2008). Its disadvantages or inability to penetrate the market is due to its sustainable large volume availability of raw material or commitment of fish gelatine producers, difficulty in obtaining certification on raw fish material which is essential for traceability in food additives especially from animal sources, price constrain compared to present source gelatine, inferior rheological or gelling properties, presence of odour and off-flavour of fish gelatine (Karim & Bhat 2009; Schrieber & Gareis 2007).

As compared to the more established mammalian gelatine, literature on the properties of fish gelatine as a pharmaceutical excipient is very limited. Fish gelatine has been studied mainly for its application in food industries and the quest for fish-sourced gelatine is a promising prospect. Aquaculture business in the country has involved many fish farmers and commercial companies practising several types of production systems. However, they almost exclusively use unimproved species and strains. It appears that presently available knowledge and experience in aquaculture systems management are not fully exploited to achieve a sustained yield and optimum fish performance. In this context, the growth and utilisation of genetically improved stocks that are more productive becomes imperative in order to effectively use the resources.

The increase in world tilapia production accompanied by a significant increase in tilapia industry has led to the production of a lot of waste in the forms of collagen-rich skins and bones which could be a valuable raw material for gelatine production (Songchotikunpan et al. 2008). However, hatchery operators and fish farmers in Malaysia, for example, have used the available tilapia strains without discriminating the history, background, performance and pedigree information. Improper brood stock management associated with high level of in-breeding has also ensued in a decline in productivity of cultured populations under various commercial backgrounds. Periodically, the tilapia broodstock has also been imported into Malaysia by private hatcheries. Crossbreeding and hybridisation are mostly practised to improve the strains performance. Traits such as growth, survival rate, body conformation and colour are of primary concerns in producing new hybrids.

At the moment, these wastes are either discarded, causing environmental pollution, or turned into low-value products like fertilisers and animal feeds. Utilisation of tilapia skin gelatine as a pharmaceutical excipient will not only provide an alternative source of gelatine which is accepted by most religions and support groups but also eliminates the scar of bovine spongiform encephalopathy related to mammalian gelatine (Karim & Bhat 2009).

OTHER RAW MATERIALS (EDIBLE INSECTS)

FAO predicts due to nations challenging for industrial development against each other, there will be a reduction in agricultural land, fishery, and nutrients. As most parts of Africa, certain parts of Asia practise entomophagy whereby some communities have reported to consume different kinds of insects as their daily meals. Thus, some experts

have estimated the potential growth due to alternative protein source to animal livestock and its benefits, such as efficiency, lower resources, increase in food security, environmental and economic sustainability (Gahukar 2011; Halloran et al. 2016; Premalatha et al. 2011; Rumpold & Schlüter 2013). Recent studies have been carried out to find an alternative gelatine source which was explored as halal gelatine consisting two types of Sudanese edible insects such as *Aspongubus viduatus* (melon bug) and *Agonoscelis pubescens* (sorghum bug). It was even demonstrated to be used as an ingredient in ice creams. It is considered halal but its acceptance due to religious viewpoint only and mainly in the African continent due to economic growth, steady decline in poverty rates which continues to grapple the food security and undernourishment of their population (Mariod & Fadul 2015; Mariod et al. 2011).

APPLICATIONS OF GELATINE IN VARIOUS INDUSTRIES

Pharmaceuticals Gelatine fulfils a versatility in pharmaceutical industry application due to its unique chemical characteristics and considered as a 'GRAS' drug delivery excipient material in vast pharmaceutical dosage forms, such as pastilles, troches, microcapsules, suppositories, effervescent tablets, sub-coating agents, and constituent in wound care products (Sahoo et al. 2015). In cases, due to severe injuries with heavy blood loss, volume replacement fluid is most sought after such as crystalloids or colloids. Colloidal plasma expanders, especially gelatine as the active ingredient is the most sought after as compared to others in its class due to side effects of the polysaccharide i.e. HES (hexaethyl starch) plasma expanders or even crystalloids. The main reasons are due to its viscosity and molecular properties which are similar to normal blood, that the HES plasma expander due to its complications such as higher molecular weight especially of its third generations which is about 130 kDa. There are newer generation being developed with a lower molecular weight, thus might result in lesser instances of kidney failure. As for now, it is used with or in caution, in medical case to case basis (Lira & Pinsky 2014; Saw et al. 2012; Zarychanski et al. 2013). The reason these volume expanders are administered into the bloodstream via an infusion, is in order to increase the amount of fluid in the bloodstream, thus preventing the onset of hypovolemic shock and stabilising the circulatory system. The body quickly and completely reabsorbs the gelatine within the blood substitutes.

While gelatine is omnipresent, in various pharmaceutical applications, such as oral applications, hard or soft elastic capsules shells, formulation of tablets due to its natural binding, disintegration agent that meets the requirements of concerned consumers about the use of synthetic or chemically modified ingredients. Gelatine is further employed as a viscosity enhancer in liquid and semisolid preparations such as emulsions, a coating agent to encapsulate dry powders which are then released when administered orally, also plays a role in the formulation of prolonged release matrices, can be treated with formaldehyde to produce a gastro-resistant coating (natural protective) and reduce unpleasant taste along with the aroma.

Till todate, there are further research being carried out to improvise the gelatine cross-linking especially for the capsule dosage, in order to improve their shelf life at high temperature and humidity. This new technology, even allows the pharmaceutical industry to explore new capsule fillings and expand their distribution into regions that are exceptionally hot and humid.

The chalky, unpleasant, inconvenient and bad tasting traditional medicinal products are delivered by an alternative delivery method or dosage form as gelatine gummies for children's vitamins and minerals. Thus, at present due to its market growth now, its expanding further into the adult dosage form category.

Cosmetics and cosmeceuticals Cosmetics and cosmeceutical segment was identified as the largest application of global collagen peptide market, with a total volume of over 4,000 tonnes, in 2013 (Research 2014). Recently gelatine used in many cosmetics and healthcare products such as collagen in tropical cosmetics creams due to its anti-aging properties or wrinkle reducer or stretch marks, along with replenishing and rejuvenating the skin, which accentuated its use in cosmeceuticals products. Hence, accretion growth in its market share of cosmeceuticals as an ingredient in face creams, body lotions, shampoos, hair sprays, sunscreens bath salts and bubbles.

This is due to dermatologically tolerated, effective moisturiser and film-forming properties help in collagen depletion, which usually starts around the early age in humans and continues to accelerate further as cellulite. Moreover, for many years, it has been used in the cosmetics industry as 'hydrolysed animal protein' as hair conditioning agent in shampoos, conditioners, lipsticks and fingernail formulas and it helps to maintain hair thickness or strength. Whereas for other cosmetics products such as face mask, it can smoothen and strengthen skin texture. But due to recent developments and most peoples' misunderstanding/ misconception, its use has decreased considerably as more brands move away from formulating cosmetics with animal-derived ingredients.

Food Gelatine has numerous benefits in the food production as it is the main source for excellent protein supplement as contains amino acids for body cells and tissue nourishment for improvement such as hair quality, growth, texture and skin health by providing more or less elasticity, low in calories, free of cholesterol, sugar and fat. Consuming gelatine or collagen directly can help improve appearance due to its effects on skin health and cellular rejuvenation by stimulating new and non-fragmented collagen thus making it useful as an anti-ageing substance. It is easily digested thus, is used as an excellent gelling agent, binding, or glazing agent for the preservation of fruits and meats (Varela & Fiszman 2013). It is also used as film coatings to improve appearance or texture of food, reduces water loss, heal digestive disorders, clarification of beverages and juices. It is further used in

the production of jellied desserts and confectionery such as ice creams, yoghurts, chewy toffees, marshmallows, sauces and countless other food products (Baldwin et al. 2011; Schrieber & Gareis 2007). As the food industry develops the dietary supplements are now given more focus by athletes in order to maintain their weight and providing energy before workouts. Therefore, nutritional bars containing gelatine are given much more emphasis.

Daily consumption of certain amounts of gelatine has shown improvement of nail strength and growth rate. Whereas for joint and bone health, it reduces joint pain related to arthritis. According to the Gelatin Manufacturers Institute of America, there are other food items that contain gelatine. They are fruit chews, gummy snacks, gum drops, marshmallows, puddings, ice-cream, yoghurt, cream pie and wafers. Commercially baked cupcakes and frosted fruit tarts frequently contain gelatine, as well. This is due to its ability in providing varying degrees of texture and elasticity it is able to replace partially the high-fat content in many products. The development of many of the low-fat products, such as half-fat margarine, fat-reduced cheese and yoghurt varieties, can be found in most food products.

Its consumption is also suggested as a sleep aid due to the presence of glycine, which helps to improve sleep cycles by stimulating certain neurotransmitters and enzymes which in turn increases the quality and duration of sleep. Proper sleep cycles and rest for the body is important for the general function and metabolism of the body, in order to help muscle building in many ways for the athletes.

Lately, there is further research being carried out to use gelatine as development as food packaging materials incorporated with natural antioxidants and antimicrobials thus having the same principal as film forming application in food products to extend food shelf-life and reducing food loss (Etxabide et al. 2017; Nur Hanani et al. 2014).

Tissue Regeneration or Engineering Tissue regeneration or engineering is considered as restoration and is a significant alternative solution for the treatment of traumatised, damaged or lost tissue, bone and cartilage or organ failure. It has brought a new paradigm shift and cutting edge for the healing of musculoskeletal conditions. It is carried out by implanting a natural, synthetic, or semisynthetic tissue, bone or organ which mimics as a fully functional, from the start or that grows into the required functionality. Development of tissue regeneration or engineering is divided into three basic elements that are cells, biodegradable scaffolds and growth factors. Gelatine plays a crucial developmental role as a biomaterial for the use as an artificial valve, bone and tissue regeneration due to its less immunogenic compared with its precursors. Its chemical modification has enormous potential, with suitable characteristics in the development of new nanomedicines and biomedicines. The modification of the gelatine protein biopolymer is based on the transformation of the carboxylic group into amido groups after their reaction with polyamines. Basically, it is due to the presence of informational signals like the Arg–Gly–Asp [RGD] sequence, helps promote cell adhesion, migration, differentiation and proliferation (Hoque et al. 2015; Lopez-Cebral et al. 2011; Persidis 1999; Silva et al. 2010; Zhu & Marchant 2011) This gelatinous mixture resembling similarly to tissues in the extracellular environment, plays a vital role as scaffolds for cell differentiation, tissue vascularization, angiogenesis and regenerate cartilage.

Further research is being carried out using crosslink with gelatine in ocular applications such as repair of the ocular components, used as a composite sponge providing sufficient structural support to the defect bone sites while enhancing the body's own reparative capacity and orthopaedic application such as osteochondral repair in a rabbit osteochondral defect model, whereby gelatine or collagen is the popular biomaterial choice. It has also been used in other areas such as bladder, skin and airways. The combination used in bone tissue engineering scaffolds with drug delivery capability, is increasingly researched as gelatine plays a vital role as a drug carrier to tissue sites, thus ultimately eliminating the need for autologous tissue harvesting or repeat operations (Mazaki et al. 2014; Mouriño et al. 2013; Murphy et al. 2013).

Conclusion

This review provides an overview on the importance of alternative sources for gelatine in food, cosmetics and pharmaceuticals. As the consumption or demand is increasing the raw materials required to produce gelatine become exhaustive, alternative source of gelatine having similar characteristics and properties as to presently available gelatine products is very much needed and has to be further researched. Furthermore, gelatine from *Gallus gallus domesticus* can be a good alternative source of animal protein to be used either as an excipient or as an active ingredient of a drug formula. It can also help the industry economically where wastage is reduced, and usage enhanced using newly developed and improved technology. Sustainable growth at present world consumption rate can also be guaranteed.

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