Scientific Bulletin. Series F. Biotechnologies, Vol. XXIII, 2019
ISSN 2285-1364, CD-ROM ISSN 2285-5521, ISSN Online 2285-1372, ISSN-L 2285-1364

TRENDS ON PHARMACEUTICAL PACKAGING MATERIALS

Denisa CIOTEA, Mona Elena POPA

University of Agronomic Sciences and Veterinary Medicine of Bucharest, 59 Mărăşti Blvd., District 1, 011464, Bucharest, Romania

Corresponding author email: denisa.ciotea@gmail.com

Abstract

Filling and packaging are very important processes in the pharmaceutical sector. Packaging is important as it provides protection of the dosage form, from the environment and keeps them safe until is opened by the customer. Environmental sustainability has to be also taken into account in this field. Pharmaceutical packaging materials should be eco-friendly. These materials are derived from natural resources, like plant or animal derived proteins, cellulose, starch etc. A type of primary packaging material is the capsule. It has the advantage that provide a slippery, smooth and a tasteless shell. This article is reviewing various aspects of eco-friendly pharmaceutical packaging materials, as: types of packaging materials like capsules as well as recent trends of pharmaceutical packaging in pharmaceutical market.

Key words*: eco-friendly, packaging material, pharmaceutical products.*

INTRODUCTION

In general, the pharmaceutical formulations have three important constituents as: the active part, excipients and the packaging material. The active ingredient is the pharmacological active substance that is generally preserved by excipients and packaged in a packaging material (Kumar, 2013)

The packaging materials should prevent the product from damage, such as light, foreign particles, temperature, atmospheric gases, microorganisms and moisture.

One of the key characteristics of packaging materials is to protect the pharmaceutical formulations from leaching, loss of any volatile material and loss or gain of water from the content.

Packaging should prevent mechanical hazards like shock, compression, abrasion, vibration and perforation. The packaging materials should not react with the product and should be able to preserve the product throughout the shelf-life (Kim et al., 2014)

MATERIALS AND METHODS

The primary, secondary and tertiary packaging of pharmaceutical products constitutes an essential element of the technological procedures. The quality control of packaging material has been done by the quality control department. They examine and analyse the sample and report it as approved or rejected.

Primary packaging is the term used to indicate that the packaging is in contact with the pharmaceutical formulations. The stability of the pharmaceutical formulations mainly depends on the packaging material because it is in direct contact (Campbell & Vallejo, 2015). A few examples of primary packaging containers are vials, ampoules and capsules.

The secondary packaging has two goals: to protect the primary packaging and the product, and it never comes in direct contact with the product. The secondary packaging is visible to the consumer and it contains information such as the name of the product, the usage, the ingredients, fabrication and expiration date as blisters, boxes (Kassarjian et al., 2014).

Tertiary packaging is removed by retailers before products are arranged for sale. The consumers don't see the tertiary packaging. The tertiary packaging containers protects the product from the damage which may occur during the shipping transportation from manufacturer to market or drugstore (Kerry, 2014). Examples of tertiary packaging materials: carton box, wooden box.

Monies and Dublane are credited with the invention of the gelatin capsule. In December of 1834 they patented a method for producing a single-piece, olive shaped, gelatin capsule, which was dosed after filling, by a drop of

concentrated warm gelatin solution. Capsules become a popular formulation because of their advantage of use as: slippery, smooth and a tasteless shell. The main advantage of capsules is that they have not unpleasant taste like tablets. Due to an inexpensive production process, they are produced in large quantities and in a wide range of colors. Capsules provide a ready availability of the compounds. Capsules are not usually used for the administration of extremely soluble materials such as potassium bromide, potassium chloride or ammonium chloride, since the sudden release in the stomach could be irritating. The dehydration of compounds could be prevented by using small volumes of inert oils in the powder mixture.

Capsules are pharmaceutical formulations made of coatings containing unit doses of active substances, associated or not with excipients, such as: solvents and lubricants. Capsules are used for oral administration. The gelatin and starch used to prepare the capsule shell as well as the substances used to adjust the consistency of the capsules must fit with the Pharmacopoeia guidelines or other quality standards like ISO. A few examples of other excipients are the opacity agents, surfactants, fragrance substances, coloring agents and preservatives. Capsules can be engraved. The contents of the capsules may be solid, liquid or solid paste. The content must not damage the coat after administration, when is attacked by the digestive juices when the capsule releases the content.

In the formulation, the talc must be at most 3%, stearic acid not more than 1%, magnesium or calcium stearate not more than 1% and aerosol not more than 10% of the weight of the capsule content. Depending on the nature of the coating, there are different types of capsules:

- gelatinous (hard and soft) capsules;
- modified released capsules;
- amylaceous capsules (cassettes).

Hard gelatin capsules (opaque capsules) are prepared from gelatin. Gelatin is a heterogeneous product, derived from treated animal collagen. Common sources of collagen are frozen pork skin and animal bones. Skin and bone collagen are available in most areas of the world. Type A gelatin is derived from a precursor and has the isoelectric point in the region of pH = 9, whereas type B gelatin has its isoelectric point in the region of pH = 4.7. In practice, hard capsules are produced from the mixture of skin and bone gelatins. This gelatin has a high strength and it produces a tough, clear and a firm film. They are in the form of elongated cylinders, rounded to the heads that are inching through the boot. They usually contain mixtures of substances in the form of powders or granules.

Soft gelatin capsules (pearls) which consist of a continuous and soft gelatin coating have a spherical or oval shape. They contain active substances in the form of paste or solids in solution. Gelatin capsules have a thicker coating than hard capsules. The capsule shell is composed of gelatin, a plasticizer, water, preservatives, coloring agents, opacity agents and flavorings. The shell may contain also active substances. Gelatin should not contain more than 15 ppm of iron. In soft gelatin capsules is used as plasticizers glycerin, propylene glycol and sorbitol. Glycerin and propylene glycol cannot be the major constituents of the capsule content, because they have softening effect on the gelatin shell, which can make the capsule more susceptible to extern factors like humidity and heat. Soft gelatin capsules can be classified according to the ratio between glycerin and gelatin in hard (0.4/1), medium (0.6/1) and soft (0.8/1). Gelatin capsules are generally formed, filled and closed by a single operation, but in some cases for extemporaneous use, the shells can be prefabricated. Liquid substances should be homogenous and air-free before they are included in the capsule, and solid compounds are generally dissolved or dispersed in a solubilizer, to obtain a solution or a dispersion of the consistency of a paste. All these substances should be formulated to produce the smallest possible capsule containing the maximum ingredient and physical stability, therapeutic effectiveness and production efficiency. The active ingredients are mostly oily, and they derive from vegetable oils (soybean oil, sea buckthorn oil), mineral oil and fish oil. These ingredients also function as solvents in vitamin capsules. Oily matrix do not retain moisture, water do not pass from the shell of the capsule into the fill material and out during the manufacture and drying of this

capsule. Depending on the nature of the substances (water miscible and volatile liquids) and the contact surface, it can cause a partial migration of the constituents from the content of the capsule in the capsule case and vice versa. Modified released capsules are hard capsules or gelatin capsules, whose contents, coating or both components contain special excipients, or they are made by special methods, in order to change the speed, place or time when the active substance will be released. Modified released capsules include extended release capsules and delayed release capsules.

Amylaceous capsules (cassettes) are solid preparations, made of a hard shell. These cassettes contain one or more active substances prepared from starch. They are flat cylinders whose diameters, slightly different in size and allow their closure by overlapping and gentle pressing. They contain substances or mixtures of powdered substances. Before administration, the cassettes are soaking in the water for a few seconds and then put on the tongue and swallow with water.

Constant innovations in the pharmaceutical industry have a direct impact on the packaging. Traditionally, medicines on the pharmaceutical market could be found in different shapes like tablets or capsules packed in blister packs or bottled into plastic pharmaceutical bottles.

Oral tablets are available in a wide range of different shapes, colors and sizes as we can see in Figure 1.

Figure 1. Oral tablets as: hard gelatin capsules colored in white, beige and green; soft gelatin capsules colored in red-garnet

Humidity and light are factors which degrade the packaging materials and also the capsule and active ingredients. Packaging of oral tablets should be easy to dispense, child resistance but in the same time adult-friendliness. Packs must also be easily recognizable by aspect, functional and hermetically sealed.

In our lifestyle the blister packs ensure hygiene and they offer convenience. Blister packs are ideal in our quick rhythm lifestyle and because of that there has been a large increase in their use across the years. Indeed, blister packaging has provided the best worldwide growth among all pharmaceutical packaging products. Pharmaceutical producers confront with cost pressures during the packaging process and also with the production process. It should be a challenge to build efficient, user friendly and easy to operate packaging machines (Kunal, 2012)

All packaging materials must be tested on stability studies. Packaging of pharmaceutical products plays a very important role in the maintenance of their quality. Eco-friendly packaging materials are packaging that uses environment safe materials in its production. These eco-friendly materials should not harm the environment and should be marked with eco-labels (Bird, 2009). For example, eco-friendly packs include paper which is recycled and corn starch because is biodegradable in nature.

Corn starch is used as an eco-friendly pack in different products including bags, boxes and trays. Corn starch is an alternative material to plastic because it has similar functional properties and it's biodegradable. When the product is in the market it is very difficult to be rebuilt so the changes should be made in an early stage of the development (Edward, 2009).

Greener packaging designs accomplish the needs of most pharmaceutical producers without sacrificing our environment. Packaging materials are manufactured and designed to allow recycling. The percentage of recycling depends on the weight or on the minimum calorific value. Eco-friendly packaging should be modernized, biodegradable, well-designed, easily recyclable or reusable (Bird, 2009).

Eco-friendly pharmaceutical packaging materials have two concepts: the first is that the material should be recyclable and the second is

that the material should be biodegradable. Some products are also enhancing their brand image by adopting this type of eco-friendly pharmaceutical packaging because is one of the hottest trends (Hunt, 2010).

Eco-friendly pharmaceutical packaging materials can be classified in several ways: based on their uses, based on the chemical constituent and polysaccharide content.

Based on their uses, the packaging materials should have a barrier protection which provides protection against moisture, light, oxygen and temperature variations, the biological protect-tion provides protection against biological contaminants, the physical protection ensures protection against any physical damage. The information communicated on the packs should offer to the consumer information about the correct usage of dosage forms, their prove-nance, their side-effects and warnings. The eco-friendly pharmaceutical packaging should have security protection from small children and against counterfeiting.

Examples of eco-friendly packs:

Starch is an eco-friendly polysaccharide and a widely available raw material. Starch is obtained from various sources like cereals and legumes. The most known source of starch is potato, corn, wheat and rice (Weber, 2000). Starch is used for flexible or rigid packaging, bags and sacks. Since starch packaging mate-rials are fragile in nature, when a high concen-tration of starch is used, various biodegradable plasticizers like glycerol and other low-molecular weight polyhydroxy compounds, polyether and urea are added. Plasticizers inhibit the microbial growth by lowering the water activity. These four types of starch based on the polymers types are thermoplastic starch products, starch synthetic aliphatic polyester blends, starch-Polyvinyl alcohol blends and starch polybutylene succinate (PBSA) polyester blends (Edward, 2009)

Cellulose is a linear polymer which is found abundantly in nature. Cellophane is the most common cellulose-based biopolymer. Methyl and ethyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose and cellulose acetate are cellulose derivatives used for packaging. These are widely used in pharmaceutical packaging (Weber, 2000).

Xylan is naturally found in plant cell walls and algae**.** It forms a group of substances called hemi-cellulose. Xylan is a biodegradable, compostable and eco-friendly derivate. Xylophane is thus used as an environment friendly packaging material.

Chitin is the second most abundant polysaccharide resource after cellulose. It is found in the exoskeleton of invertebrates. Chitin is used in packaging because it has antimicrobial property, protects the product from unnecessary microbial growth and it maintains the preservative action. Heavy metal ions are absorbed by the chitin. Chitin is mostly used as packaging material in edible coatings (Srinivasa & Tharanathan, 2007)

Protein. A protein is formed of repeating units of amino acids. Protein based materials are derived from agricultural materials or agro-packaging materials that are renewable and biodegradable and they are used in edible packaging. Agro-packaging concept refers to the use of renewable products and control of the end products. Numerous animal proteins and plant proteins are commonly used as raw material for agro-packaging materials. Thus proteins can be split into plant origin proteins (e.g. soy, gluten, pea, potato etc.) and animal origin proteins (e.g. casein, whey, collagen, keratin etc.) (Platt, 2006).

The point of eco-friendly packaging materials is the decrease of the amount of packaging material which ought to be effectively biodegradable, nontoxic, reusable and inert. Recycling of materials like aluminum, paper and glass creates less or no waste and they are environmentally safe. Incineration of pharmaceutical packaging is recommended to eliminate the contaminated packs. The plastic materials that cannot be recycled are therefore incinerated. The recycled materials (glass and metal) are considerate safer for formulations against microorganisms (Marsh & Bugusu, 2007). Renewing the materials is the property of eco-friendly packaging obtained from renewable natural resources that can be reprocessed into new packaging, e.g. thermoplastic. Repurpose the materials the property of eco-friendly packaging material to be molded in another new forms with another pharmaceutical purpose in mind.

Agro-based materials are renewable and biodegradable, and they contribute to development of pharmaceutical sustainable packaging and this reduces their environmental impact. Such biodegradable packaging materials are suitable for single use disposable packaging applications.

The primary idea of eco-friendly packaging materials depends on its biodegradable viability. The biodegradation of pharmaceutical packaging materials mechanism is the initial scission of the enzyme forming a chain. Then the metabolized portions are leading to the enzymatic dissimilation of the macromolecule from the chain ends. The oxidative cleavage of macromolecules constitutes the basic skeleton of pharmaceutical packaging material. This is often leads to better metabolization of the fragments. These fragments are converted by microorganisms because they are smaller enough. The decomposed of eco-friendly pharmaceutical packaging material is made in a bio-waste collection. This bio–waste collection is composted into environment friendly products like carbon dioxide and water (Petkewich, 2003).

Another mechanism is the photo degradation of pharmaceutical packaging material. The photo degradation role is to make smaller disposable materials which do not create any environmental hazard. When biodegradable pharmaceutical packaging material are exposed to chemical based aqueous solutions they rapidly dissolute it. After the rapid dissolution the materials suffers a microbial digestion. These packaging materials disintegrate when they are exposed to aqueous solutions, which are used for the transport and disposal of pharmaceutical wastes (Petkewich, 2003).

RESULTS AND DISCUSSIONS

Organizations such as ISO (International Organization for Standardization) and WHO (World Health Organization) have officially set the standards for protected and effective packaging materials and technologies which ought to be pursued. Therefore, the Pharmaceutical sector has to be specific when is using these eco-friendly materials for packaging because the packaging materials should protect the product against damages produced by external factors as: light, foreign particles, temperature, atmospheric gases, microorganisms and moisture. One of the key attributes of packaging materials is to protect the pharmaceutical formulation from draining, loss of volatile substances and misfortune or increase of water from the content. Packaging ought to avert mechanical dangers like shock, abrasion, compression, perforation and vibration. The materials ought not react with the product and ought to have the capacity to preserve the product throughout the shelf life. Eco-friendly packaging materials should be packaging that uses environment safe materials in its production and it should not harm the environment. This types of environmentally friendly pharmaceutical packaging materials are marked with eco-labels. Eco-friendly pharmaceutical packaging materials should have two concepts the first is that the material should be recyclable and the second is that the material should be biodegradable. For example, starch is an eco-friendly polysaccharide and it's a widely available raw material. It is obtained from various sources like potato, corn, wheat and rice and it is used for flexible or rigid packaging, bags and sacks. Cellulose is another eco-friendly material which is found abundantly in nature. Xylan is also a biodegradable, compostable and an eco-friendly derivate. Xylophane is used as an environment friendly packaging material. Chitin is used in packaging because it has antimicrobial property, protects the product from unnecessary microbial growth, it maintains the preservative action and it has the unique property to absorb heavy metal ions. Protein based eco-friendly materials are derived from agricultural materials or agro-packaging materials and they are renewable and biodegradable.

CONCLUSIONS

Nowadays, packaging of pharmaceutical products plays a very important role in the pharmaceutical sector. The pharmaceutical industry need to focus on the development of new biodegradable materials, regarding the generation of environmental friendly packaging material that adds value to the pharmaceutical

products as well as it creates a new outlook into the concept of eco-friendly pharmaceutical packaging materials. The objective for pharmaceutical organizations is to concentrate on the development of a single eco-friendly packaging material that acknowledge the combined characteristics of glass, plastic, paper, metal and rubber. Starch, cellulose, xylan and chitin could be used as eco-friendly packaging materials because they have antimicrobial properties and because they are compostable and biodegradable.

REFERENCES

Bird, K. (2009). *Green Packaging is more about improving recycling than new materials.* Decision News Media.

Campbell, G. A., Vallejo, E. (2015). Primary packaging considerations in developing medicines for children: oral liquid and powder for constitution. *J. Pharm. Sci*., *104*(1), 52–62.

Edward, J. B. (2009). *Pharmaceutical Packaging. Handbook. Informa Healthcare* (pp: 200–240).

European Pharmacopoeia 9th edition (2017).

Hunt, J., 2010. *All the Types of Packaging. Ezine Articles;* http://www.Eco-Friendly Packaging Concepts Design Reviver.html.

International Standard ISO, 8362-6: Injection containers for injectables and accessories (2010). Caps made of aluminium plastics combinations for injection vials.

Kassarjian, O. K., Bello, N., Bix, L., Burgess, G., Linz, J. (2014). Examining the effect of secondary packaging on microbial penetration into sterile medical device trays. *J. Appl. Packag. Res., 6*(1), 2.

Kerry, J. P. (2014). New packaging technologies, materials and formats for fast-moving consumer products. *Innovations in Food Packaging*, 2nd ed. Elsevier.

Kim, Y. T., Min, B., Kim, K. W. (2014). General characteristics of packaging materials for food system. *Innovations in Food Packaging,* 2nd ed. Elsevier.

Kumar, S. (2013). Pharmaceutical packaging technology - A review. *Int. J. Res. Pharm. Biomed. Sci.*, *4*, 1400–1414.

Kunal, M., Akhilesh, D., Kumar, B. S. (2012). Recent Trends in Pharmaceutical Packaging: A Review. *International Journal of Pharmaceutical and Chemical Sciences*, *1*, 1282–1292.

Marsh K. S., Bugusu B. (2007). Food Packaging-Roles, Materials and Environmental Issues. *Journal of Food Sci*., *72*(3), 39–53.

Petkewich, R. (2003). Microbes manufacture plastic from food waste. *Environmental Science and Technol*., *5*, 175–176.

Platt, D. K. (2006). Biodegradable polymers: market report. *Smithers Rapra Press*, *4*, 57–60.

Srinivasa, P. C., Tharanathan, R. N. (2007). Chitin/Chitosan - Safe, Eco friendly Packaging Materials with Multiple Potential Uses. *Food Reviews International*, *23*(1), 53–72.

Tiwari, B. N. (2016). Current aspect of pharmaceutical packing materials, importance and its future trend. A review. *Int. J. Chem. Pharm. Anal.*, *3*(1).

US Environmental Protection Agency (2008). http://www.epa.gov/smartway/transport/documents/faqs/partnership_overview.pdf.

Weber, C. J. (2000). *Bio based Packaging Materials for the Food Industry. Status and Perspectives*. A European Concerted Action, 3–39.

World Health Organization (2002). Annex 9-Guidelines on packaging for pharmaceutical Products. *WHO Technical Report Series*, No. 902.