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REVIEW

Importance and globalization status of good manufacturing practice (GMP) requirements for pharmaceutical excipients

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Abstract Pharmaceutical excipients are no longer inert materials but it is effective and able to improve the characteristics of the products' quality, stability, functionality, safety, solubility and acceptance of patients. It can interact with the active ingredients and alter the medicament characteristics. The globalization of medicines' supply enhances the importance of globalized good manufacturing practice (GMP) requirements for pharmaceutical excipients. This review was intended to assess the globalization status of good manufacturing practice (GMP) requirements for pharmaceutical excipients. The review outcomes demonstrate that there is a lack of accurately defined methods to evaluate and measure excipients' safety. Furthermore good manufacturing practice requirements for excipients are not effectively globalized.

Contents

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1. Introduction

The word excipient comes from Latin name meaning to receive, to gather or to take out (Pifferi and Restani, 2003). International Pharmaceutical Excipients Council (IPEC) defined excipients as the other substances in the pharmaceutical formulation than the active pharmaceutical ingredients (API) which have been appropriately evaluated for the safety in order to help in processing, manufacturing, protection and give support or to enhance stability, bioavailability or patient acceptability or to assist in product identification or improve any features of the safety or effectiveness of the drug delivery system during storage or use (Apte et al., 2003; Ahjel and Lupuliasa, 2008). Excipient can be of animal origin such as stearic acid and gelatin, plant origin like starch and cellulose, mineral such as calcium phosphate and silica or synthetically produced such as polysorbates and povidone (Pifferi and Restani, 2003).

The basic requirements for pharmaceutical excipient include safety, functionality and quality (Pifferi and Restani, 2003). Regulatory layers have been implemented through the regulatory bodies to ensure the positive impact of excipients on the final products' safety, quality, effectiveness, functionality and stability due to an increase in the percentage of counterfeit medicines and gradually losses of patent protection. We can conclude that importance of pharmaceutical excipients encompasses three parts: functions, quality evaluation and safety of pharmaceutical excipients. Toxicity and bioavailability are the main problems of excipients regarding safety and function requirements consequently.

Determination of optimum concentration in addition to compatibility studies of excipients with active ingredients and other excipients are required (U.S. Department of Health and Human Services, 2006). Excipient can interact physically with the active ingredient such as degradation of nitrazepam due to the adsorption interaction with colloidal silica, or interact chemically like incompatibility between hydrogen donating drugs such as lansoprazole and famotidine with polyvinylpyrrolidone (Crowley and Martini, 2001).

The term globalization was first used in 1940s. The political economist George Modelski reintroduced the term in 1972 to describe the impact of multinational cooperation on economic relations within and between countries (Collins, 2003). The concept of globalizations means that countries and regions of the world come together toward policies and regulations (Abraham and Reed, 2003). In other words it is a global network where there is a better interconnection between different countries and regions (Alasuutari, 2000). It dismantles the state barriers to trade, economic, social and politics and help poor countries to fasten their growth and reduce poverty (Srinivasan, 2002).

Globalization of pharmaceutical regulations helps in removing the trade barriers, improving technical cooperation, and increasing cost saving of testing and evaluation processes, supporting free market competition and information transformation. Denmark, Finland, Norway and Sweden started regional harmonization of pharmaceutical regulations by adoption of Nordic pharmacopeia, then European pharmacopeia in 1964, followed by establishment of the European Medicine Evaluation Agency in 1996 and European pharmacopeia commission (Wehrli, 1997). World Health Organization (WHO) started the globalization of pharmaceutical regulations by considering rational medicine use, medicine affordability, financial support of healthcare and an efficient health and medicine supply system (Chua et al., 2010), International Nonproprietary (generic names) and International pharmacopeia.

Globalized good manufacturing practice requirements for pharmaceutical excipients are crucial to face the impact of globalized medicines' supply. In fact no country is protected from the globalization of medicines' supply. For example in 2006 the United States of America which is a very developed country received 145,000 line entries of imported drugs from 160 countries (Woo et al., 2008).

The study was intended to review the importance and globalization status of good manufacturing practice requirements for pharmaceutical excipients.

2. Method

Searching from Google scholar and science direct data base was used as a method to review the articles related to the intended subject. The searching focused on the modern role of pharmaceutical excipients, the concept of globalization and the regulatory status of good manufacturing practice for pharmaceutical excipients.

3. Functions of excipients

Historically excipients are considered as inert materials. However, they are effective materials mainly to enhance the stability of the formulation, release or absorption of the active ingredients (Pifferi et al., 1999a,b). The largest group of excipients in the pharmaceutical formulations is used to improve solubility of the active ingredients as shown in Table 1 (Strickley, 2004). Others are used as a disintegrant, binder, lubricant, filler agent to facilitate manufacturing of medicine and sweetener to give a pleasant taste to patients as shown in Table 2 (Akers, 2002; Koizumi et al., 2004; Jivraj et al., 2000). Some excipients are used for identification and coloring agents. In particular certain excipients have multiple functions. In fact excipients may interact positively or adversely affect the formulations especially in side living cells (Jackson et al., 2000). This intensified sophistication of in vivo researches about drug bioavailability using various excipients.

4. Evaluation of the pharmaceutical excipients' quality

Shortage of testing strategies, protocols or guidelines affects efficient evaluation of excipients. One of the debates about

Table 1 Commonly used solubilizer excipients based on its functions.

No.	PH modifier	Water soluble organic solvents	Water insoluble organic solvents	Nonionic surfactants	Water insoluble lipids (triglycerides)	Cyclodextrins	Phospholipids
1	Citric acid	Polyethylene glycol 300 & 400	Beeswax	Cremphor	Peanut oil	α-cyclodextrins	Glycerol
2	Tartaric acid	Ethanol	D-α tocopherol	Tween 20	Corn oil	β-cyclodextrins	Choline
3	Benzoic acid	Propylene glycol	Oleic acid	Tween 20	Soybean oil	γ-Cyclodextrins	DSPG
4		Glycerin	Mono & di glycerides	Sorbitan monooleate (Span 20)	Sesame oil	Sulfobutylether-cyclodextrin	DMPC
5		N-methyl 2-pyrrolidone		Peppermint oil	Olive oil	Hydroxypropyl-cyclodextrin	DMPG
6		Dimethyl acetamide		Polysorbate 20 & 80	Cotton seed oil		

Adapted from: (Cornaire et al., 2004, Kornblum and Stoopak, 1973, Gohel and Jogani, 2005).

excipient production is the difficulty of consistency which is one of the fundamental issues in the GMP implementation, other is the variation between test cost and profit from such industry (Moreton, 2006). But the studies assert the need for excipient testing strategy (Baldrick, 2000). One example of that is the impurity test for hydro peroxide (HPO) (Wasylaschuk et al., 2007). Proxides are commonly available as impurities in povidone, crospovidone and polysorbate (Crowley and Martini, 2001). Qualification of the suppliers is an efficient method to evaluate the quality of the excipients and combatting the counterfeit materials (Chow et al., 2009) 1, 2. Toxicity tests are used to evaluate pharmaceutical excipients such as tolerance study and mucociliary clearance test (Ilium, 1998).

5. Pharmaceutical excipients' safety

The use of some excipients results in many health problems. Some of the excipients display toxicity effects on the kidneys, neonates and gastrointestinal tract. Tragic events happened due to the lack of excipient safety like E-ferol incident in the United States of America in which many cases of infants died due to intravenous administeration of vitamin E to premature infants using polysorbate as an emulsifying agent in 1983 and 1984 to help in the treatment of retrolental fibroplasia (RLF), (Golightly et al., 1988) and a disaster occurred in Haiti in 1996 in which 90 people died due to mislabeling cough syrup (Steinberg et al., 2001). In 2009 another catastrophic event happened in which twenty four children died in Bangladesh due to paracetamol syrup adulterated with ethylene glycol (Sheehan, 2010). All these events imposed the world to adopt regulations for excipient to ensure quality and safety.

Pharmaceutical formulation consists of two categories of ingredients, active materials and excipients. However, attention was paid to the active constituents to cause toxicity but excipients elicited toxicity; as displayed in Table 3. Information on the package of medicines should include excipients to increase awareness of doctors, pharmacists and people on safe use of excipients (Pifferi and Restani, 2003).

6. The globalization status of GMP requirements for pharmaceutical excipients

GMP requirements for excipients include three main issues safety, quality and functionality instead of efficacy for the active ingredients (Pifferi and Restani, 2003). The excipient cost plays a crucial role on leading control measurements of these requirements as the manufacturers seek to minimizing the cost (Rafidison and Ulman, 2003). Progressing of new excipients usage in the pharmaceutical formulations is slow due to a lack of global specific guidance to assess and ensure of its safety (Baldrick, 2010). On the other hand the pharmaceutical industry needs an innovation of excipients that can enhance the efficacy and quality of the pharmaceutical formulation (Ermens, 2004).

There are essential needs to assess the compatibility of the currently used excipients to each other and their functionality in the pharmaceutical formulation (Guideline, 2009). Although the United States of America food and drug administration (FDA) arises the importance of excipient GMP compliance in 2008, currently there are no global regulation standards for excipients, in other words the regulations are scattered despite the fact that drug authorities are trying to improve the regulatory status of pharmaceutical excipients. For instance in 2010 GMP certificate of quality management system for silicon dioxide was adopted in Grace as the first certificate of excipient GMP conformance (Monsuur and Poncher, 2010).

Globalization of the medicine market motivates manufacturers especially in the developed countries to consider various pharmacopeia requirements to facilitate exportation of their products (Larner et al., 2006). In fact globalization of the finished products' supply chain elevated gradually even in the developed countries, for example the United States Food and Drug Administration (FDA) registered manufacturing sites from China increase from 140 sites with 797 drug items in 2001 to 815 registered sites of 3000 listed items (Woo et al., 2008), so there is no country protected from this globalization.

Moreover, the current situation needs globalization of the excipients' supply chain as well to improve the GMP compliance and appropriately counteract counterfeit and substandard ingredients besides lowering of the pharmaceutical excipients' cost (Sheehan, 2010) in addition to that traceability and contamination control are fundamental elements and should be revised by suppliers (Rafidison and Ulman, 2003). There are three main bodies concern with pharmaceuitical exicipents in the world as shown in Fig. 1. These organizations are associations of producers, distributors and users.

Table 2 Other functions of pharmaceutical excipients.

Functions	1	2
Enhance absorption	Chitosan	D-α-tocopheryl polyethylene glycol 1000 succinate
Disintegration agent	Microcrystalline cellulose	Citric acid
Binding agent	Corn starch	Xanthane gum
Lubricant	Magnesium stearate	Stearic acid
Compaction filler	Sorbitol	Mannitol
Compression filler	Granulated lactitol	Crystalline maltose
Sweetener	Acesulfame potassium	Mannitol
Stability	Polyvinylpyrollidone (Povidone) (PVP)	Alginic acid
Antioxidant	Butylated hydroxy toluene	Sodium metabisulfite
Preservative	Butyl paraben	Sodium propoinate
Buffers	Di sodium hydrogen phosphate	Sodium citrate dihydrate
Filler diluents	Lactose	Microcrystalline cellulose

Adapted from: (Cornaire et al., 2004, Kornblum and Stoopak, 1973, Gohel and Jogani, 2005).

Table 3 Examples of pharmaceutical excipient toxicity.

Number	Excipient	Toxicity
1	Parenteral β-cyclodextrins	Nephrotoxicity
2	Ethylene glycol	Renal failure
3	Mannitol	Osmotic diarrhea
4	Parabens & sodium metabisulfite	Neonatal toxicity
5	Sulfiting agents in asthmatic patients	Sensitive to excipient toxicity
6	Doxapram	Very low birth weight infants
7	Phenolic excipients	Dermatitis, irritation and allergy

Adapted from: (Brewster and Loftsson, 2007, Osterberg and See, 2003, Lass et al., 2012, Golightly et al., 1988).

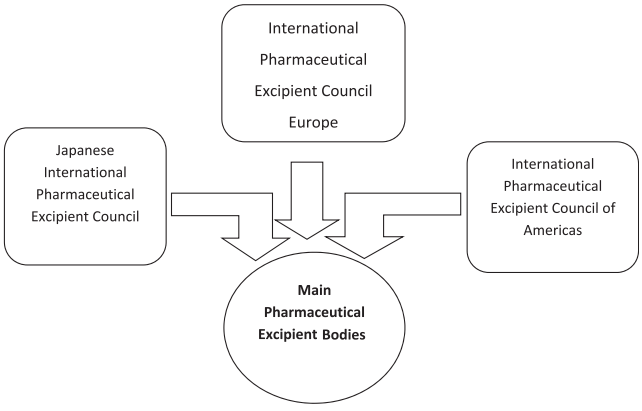

Figure 1 The biggest bodies concerned with pharmaceutical excipient regulations.

7. Conclusion

Due to incorporating of excipients in both the pharmaceutical and food industries great attention is paid to the safety, quality and functionality of excipients. This review suggests deficiency in studies to measure excipients' safety and a lack of effective global work to adopt specific requirements on improving pharmaceutical excipients' standards, although of the efforts to improve excipient regulations by the regulatory authorities. However, the information and findings of numerous studies prove that globalization for GMP requirements for pharmaceutical excipients is fundamental to counteract a negative impact of globalization of the medicines' supply, enhance GMP compliance, minimize pharmaceutical excipient cost, maximize the degree of safety and quality and elevate standards of consumer protection to meet health care providers and customers' expectations.

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