Title: Importance and Globalization Status of Good Manufacturing Practice (GMP) Requirements for Pharmaceutical Excipients

Article Type: Review Article

Corresponding Author: Mr. Abubaker Ahmed,

Corresponding Author's Institution: Department of Pharmacy, Faculty of Medicine, University of Malaya, Malaysia

First Author: Abubaker Ahmed

Order of Authors: Abubaker Ahmed; Mohamed Ibrahim Noordin; Wan Azman Wan Ismail

Abstract: Pharmaceutical excipients are no longer an inert materials but it is an 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 medicaments 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 demonstrates that there is a lack of accurately define methods to evaluate and measure excipients safety. Furthermore good manufacturing practice requirements for excipients is not effectively globalized.
Author Agreement

Submission of work requires that the piece to be reviewed has not been previously published. Upon acceptance, the Author assigns to the Saudi Pharmaceutical Journal (SPJ) the right to publish and distribute the manuscript in part or in its entirety. The Author's name will always be included with the publication of the manuscript.

The Author has the following nonexclusive rights: (1) to use the manuscript in the Author's teaching activities; (2) to publish the manuscript, or permit its publication, as part of any book the Author may write; (3) to include the manuscript in the Author's own personal or departmental (but not institutional) database or on-line site; and (4) to license reprints of the manuscript to third persons for educational photocopying. The Author also agrees to properly credit the Saudi Pharmaceutical Journal (SPJ) as the original place of publication.

The Author hereby grants the Saudi Pharmaceutical Journal (SPJ) full and exclusive rights to the manuscript, all revisions, and the full copyright. The Saudi Pharmaceutical Journal (SPJ) rights include but are not limited to the following: (1) to reproduce, publish, sell, and distribute copies of the manuscript, selections of the manuscript, and translations and other derivative works based upon the manuscript, in print, audio-visual, electronic, or by any and all media now or hereafter known or devised; (2) to license reprints of the manuscript to third persons for educational photocopying; (3) to license others to create abstracts of the manuscript and to index the manuscript; (4) to license secondary publishers to reproduce the manuscript in print, microform, or any computer-readable form, including electronic on-line databases; and (5) to license the manuscript for document delivery. These exclusive rights run the full term of the copyright, and all renewals and extensions thereof.

I hereby accept the terms of the above Author Agreement.

Abubaker Abdellah Ahmed  21/5/2013
Author :-

Date :-

Editor in Chief:- Ibrahim Al-Sarra

Date:-
Dear Sir

The Editor in Chief

Saudi Pharmaceutical Journal

I hope you are keeping well and happy

Topic: Submission of full length article to Saudi Pharmaceutical Journal

I am enclosing herewith a review article entitled “Importance and Globalization Status of Good Manufacturing Practice (GMP) Requirements for Pharmaceutical Excipients” for publication in the Saudi Pharmaceutical Journal for possible evaluation.

Due to globalization of medicines supply we need to effectively globalize good manufacturing practice (GMP) requirements for pharmaceutical excipients. This review highlights key issues about efficiency of current GMP requirements and globalization status of pharmaceutical excipients regulations.

With the submission of this manuscript I would like to undertake that the authors have approved the final article. Moreover the above mentioned manuscript has not been published elsewhere, accepted for publication elsewhere or under editorial review for publication elsewhere; and that my Institute’s (University of Malaya) representative is fully aware of this submission.

Thanks and regards

Abubaker Abdellah Ahmed

University of Malaya,
50603 Kuala Lumpur, Malaysia.
Tel: +60169721308
Email: abub_006@yahoo.com
Importance and Globalization Status of Good Manufacturing Practice (GMP) Requirements for Pharmaceutical Excipients

Abubaker Abdellah, Mohamed Ibrahim Noordin, Wan Azman

Department of Pharmacy, Faculty of Medicine, University of Malaya, 50603, Kuala Lumpur, Malaysia

Corresponding author: Abubaker Abdellah, Department of Pharmacy, Faculty of Medicine, University of Malaya, Kuala Lumpur, 50603, Malaysia. Tel: (603)79674909/4910, H/P: (0060)169721308, Fax: (603)79674964; Email: abub_006@yahoo.com

Email addresses of Co authors:
Mohamed Ibrahim Noordin: Ibrahimn@um.edu.my
Wan Azman: wanazman@mahsa.edu.my
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 and Ugwu 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 increase 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.

Chosen of the excipient with certain concentration and Compatibility studies of excipient with active ingredients and with 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 towards 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 & 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, Hassali 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 examples in 2006 United States of America which is a very developed country received 145000 line entries of imported drugs from 160 countries (Woo, Wolfgang 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, Santoro et al. 1999) (Pifferi, Santoro et al. 1999). The largest group of excipients in the pharmaceutical formulations are 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, Fujii et al. 2004), (Jivraj, Martini 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, Young 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 debate about excipient production is the difficulty of consistency which it is one of the fundamental issues in the GMP implementation, other is the variation between tests 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 impurities test for hydro peroxide (HPO) (Wasylaschuk, Harmon 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, DAVIDSON et al.) 1, 2. Toxicity tests are used to evaluate pharmaceutical excipients such as tolerance study and mucociliary clearance test (Illium 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. Tragedies events happened due to the lack of excipient safety like E-ferol incident in United States of America in which many cases of infants death due to vitamin E administered intravenously to premature infants using polysorbate as an emulsifying agent in 1983 and 1984 to help in the treatment of retrolental fibroplasia (RLF), (Golightly, Smolinske et al. 1988) and disaster occurred in Haiti in 1996 in which 90 people died due to mislabeling cough syrup (Steinberg, Blecher et al. 2001). In 2009 another catastrophe 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 the table No (4). Information on the package of medicines should include excipients to increase awareness of doctors, pharmacists and people on safety 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 play a crucial role on leading control measurements of these requirements as the manufacturers are seek to minimizing the cost (Rafidison and Ulman 2003). Progressing of new excipients usage in the pharmaceutical formulations is slow due to lack of Global specific
guidance to assess and ensure of its safety (Baldrick 2010). On the other hand the pharmaceutical industrial need an innovation of an excipients that can enhance the efficacy and quality of the Pharmaceutical formulation (Ermens 2004).

There are essential need to assess the compatibility of current used excipients to each other and their functionality in the Pharmaceutical Formulation (Guideline 2009). Although United States of America food and drug administration (FDA) arise 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 adopted in Grace as the first certificate of excipient GMP conformance (MONSUUR and PONCHER 2010).

Globalization of the medicines market motivate manufacturers especially in the developed countries to consider various pharmacopeias requirements to facilitate exportation of their products (Larner, Schoneker et al. 2006). In fact globalization of the finished products supply chain elevated gradually even in the developed countries, for example 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, Wolfgang et al. 2008), so there is no country protected from this globalization.

More over current situation need globalization of the excipients supply chain as well to improve the GMP compliance and appropriately counteract counterfeit and substandard ingredients beside lowering of the pharmaceutical excipients cost (Sheehan 2010) in addition to that traceability and contamination control are fundamental elements to be revise and arise by the supplier (Rafidison and Ulman 2003). The main bodies concern with the pharmaceutical excipients in the world consists of three as shown in figure No (1) which are associations of producers, distributors and users.
7. Conclusion:

Due to incorporating of excipients in both the pharmaceutical and food industries great attention 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 excipient’s standards, although of the efforts to improve excipients regulations by the regulatory authorities. However, the information and findings of numerous studies proof that globalization for GMP requirements for pharmaceutical excipients is fundamental to counteract 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.

References:


CHOW, F., et al. "the qualification of excipient suppliers."


Table.1: Commonly use Solubilizers Excipients based on its functions:

<table>
<thead>
<tr>
<th>No</th>
<th>PH Modifier</th>
<th>Water soluble organic solvents</th>
<th>Water insoluble organic solvents</th>
<th>Nonionic Surfactants</th>
<th>Water insoluble lipids (triglycerides)</th>
<th>Cyclodextrins</th>
<th>Phospholipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>citric acid</td>
<td>Polyethylene glycol 300&amp;400 Beeswax</td>
<td>Cremphor</td>
<td>Peanut oil</td>
<td>α-cyclodextrins</td>
<td>Glycerol</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>tartaric acid</td>
<td>Ethanol D-α-tocopherol</td>
<td>Tween 20</td>
<td>Corn oil</td>
<td>β-cyclodextrins</td>
<td>Choline</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>benzoic acid</td>
<td>Propylene Glycol Oleic acid</td>
<td>Tween 20</td>
<td>Soybean oil</td>
<td>Y-Cyclodextrins</td>
<td>DSPG</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Glycerin Mono &amp; di glycerides</td>
<td>Sorbitan monooleate (Span 20) Sesame oil</td>
<td>sulfobutylether- cyclodextrin</td>
<td>DMPC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>N-methyl 2-pyrrolidone</td>
<td>Peppermint oil Olive oil</td>
<td>hydroxypropyl- cyclodextrin</td>
<td>DMPG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Dimethyl acetamide</td>
<td>Polysorbate 20&amp;80 Cotton seed oil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from: (Cornaire, Woodley et al. 2004), (Kornblum and Stoopak 1973), (Gohel and Jogani 2005).
Table 2: Other functions of pharmaceutical excipients:

<table>
<thead>
<tr>
<th>Functions</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhance absorption</td>
<td>chitosan</td>
<td>D-α-tocopheryl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>polyethylene glycol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1000 succinate</td>
</tr>
<tr>
<td>Disintegration agent</td>
<td>Microcrystalline cellulose</td>
<td>Citric acid</td>
</tr>
<tr>
<td>binding agent</td>
<td>Corn Starch</td>
<td>Xanthane gum</td>
</tr>
<tr>
<td>lubricant</td>
<td>Magnesium stearate</td>
<td>Stearic acid</td>
</tr>
<tr>
<td>Compaction filler</td>
<td>sorbitol</td>
<td>Mannitol</td>
</tr>
<tr>
<td>Compression filler</td>
<td>Granulated Lactitol</td>
<td>Crystalline maltose</td>
</tr>
<tr>
<td>Sweetener</td>
<td>Acesulfame</td>
<td>Mannitol</td>
</tr>
<tr>
<td></td>
<td>Potassium</td>
<td></td>
</tr>
<tr>
<td>stability</td>
<td>Polyvinylpyrollidone (PVP)</td>
<td>Alginic acid</td>
</tr>
<tr>
<td>antioxident</td>
<td>Butylated hydroxy toluene</td>
<td>Sodium metabisulfite</td>
</tr>
<tr>
<td>preservative</td>
<td>Butyl Paraben</td>
<td>Sodium propionate</td>
</tr>
<tr>
<td>Buffers</td>
<td>Di sodium hydrogen phosphate</td>
<td>Sodium citrate dihydrate</td>
</tr>
<tr>
<td>Filler diluents</td>
<td>Lactose</td>
<td>Microcrystalline cellulose</td>
</tr>
</tbody>
</table>

Adapted from: (Cornaire, Woodley et al. 2004), (Kornblum and Stoopak 1973), (Gohel and Jogani 2005).
Table 3: Examples of pharmaceutical excipient toxicity

<table>
<thead>
<tr>
<th>Number</th>
<th>Excipient</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Parenteralβ-Cyclodextrins</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td>2</td>
<td>Ethylene glycol</td>
<td>Renal failure</td>
</tr>
<tr>
<td>3</td>
<td>Mannitol</td>
<td>Osmotic diarrhea</td>
</tr>
<tr>
<td>4</td>
<td>Parabens &amp; Sodium Metabisulfite</td>
<td>Neonatal toxicity</td>
</tr>
<tr>
<td>5</td>
<td>Sulphiting agents in asthmatic patients</td>
<td>Sensitive to excipient toxicity</td>
</tr>
<tr>
<td>6</td>
<td>Doxapram</td>
<td>Very low birth weight infants</td>
</tr>
<tr>
<td>7</td>
<td>Phenolic excipients</td>
<td>Dermatitis, Irritation and allergy</td>
</tr>
</tbody>
</table>

Adapted from: (Brewster and Loftsson 2007), (Osterberg and See 2003), (Lass, Naelapää et al. 2012), (Golightly, Smolinske et al. 1988).
International Pharmaceutical Excipient Council
Europe

Japanese International Pharmaceutical Excipient Council

International Pharmaceutical Excipient Council of Americas

Main Pharmaceutical Excipient Bodies
Figure No (1). The biggest bodies concerned with Pharmaceutical Excipient Regulations