



REVIEW ARTICLE

PHARMACEUTICAL DILUENTS AND THEIR UNWANTED EFFECTS: A REVIEW

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Diluents are chemically inactive excipients, mostly used to make up the required bulk of solid dosage form and used up to 80% in a formulation. Various studies reported that diluents used in the solid dosage forms shows unwanted effects in body on long term and some time in short duration therapy. So, it is necessary to study the unwanted effects of diluents by researchers and production chemists before preparation of a pharmaceutical formulation to reduce the unwanted actions. Present review provides toxicological data of commonly used pharmaceutical diluents and summarizes the unwanted effects of pharmaceutical diluents on public health.

Key words: Diluents, Solid dosage form, Tablets, Unwanted effects.

INTRODUCTION

Diluents or fillers are pharmaceutical ingredients which lack pharmacological activity but are desirable or necessary in pharmaceutical preparations. Diluents comprise of heterogeneous groups of substances, designed to make up the required bulk of the tablet when the drug dosage itself is inadequate to produce the bulk (Nahata, 2009). In order to facilitate tablet handling during manufacture and to achieve targeted content uniformity, the tablet size should be kept above 2-3 mm and weight of tablet should be above 50 mg. The range of diluent may vary from 5-80% in a pharmaceutical formulation (Pandey *et al* 2009). Diluents are often added to tablet formulation for secondary reason like to provide better tablet properties such as, to allow direct compression, provide improved cohesion, enhance flow and adjust weight of tablet as per die capacity (Chaudhari and Patil, 2012). Ideally Diluents should not show any effect on the other excipients used in the formulation

(Allen, 2000). Diluents should be able to mill into small sized when needed (Steinberg *et al* 2001). It should not support microbial growth in the dosage form, should not affect the dissolution of the product, should not interfere with the bioavailability of active ingredients. It should not affect the pharmacological activity of active ingredients (Fathima *et al* 2011).

Classification of diluents

Diluents are classified on the basis of chemical nature and solubility:

Chemical nature

Diluents are further divided into three subtypes on the basis of their chemical structure: as organic, inorganic and co-processed.

Organic materials

Carbohydrates and modified carbohydrates are the major examples of this category *i.e.* lactose, starch and pre-gelatinized starch, sucrose, mannitol, sorbitol, powdered and

microcrystalline cellulose (Vaidya and Avachat, 2011).

Inorganic materials

These materials are also used commonly in pharmaceutical industries now a days. Calcium phosphates *i.e.* anhydrous Dibasic Calcium phosphate, dibasic calcium phosphate and tribasic calcium phosphate are main examples of this category (Vaidya and Avachat, 2011).

Co-processed diluents

Co-processed diluents are prepared from combination of two or more diluents by an appropriate process. The product thus formed are physically modified in such a way that product do not lose their stability and chemical nature. *e.g.* Sugartab^r, Emdex^r (Gohel, 2005).

Diluents are also divided into water insoluble and water soluble:

Water insoluble diluents

Examples of water insoluble diluents are starch, powdered cellulose, microcrystalline cellulose and calcium phosphate etc.

Water soluble diluents

Lactose, sucrose, mannitol, sorbitol etc. (Gohel, 2005).

Unwanted effects of mostly used diluents

Sucrose

Sucrose is a disaccharide in nature and used as a sweetening agent. It is used even in larger amount as a diluent/sweetener in tablets and liquids (Allen *et al* 2004). Sucrose is absorbed when it get hydrolysed into glucose and fructose in small intestine. Sucrose is excreted unchanged

in urine when given by IV route (Hill *et al* 1988). Sucrose causes a decrease in dental plaque pH, dissolving tooth enamel and promoting dental caries and risk in patients having hereditary problems *i.e.* fructose intolerance, glucose-galactosemal-absorption, or sucrose-isomaltase insufficiency (Ali *et al* 1998).

Lactose

Lactose is widely used as an excipient in pharmaceutical manufacturing as a filler or diluent in tablets, capsules and to give bulk to powders (**Figure 1**). Lactose has no reaction with most drugs, whether it is used in hydrous or anhydrous form (Lachman *et al* 1987). Lactose is a disaccharide that consists of galactose and glucose molecules bonded through a β 1-4 glycosidic linkage. The enzyme lactase-phlorizin hydrolase, more commonly known as lactase, is responsible for the hydrolysis of lactose to the monosaccharides glucose and galactose (Ursino *et al* 2011). Lactase activity is high during infancy but in adult life, it is at a variable level, determined by genetic predisposition, ethnicity, gastrointestinal disorders or infections (Heyman, 2006).

Adverse reactions to lactose are largely attributed to "lactose intolerance (Li)", which occurs in persons with a deficiency of the intestinal enzyme lactase (Pawłowska *et al* 2016). The primary form of adult-type hypolactasia is an autosomal recessive condition resulting from the physiological decline in activity of the lactase enzyme in intestinal cells after weaning. The secondary form of lactose intolerance occurs in individuals with low lactase level, any quantity of lactose that is ingested is not completely hydrolysed (Campbell *et al* 2005).

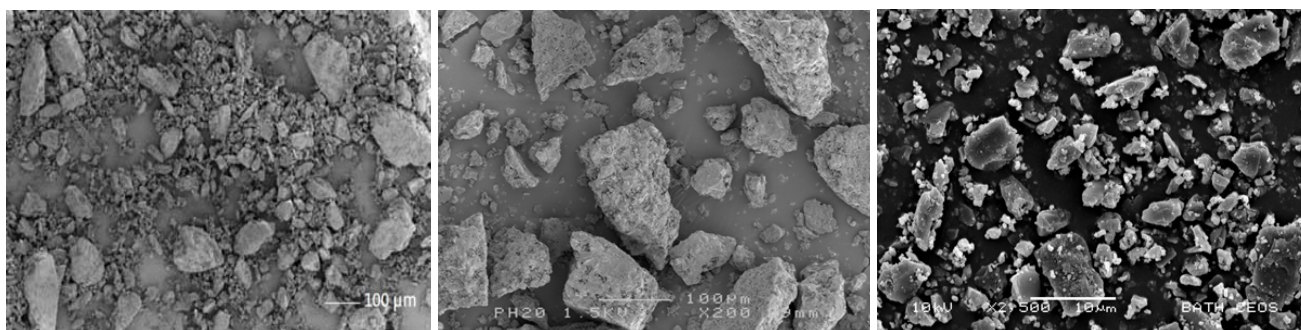


Fig. 1. SEM images of pharmaceutical diluent - lactose

As a consequence, there is a large production of gases such as hydrogen, methane as well as small peptides and toxins due to bacterial

metabolization in large intestine. These gases cause abdominal and systemic symptoms including stomach cramps, bloating, flatulence,

diarrhoea, muscle cramps and headache. Moreover, the unabsorbed lactose raises the osmotic pressure in the colon, preventing water re-absorption and causing laxative effect (Eadala *et al* 2009).

In two studies, approximately 10–20% of lactose-intolerant individuals showed clinical symptoms of intolerance after ingestion of 3–5 g of lactose. In one of these studies, 75% of the subjects had symptoms with 12 g of lactose (Arola, 1994). In the other study, 8 out of 13 individuals developed diarrhoea after the administration of 20 g of lactose, and 9 out of 13 after the administration of 25 g (Arola and Tamm, 1994). Others consider the safety limit to be as low as 5 g (Lomer *et al* 2008).

Most patients with lactose intolerance can ingest up to 12 g of lactose before reporting symptoms (Suarez *et al* 1995). In some cases the ingestion of 400 mg of lactose from oral medications does not cause a significant difference in breath or in the severity of gastrointestinal symptoms compared to placebo (Montalto *et al* 2008). Lactose ingestion causes the following three main side effects:

Flatulence

If sufficient lactose enters the colon, the subject may experience symptoms of abdominal pain, bloating, excess flatulence, and diarrhea, a condition known as lactose intolerance (Hammer *et al* 1996).

Nausea

Nausea is the side effect of ingesting lactose when the body has intolerance for it. From the irritation in the body, the sensation of having an urge to vomit, results in the nausea (Pettifor and Hansen, 1974).

Malnutrition

It occurs as the side effect of lactose ingestion. Malnutrition is a condition which shows impact on both physical and mental health because of the lack of nutrients necessary to maintain health. Malnutrition can lead to weight loss, fatigue, dizziness, swollen and bleeding gums, muscle and bone weakness, and immune deficiency (Verma and Saxena, 1980).

Mannitol

Mannitol is also widely used as an excipient in pharmaceutical preparations. It is frequently used as a diluent in chewable and dispersible tablets. Mannitol is comparatively less cariogenic

than sugars (McNeill, 1985).

In some cases hypersensitivity reactions are reported after the intravenous infusion of 10% or 20% (w/v) mannitol solution. These anaphylactic reactions seem to be caused by direct action of mannitol at hyperosmolar concentrations on mast cells in a limited number of subjects (Hegde and Venkatesh, 2004).

When used orally, the absorption of mannitol is not higher than 20%. Mannitol shows the unwanted effects similar to the sorbitol and other polyalcohol and it may also show impact on gastric emptying rate and intestinal transit time. Mannitol causes the diarrhoea after the oral administration (Lamb and Keogh, 1979).

A number of adverse reactions to mannitol have been reported, primarily following the therapeutic use of 20% w/v aqueous intravenous infusions (Rowe *et al* 2009). The quantity of mannitol used as an excipient is considerably less than that used therapeutically and is consequently associated with a lower incidence of adverse reactions. However, allergic, hypersensitive-type reactions, cardiac injury and apoptosis in kidney and heart may occur when mannitol is used as an excipient (Zhang *et al* 1999).

Methyl cellulose

Methylcellulose is the organic material used as a diluent in the pharmaceutical formulation. It is the cellulose derivative. On the long term use as a diluent in the pharmaceutical formulation it causes the various side effects (Duro *et al* 2002). Mostly it causes the abdominal fullness. It also causes the severe allergic reactions (rash, hives, itching, difficulty in breathing, tightness in the chest, swelling of the mouth, face, lips or tongue) chest pain, difficulty swallowing, nausea, rectal bleeding, stomach pain, and vomiting (Edes *et al* 1990).

Dicalcium phosphate

Dicalcium phosphate (DCP) is a combination of positively charged particles of calcium and negatively charged particles of hydrogen phosphate which is interchangeable with the phosphate in the body. Long term use of DCP results in upset in the balance of phosphates and other chemicals in the body. According to the material safety data sheet, the powdered form of DCP may irritate skin. Prolonged skin contact may lead to dry or chapped skin. People with an allergy to DCP could develop contact dermatitis, a specific allergic reaction characterized by

redness, swelling or itching on skin areas that come into contact with an irritating substance (Grobben *et al* 2006). In severe cases, this allergic reaction may spread elsewhere, even to areas that have not been in direct contact with dicalcium phosphate. Inhalation of dicalcium phosphate powder may irritate the lung and nasal passage and causes cough and sneezing (Osterberg and See, 2003).

High level of this diluent may upset the gastrointestinal system. It causes the nausea, vomiting, loss of appetite, constipation, stomach pain, dry mouth and increase urination (Wasserman, 2013).

Calcium carbonate

It is the principal form of calcium found in bovine milk and blood. It is used in the variety of dental products for remineralisation and as a diluent in some medications where it gives the tablet a grey colour in the absence of colouring agents. It causes the constipation, allergic reaction (redness, itching, tightness in chest, swelling of the mouth, face, lips) confusion, increased urination, loss of appetite, mood changes, nausea, stomach pain, weakness and vomiting (Clemens and Feinstein, 1977).

Rare cases of calcium carbonate gallstones have been reported in the paediatric (Frithz *et al* 1991). Prolonged ingestion of large amount of calcium carbonate results in the milk alkali syndrome and calcinosis. The milk alkali syndrome is characterized by the triad of hypercalcemia, metabolic alkalosis and renal insufficiency. Metabolic side effects included hypercalcemia and hypophosphatemia (Ullion and Linas, 1988).

Polyethylene glycol

Polyethylene glycol used as an inactive ingredient in the pharmaceutical industry. At the high doses causes the teratogenic activity which increases the fetal loss, decrease body weight and malformation (Baldrick, 2000).

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Dextrose

Dextrose is a common name for the ubiquitous sugar molecule, glucose. Over use of the dextrose can result in some very undesirable side effects. Too much dextrose can actually lead to a paradoxical effect in individuals without diabetes (Oppelt *et al* 2015). If blood sugar rises very high very quickly, the pancreas secretes very large quantities of insulin. This signals the cells to take up blood sugar quickly, since hyperglycaemia is damaging to the tissues. As a result of the pancreatic over reaction to very high blood sugar, the cell can take up too much blood sugar, leading to hypoglycaemia. High dextrose consumption also results in hyperglycaemia, if untreated, can lead to tissue damage, coma and death. One other side effect of excess dextrose consumption is an increase in body fat (Martin and Lewis, 2004).

To reduce the unwanted effects of the diluents there is a deemed needs to establish new herbal pharmaceutical diluents which are inert or provide their nutraceutical value for treating such disease.

CONCLUSION

Information related to pharmaceutical diluents with known potential side effects is important in clinical practice, in particular for patients suffering from disorders that could be aggravated by the ingestion of these substances. Diluents being an indispensable component of some dosage forms, they must be evaluated for their safety and stability. The safety assurance of diluent helps the formulator to design an effective and safe dosage form with the use of efficient and safe diluents. It seems to be necessary to improve the information about the diluents in patient information leaflets. Although the safety profile of some diluents discussed in this review has already well established, paying attention to pharmaceutical diluents and their safety issues is an indispensable initial step to the success of drug products.

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