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The Excipients between Effects and the Side Effects

Mohammed Abdul-Mutalib Abdul-Bari

ABSTRACT: Most of the medicines contain excipients. They are added for a number of purposes and can improve product performance, Excipients are generally added along with the active pharmaceutical ingredients Historically, it considered as inactive materials from pharmacology and come from various sources such as biological, mineral and synthesis. The safety of excipients has received less attention because of its inertia. However, it is now known that three problems may compromise drug safety: production, distribution, and use; also drug-excipient interactions; and toxicity, it was concluded that , the potential adverse effect of the excipients should not be underestimated and a periodic review and follow up of side effects that may appear and occur after a drug administration should not be limited to the active medication in the drug formula but also the excipient should be taken into account.

Key wards: excipients binders lubricants alcohol acids organic

What are the Excipients

Most of the medicines contain excipients. They are added for a number of purposes and can improve product performance, including enabling formulations, the patient's acceptance and compliance, or provide a more effective and safe drug, as modified release formulations or taste masked syrups for children. The latter can be achieved, for example, by ensuring peak plasma levels are kept below toxic levels^[1]

Dosing forms together with active pharmaceutical ingredients play an important role in forming a dosage formula. The Excipient is defined as "the any substance other than active medication or pro-drug that are included within the manufacturing process or is contained in finished pharmaceutical dosage form," and can also be used to increase the bioavailability of pharmaceutical products in certain instances.^[2-6]

Excipients are generally added along with the active pharmaceutical ingredients in order to:

1. Protect, support or enhance stability of the formulation
2. Improve patient acceptance.
3. Help improve bioavailability of active drug

- 4.
5. Enhance overall safety and effectiveness of the formulation during its storage and use.^[2-6,7]

History of excipients

Historically, excipients are considered inactive materials from pharmacology and come from various sources such as biological, mineral and synthesis. It frequently contains components, processing aids and impurities related to production. Excipients in the dose form can usually exceed API (active pharmaceutical ingredient) significantly..^[8]

Approximately 800 different excipients were used in marketed pharmaceutical products in the United States.^[9]

Typically, excipients have multiple uses in a formulation and microcrystalline cellulose, for example, can be a filler / diluent, solid-dosing binder. To improve powder or compression and improve production capabilities, for example, diluents / fillers, lubricants and gliders, excipients are possible to be added.

Excipients are also used to improve drug stability, e.g. low humidity rates of ordinary fillers or antioxidants (in case of oxidative instability); to improve disintegration and, as such, dissolution,

e.g. disintegrants; to improve palatability, e.g. sweeteners and flavourers. Excipients are also used for improving drug stability. The look of the complete package^[10]

Classification of excipients:

1. Classification of excipients based on their Functions:

- Diluents are soluble substances used in order to increase the bulk volume of solid dosage forms if the medicine itself is insufficient to produce a solid dosage form, weighing enough and of sufficient size.^[11]
- In tablet formulations, binders are commonly used to give powder mix cohesion to improved granule flow characteristics. Like starch.^[11]
- Disintegrants are used to counteract lubricants in solid dosage forms. These disintegrants swell to the extent of a tablet content by forming a soft solid mass in the presence of an external solvent. The commonly used disintegrants are starch and its modified versions:^[12]
- In mouth-dissolution or orodispersible tablets, super-disintegrants are used for immediate drug release from the oral medicine delivery system. These substances are hydrophilic, absorbing water and swell which result in the solid dosage leakage of the drug. Sodium starch glycolate is some of the common superdisintegrants.^[11]
- Lubricants reduce friction at the interface between the tablet surface and the die wall, preventing tablets from sticking onto the punch faces, making it easy to eject tablets from the die cavity and thus reducing the wear of tablet compression punches and dies. • Also, they are added to glidants by reducing interparticle friction when they are used to increase powder flow. The fatty acid lubricant with optimal concentrations of 0.5% to 2.0% (w/w) is the most widely employed stearic acid.^[13]

2. Classification of Excipient based on their origin:

- Animal source: - Lactose, Gelatin, Stearic acid, Bees wax, Honey, Musk, Lanolin etc.^[6]
- Vegetable source: - Starch, Peppermint, Turmeric, Guar gum, Arginates, Acacia etc.

- Mineral source: - Calcium phosphate, Silica, Talc, Calamine, Asbestos, Kaolin, Paraffin, etc.
- Synthetic: - Boric acid, Saccharin, Lactic acid, Polyethylene glycols, Polysorbates, Povidone etc.^[2-6]

The International Pharmaceutical Excipient Council (IPEC) classified

excipients into four classes based upon available safety information:^[14]

New excipients of chemicals. If the pre-clinical safety evaluation of the material in its intended pharmaceutical application demonstrates the safety of the material, the material must be considered a new excipient and the pre-clinical safety assessment must be carried out.^[15]

Existing chemical excipients. These are a class of excipients where animal safety data does exist, as data may have been used in another regulatory application. In order to justify their use in humans depending upon route and duration of use, additional security information may have to be collected.^[10]

Existing chemical excipients. These are excipients that have been used in man, but for another route of administration, higher dose etc., and hence additional safety data may be required.^[10]

4. The last class of established excipients is the new changes or combinations that would not necessitate safety assessment.^[16]

Excipient uses and benefits

Most pharmaceutical excipients used in oral dosage forms of immediate release have traditionally been considered to be "inert."

These excipients are simply employed to improve handling and dosing uniformity (for example, fillers or diluents), to ensure the stability of drugs (for example, antioxidants), good taste (for example, flavors and sweetening agents) or appearance (for example, components of coloration or coating). Other excipients are essential to the manufacturing process (e.g., glidants, lubricants and binders), while some contribute to the release of the drug from the dosage form (e.g., disintegrants) so that drug availability is not impaired by the incorporation of the drug into a solid dosage form. Other dosage forms (e.g., suspensions) require additional excipients (e.g., suspending agents) to

avoid drug agglomeration, precipitation, and to facilitate drug dispersion with agitation.^[17]

Low solubility drugs have traditionally required excipients like surfactants or wetting agents, which are an essential preliminary step for drug absorption to facilitate or speed up release and dissolution. These excipients "actively" contribute to the bioavailability of drugs with low solubility. In addition, some of these excipients can improve drug permeability (i.e. enhancers of absorption) and others may lower absorption by affecting gastrointestinal physiology (e.g. motility).^[17]

Some excipients, such as nonionic tocopheryl surfactants, are able to enhance oral bioavailability of drugs by inhibiting the efflux pumps of the GI mucosa.^[18]

There are numerous examples of typical excipients affecting drug absorption. For example, carbohydrates^[19] and phosphoric acid delay gastric emptying, due to their caloric content and pH, respectively, and affect the saturable absorption of riboflavin and the saturable biotransformation of salicylamide.^[20]

As another example, Bicarbonate speeds up gastric emptying and increases paracetamol absorption rate^[21], and alters fluvastatin interaction with membrane phospholipids^[22].

Sodium acid pyrophosphate decreased small intestinal transit times by 43 percent and reduced the absorption of ranitidine from a effervescent tablet.^[23]

To further complicate the issue, these effects can be drug and/or dose-dependent. Mannitol (2.264 g) reduced small intestine transit time by 23%, cimetidine AUC by 30% and C_{max} by 50% when compared with sucrose, because sucrose does not alter small intestine Transit. The magnitude of mannitol's effect was shown to be dose-dependent in the range between 0.755 and 2.265 g.^[24]

PEG 400 (polyethylene glycol), which stimulates gastrointestinal motility and accelerates small intestine transit^[25], at a dose of 10 g reduced ranitidine bioavailability by 30% first^[26], but later doses of 1 g proved to increase the bioavailability by 41%, whereas doses of 2.5 and 5 g decreased the bioavailability by 38%.^[27]

Subsequently, it was shown that PEG 400 enhanced the bioavailability of ranitidine in males, but not in females^[27], when used in a range between 0.5 and 5 g, with a maximum effect at 0.75 g (63% increase). PEG 400 showed a non-linear concentration dependence with a maximum at 1%^[28].

The same mechanism of action has been described for other PEG and PEG derivatives.^[29]

Certain excipients, such as sorbitol, can reduce the bioavailability of drugs in solution with high intestinal permeability, not only at large doses, but also at very low doses (e.g., 7, 50 or 60 mg). This effect may be drug dependent and thus it cannot be extrapolated between drugs or drug classes. More importantly, the effect appears to be subject-dependent since it seems to affect only sensitive patients.^[17]

Although the oral solution of lamivudine has shown to be bioequivalent to the oral tablet of the reference product in adult patients^[30], the exposure after the administration of the reference oral solution of lamivudine when administered with reference zidovudine and abacavir oral solutions was 45% lower than that observed with the corresponding reference tablets in children.^[31]

The bioavailability of risperidone could be reduced by a small amount of sodium lauryl sulfate (3.64 mg), and comparisons between the dissolutions profiles can not be detected. The surfactant, however, accelerate wetting and dissolving risperidone easier and dissolves very quickly. Sodium lauryl sulfate can be used to improve dissolution and permeability, but the deleterious effects have been described on permeability / absorption.^[32]

Carboxymethylcellulose.^[33] Carrageenan^[34], ascorbic acid^[35], and EDTA^[36] may also enhance the absorption of drugs.

Two experiments on bioequivalence were conducted by García-Arieta with ranitidine, and metoprolol solutions containing 5 g of sorbitol. These studies demonstrated that a higher effect of sorbitol on ranitidine compared to metoprolol. Ranitidine C_{max} and AUC decreased by 50% and 45% respectively, whereas metoprolol C_{max} and AUC only decreased by 23% and 7%, respectively.^[17]

Low solubility drugs traditionally have required surface substances or weighting agents, which is a necessary pre-acceptance step for drug absorption, to facilitate or accelerate drug release and dissolution. These excipients "actively" contribute to low solubility medicines' pharmacological bioavailability. Further, the permeability of low-permeability medicinal products (i.e., enhancer absorption) has been increased in some of these excipients while others can reduce absorption, affecting gastrointestinal physiology (e.g. motility).^[17]

Excipients typically have multiple uses within a formulation and for example microcrystalline cellulose can be a filler/diluent, binder or disintegrant in a solid dosage form.^[1]

For the development of solid dosage forms, natural polysaccharides are widely used. These monosaccharide (sugar) polymers are cheap and available in various structures with various features. They are extremely stable, safe, toxic, and naturally form hydrophilic and gel. Pectin, amylase and starch are a few polysaccharides commonly used in dosage forms controlled release. In the physiological environment of the stomach and small intestine, non-starch linear polysaccharides remain intact but degrade with the bacterial inhabitants of the human colon which make them potential for the benefit of targeted systems of colon delivery..^[37]

The tolerability and/or local toxicity of several compounds has been shown to be improved by cyclodextrine (CDs). In particular, the gastroduodenal and eye damage of several NSAIDs is reduced^{[38], [39]}

protect against the tissue irritation/injuries in a parenterally or topically administered compounds (such as β -CD, and chlorpromazine in rats and retinal acid in humans).^[40]

Whilst the decrease in prostaglandin synthesis incurred by NSAID is well established as a leader in gastrointestinal toxicity, NSAIDs are also known to be direct gastrointestinal mucosal irritants. The fact that NSAIDs such as indomethacin, rofecoxib or flurbiprofen are used to decrease gastrointestinal toxicity substantially suggests cyclodextrins are

reduced local toxins, and/or are increased tolerances by forming integration complexes that effectively reduce direct contact / exposures to the compounds.^[41]

Possible side effects of excipients

In the handling of pharmaceutical products safety was always the most important requirement and most studied. The safety of excipients has received less attention because of its inertia. However, it is now known that three problems may compromise drug safety: (a) production, distribution, and use; (b) drug-excipient interactions; and (c) toxicity, which may be responsible for frequent 'adverse effects' that are sometimes notable. Several cases have demonstrated that excipients are responsible rather than the active ingredient for several adverse drug reactions. Various reports describe adverse drug reactions. Various reports describe adverse drug reactions due to the addition of excipients.^[6]

Many popular excipients, such as alcohol, organic acids, (citric acid and parabens) have functional chemical groups ; reactions are possible between different medicines and these substances and even responses between the excipients in drug formulation. The reactions can occur in a solid and solution state^[42].

The effect of reactions between the active pharmaceutical substance and the excipients could be a reduction in drug concentration, but at the same time unknown structure and biological activity would appear and, in the worst case, this could lead to adverse effects.^[43]

In principle, to protect the population from undesirable effects, excipients should be submitted to the same studies of toxicity as those required for active principles.^[44]

This certainly applies to many compounds, in particular food additives. However, additional substances used since decades can be classified as 'safe,' since it has had no adverse effects for human. The JECFA (Joint Expert Committee on Food Additives) has assessed excipients authorised to use them as food additives with respect to the toxicology involved in assessing the risk associated with the consumption of food additives or contaminants.^{[45][46]}

In adults (clinically as well as pre-clinically), most of this supporting data was generated. In fact, many good-looking excipients commonly used in adult medicinal products are linked to safety issues in paediatrics. This information is sparse in nature and difficult to access, unfortunately. In kids, severe adverse reactions to common excipients are documented in several cases.^[47]

In children, these excipients have been reported to have adverse reactions, including Lactose intolerance, Lactic acidosis induced by propylene glycol^[48] and Headache and Seizure induced aspartame^[49].

Cross-sensitivity in children with a sulphonamide allergy to saccharin reactions and dye induced reactions in aspirin sensitive patients.^[50]

It is often difficult to access information quickly for patients with known excipient sensitivities — not all excipients are listed on the label. Formulations may vary and may not be published always.^[51]

Aspartame is considered a highly hazardous substance, a widespread sweetener used in many food products. Aspartame was found in 1965. It is split into phenylalanine, aspartic acid, and methanol and has a lot of controversy to date. The excess phenylalanine prevents the transport of significant amino acids into the brain, thus reducing dopamine and serotonin levels. A high concentration of aspartic acid is a toxin that causes neurons to hyperaxially excitate and also precursors other glutamates as an excitatory amino acid. Their excess quantities and astrocytic absorption induces excitotoxicity and leads to astrocytes and neurons degeneration. The methanol metabolites cause CNS depression, vision disorders and other symptoms leading ultimately to metabolic acidosis and coma.^[52]

Titanium dioxide nanoparticles were shown to cause an increases in the generation of reactive oxygen species and a decrease in the potential of mitochondrial membranes [53]. Exposure to titanium dioxide nanoparticles also resulted in changes confirmed by mitochondrial stain to the mitochondrial morphology. This information collectively provides clear evidence that TiO₂ nanoparticles have a potential implications for neurological astrocyte dysthrocytes.^[54]

In the case of BBT (butyl hydroxytoluene), which serves as antiseptic and for their antioxidants and radical anti-free activities, lesions in hepatic cells which are probably due to its inductive effect on hepatic enzymes are the toxic effects most commonly encountered in the laboratory animals after chronic administration.^[6]

People with allergies and intolerances are at risk of being carefully considered. Immune system reactions occur in patients with allergies, whereas intolerance is determined by the genetically transmitted metabolic abnormalities (phenylketonuria, Galactosemia, etc.) or family predisposition (diabetes, etc.). Contrary to what is generally assumed, the greatest risk from colours, as extraction processes can leave traces of natural-origin products^[55]

For antioxidants that are human or natural substances which prevent or delay certain types of cell damage, sulphites are present in a specific group of antioxidants: sodiium and potassium bisulfites, sodium and potassium metabisulfites, sodium sulfites and sulfurous anhydrides. In both the pharmaceutical and food industries, sulphites are widely used as antioxidants. In the case of sulfites, we have to bear in mind the hypersensitivity of vulnerable populations. Broncoconstriction, pruritise, hives, chest pain, angioedema, and hypotension sometimes lead to loss of awareness are characteristic of hypersensitive reactions. These reactions usually involve patients who have already suffered asthma attacks and typically occur when eating sulfite-containing food. Unfavorable phenomena in the use of pharmaceutical sulfites are far less frequent.^[56]

Sulfites, often added to parenteral or topical formulations and the medicines have to be marked as containing sulfites. Some ketoconazole, parenteral chlorpromazine, chlorpheniramine, dopamine, and dexamethasone injections have been added to sulphites, for instance.^[57]

Gluten is a protein in wheat that is coeliac disease is sensitive to. The classic manifestation of these patients' intolerance is an enteropathology (malabsorption syndrome), but atypical symptoms such as herpetic dermatitis, iron deficiency anæmia, alopecia and osteoporosis are also

encountered.^[6] It can be difficult to recognize gluten-containing excipients. Starch, dextrans, or dextrins, alcohol, caramel or brown rice syrups may contain excipients that may potentially contain gluten.^[57]

Excipients toxicities (cases)

In Nigeria, 84 kids died of diethylene glycol contaminated glycerin in a teething formula. Nigerian National Agency for Food and Drug Administration and Control discovered diethylene glycol (DEG) in four batches of the teething medication. The toxic alcohol DEG is used as a cheap excipient for brake fluids and paints as well as for household cleaning products.^[58]

In Panama (2006), 46 persons also died of diethylene glycol after taking cough syrup. We have two possible scenarios: one of mislabeling and the other of misuse-be they deliberate or unintentional. If the role of excipient and their possible adverse effects is better known to clinicians and patients, many unnecessary adversities can be prevented.^[59]

In paediatric populations, co-administration of benzyl, propylene glycol and polysorbate has resulted in a range of different toxicological syndromes. Medicines with potentially harmful drug formulants were received by hospitalized neonates, in particular.^[60]

It is possible to prevent the daily intake exceeding the toxic threshold due to the small quantities used in drug formulations, even if the excipient is known to be potentially harmful. However, because the Summary of Product Features does not generally include quantitative information of the excipient amount, it is difficult for the practitioner to make an informed decision. The extent of possible harm caused by the formulation excipients has not been established.^[61]

The toxicity of a drug excipient in clindamycin injection is investigated in a case report. A kid has been infected with clindamycin-treated staphylococcal septicaemia. The first two doses of clindamycin had no problem, but the baby was deeply desaturated and the chest splitting was needed after the third and fourth doses. In view of problems that could have occurred as a cause, clindamycin was discontinued. In many

pharmaceutical formulations, benzyl alcohol is used as a preservative. The toxicity of benzyl alcohol in neonates began to appear in the beginning of the 1980s. In 10 premature babies, they reported a gasping syndrome.^[62]

Benzyl alcohol is oxidized to benzoic acid, then combined with the liver's glycine and released into the urine as hippuric acid. Benzyl alcohol has accumulated in these infants as the way benzyl alcohol is metabolized in premature babies is immature. The cause of the gasping syndrome is considered to be the immature pathways associated with the relatively high dose of benzyl alcohol. The most striking feature of the gasping syndrome has been reported but there were other symptoms, such as metabolic acidosis, hemorrhage and neurology. Seventeen deaths from neonats were reported believed to be due to the toxicity of benzyl alcohol.^[63]

Conclusion

As shown above, excipients have been used for a long time because of its benefit in enhancing drug effect, performance, solubility and other beneficial properties that make the drug more effective and safe.

On the other hand, the potential adverse effect of the excipients should not be underestimated and a periodic review and follow up of side effects that may appear and occur after a drug administration should not be limited to the active medication in the drug formula but also the excipient should be taken into account.

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