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REVIEW ON THE EFFECTS OF EXCIPIENT IN HEART FAILURE

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ABSTRACT

Excipients are included in dosage forms to aid manufacture, administration or absorption. They are considered pharmacologically inert, excipients can initiate, propagate or participate in chemical or physical interactions with drug compounds, which may compromise the effectiveness of a medication. Exicipients are not exquisitely pure. Even for the most commonly used excipients, it is necessary to understand the context of their manufacture in order to identify potential active pharmaceutical ingredients interactions with trace components .Heart failure is a common and debilating syndrome that is associated with a highly complex drug region. All of these factors conspire to increase the risk of heart failure exacerbation by direct myocardial toxicity, drug interaction or both. The potential role in the occurrence of heart failure of cytostatics, immunomodulating drugs, calcium channelblocking agent, beta blockers and miscellaneous agents.Active pharmaceutical ingredient (API) is "a substance used in a finished pharmaceutical product, intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings." Ideally,an excipient is pharmacologically inactive, non-toxic and doesnot interact with the active ingredients or other excipients.Toxicity may relate to compounds used as excipients in the final dosage form or to residues of compounds (such as solvent) used during the manufacturing process.Examples of adverse reactions that occurs : Tartrazine - Colouring agent - Caution in patient with hypersensitivity and hyperkinetic activity in children.Aspartame – Sweetener- Caution in patient with phenyl ketonouria.

INTRODUCTION

An excipient is a substance formulated alongside the active ingredient of a medication, included for the purpose of long-term stabilization, bulking up solid formulations that contain potent active ingredients in small amount or to confer a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug absorption reducing viscosity, or enhancing solubility. The selection of appropriate excipients also depends upon the route of administration and the dosage form, as well as the active ingredient and other factors. "The word excipient is derived from the Latin word excipere, meaning 'to receive', which is simply explained as, other than, Pharmaceutical excipients are basically everything other than the active pharmaceutical ingredient.[1]

Role of Excipient

 Ease of administration to the target patient population by the intended route.

 Improved dosing compliance

 Facilitate drug absorption

 Modulating solubility and bioavailability

 Maintains a polymorphic forms

 Maintaining the PH

 Preventing aggregation or dissociation

Classification

Excipients are classified according to their functions.

They are:

 Binder

 Disintegrants

 Fillers (diluents)

 Lubricants

 Glidants

 Compression aids

 Colors

 Sweeteners

 Preservatives

 Flavors

 Film formers/coatings

Suspending/dispersing agents/surfactants[2]

Drug – Excipient Interactions

Exact mechanism of drug excipients interaction is not clear. Drug-excipients interaction can either be beneficial or detrimental, which can be simply classified as:

1. Physical interactions 2. Chemical interactions

Physical interaction: It is quite common, but is very difficult to detect. A physical interaction doesn't involve any chemical changes. Physical interactions are frequently used in manufacturing of dosage form, for example to modify drug dissolution. Physical interaction can either be beneficial or detrimental to product performance. An example of a physical interaction between an API and an excipient is that between primary amine drugs and microcrystalline cellulose. When dissolution is carried out in water a small percentage of the drug may be bound to the microcrystalline cellulose and not released. For high-dose drugs, this may not be a major issue, but for low dose drugs it can lead to dissolution failures. In this way we obtain a more homogenous powder blend. After the medicine, e.g., a tablet has been administered to the patient, the aqueous environment of the gastrointestinal tract (GIT) either causes the smaller API particle or other carrier particles to dissolve or causes the surface interactions to change to allow the smaller particles to be released from the larger carrier particles. But as we have already stated, physical interactions can also be detrimental, and magnesium stearate is recognized within the pharmaceutical industry for causing problems such as reduced tablet "hardness" and dissolution from tablets and capsules. Adsorption of drug molecules onto the surface of excipients can render the drug unavailable for dissolution and diffusion, which can result in reduced bioavailability. For example, antibacterial activity of cetylpyridinium chloride was decreased when magnesium stearate was used as lubricants in tablet containing cetylpyridinium chloride; this was due to adsorption of cetylpyridinium cation by stearate anion on magnesium stearate particle.

Chemical interaction: 1.Chemical interaction involves chemical reaction between drugs and excipients or drugs

2. Impurities/ residues present in the excipients to form different molecules.[3].

Chemical interactions between drug and excipient

Primary amine group of chlorpromazine undergoes reaction with glycosidic hydroxyl group of reducing sugar dextrose to form amine, which finally breakdown to form Amidori compounds In one another study it was observed that release ofdiclofenac sodium from matrix tablet was inhibited by polymer chitosan at low pH, most possibly via formation of ionic complex between diclofenac sodium and ionized cationic polymer Secondary amines may also interact with reducing sugars. Examples of excipients that contain double bonds include sodium stearyl fumarate and sorbitan monooleate.

Interaction of drug with excipient residues/ impurities

Exicipients are not exquisitely pure. In common with virtually all materials of minerals, synthetic, semi-synthetic or natural origin manufacture involves using starting materials, reagents and solvents. Residues invariably remain after isolation. Low levels of residues may have a greater impact than might be expected, however-particularly where the ration of excipient to drug is very high, or where the residue has low molecular weight or acts as a catalyst. Impurities found in common excipients Excipient Residue Povidone, crospovidone, polysorbates Magnesium stearate, fixed oils, lipids Lactose Benzyl alcohol Polyethylene glycol Microcrystalline cellulose Starch Talc Dibasic calcium phosphate dihydrate Stearate lubricants Hydroxypropylmethyl/ethyl celluloses Peroxides Antioxidants Aldehydes, reducing sugars Benzaldehyde Aldehydes, peroxides, organic acids Lignin, hemicelluloses, water Formaldehyde Heavy metals Alkaline residues Alkaline residues Glyoxal Dextrose is widely used as tonicity modifier in the parenterals dosage form and it is used as nutrition solution. Sterilizations by autoclaving of such parenteral preparations containing dextrose can cause isomerization of dextrose in fructose and formation of aldehyde (5-hydroxymethyl furfuraldehyde), which can react with primary amino group to form shiff base and colour development Thorough characterization of the drug substance and awareness of residues in excipients may help resolve or obviate such mysteries. For example Oxazolam degrades in the presence of microcrystalline cellulose may be attribute to carboxylic acid groups on the cellulose surface in addition to effect of water.[4].

Nanoformulations Cardiovascular System

The cardiovascular system plays a major role in health and disease in the body, and any deregulation in the cardiovascular system can lead to cardiovascular diseases, including atherosclerosis, myocardial infarction and microvascular disease. One of the major risk factors for cardiovascular disease is high blood pressure. Numerous antihypertensive drugs are used to control hypertension including beta-blocking agents, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, diuretics, calcium antagonist and alpha-receptor blocking agents. The optimal results for blood pressure control are obtained by combinations of two or more of antihypertensive agents. Deregulation in the cardiovascular system can lead to cardiovascular diseases. Before targeting any system, it is important to understand the physiology and pharmacology; otherwise compensatory systems may overshadow the effects of the target. Adenosine is a purine nucleoside, involved in different physiological and metabolic activities. The adenosine has its physiological effects in most tissues and organs. Thus, it plays an important role in vascular regulation by the interaction with

four subtype's receptors: A1, A2A, A2B, and A3 adenosine receptor. In vascular tissue, the vasodilation effect is mainly induced by both A2A AR and A2B AR whereas the vasoconstriction effect is through A1 AR and A3 AR As mentioned earlier, A2AAR is involved in vascular relaxation is through an endothelium-dependent mechanism. Another study demonstrated the involvement of CYP-epoxygenases in vascular relaxation.[5]

Polymer System

Drug/ therapeutic

Disease state

Liposomes

Telmisartan

Hypertension

PLGA

Pitavastatin

Atherosclerosis

Pioglitazone

Atherosclerosis

PEG

Myocardial infraction

Liposomes

SiRNA

Atherosclerosis

Exosomes

SiRNA

Inflammation

PEG

Peptide

Atherosclerosis

Drugs Used In Heart Failure

 ACE inhibitors (angiotensin converting enzyme): This class of drugs is used in the treatment of congestive heart failure. These medications block the formation of angiotensin II, a hormone with many potentially adverse effects on the heart and circulation in patients with heart failure. They prevent the development of heart failure and heart attacks. The wealth of the evidence supporting the use of these agents in heart failure is so strong that ACE inhibitors should be considered in all patients with heart failure, especially those with heart muscle weakness. Possible side effects of these drugs include, a nagging, dry cough, low blood pressure, worsening kidney function and electrolyte imbalances and allergic reactions.When used carefully with proper monitoring, however, the majority of individuals with congestive heart failure tolerate these medications without significant problems. Examples of ACE inhibitorsinclude captopril,enalapril.

 Angiotensin Receptor blockers: For those individuals who are unable to tolerate the ACE inhibitors, an alternative group of drugs, called the angiotensin receptor blockers (ARBs), may be used. These drugs act on the same hormonal pathway as the ACE inhibitors, but instead block the action of angiotensin II at its receptor site directly. A small, early study of one of these agents suggested a greater survival benefit in elderly congestive heart failure patients as compared to an ACE inhibitor. However, a larger, follow-up study failed to demonstrate the superiority of the ARBs over the ACE inhibitors. Possible side effects of these drugs are similar to those associated with the ACE inhibitors, although the dry cough is much less common. Examples of this class of medicationsinclude:Losartan,candesartan,telmisartan,valsartan,olmesartan.[6,7,8].

 Beta-blockers: Certain hormones, such as epinephrine (adrenaline),

norepinephrine, and other similar hormones, act on the beta receptors of various body tissues and produce a stimulative effect. The effect of these hormones on the beta receptors of the heart is a more forceful contraction of the heart muscle. Beta-blockers are agents that block the action of these stimulating hormones on the beta receptors of the body's tissues. Since it was assumed that blocking the beta receptors further depressed the function of the heart, beta-blockers have traditionally not been used in persons with congestive heart failure. In congestive heart failure, however, the stimulating effect of these hormones, while initially useful in maintaining heart function, appears to have detrimental effects on the heart muscle over time.. It appears that the key to success in using beta-blockers in congestive heart failure is to start with a low dose and increase the dose very slowly.Possible side effects include:fluid retention, low blood pressure. Low pulse, and general fatigue and light-headedness.Beta-blockers should generally not be used in people with certain significant diseases of the airways [for example emphysema, asthma] or very low resting heart rates. While carvedilol has been the most thoroughly studied drug in the setting of congestive heart failure, studies of other beta-blockers have also been promising. Research comparing carvedilol directly with other beta-blockers in the treatment of congestive heart failure is on-going. Long acting metoprolol is also very effective in individuals with congestive heart failure.

 Digoxin: Digoxin has been used in the treatment of congestive heart failure for hundreds of years. It is naturally produced by the foxglove flowering plant. Digoxin stimulates the heart muscle to contract more forcefully. It also has other actions, which are not completely understood, that improves congestive heart failure symptoms and can prevent further heart failure. However, a large-scale randomized study failed to demonstrate any effect of digoxin on mortality. Digoxin is useful for many patients with significant congestive heart failure symptoms, even though long-term survival may not be affected. Potential side effects include nausea, vomiting, heart rhythm disturbances, electrolyte abnormalities.[9,10,11].

 Diuretics: Diuretics are often an important component of the treatment of congestive heart failure to prevent or alleviate the symptoms of fluid retention. These drugs help keep fluid from building up in the lungs and other tissues by promoting the flow of fluid through the kidneys. Although they are effective in relieving symptoms such as shortness of breath and leg swelling they have not been demonstrated to positively impact long-term survival.Nevertheless, diuretics remain key in preventing deterioration of the patient's condition thereby requiring hospitalization. When hospitalization is required, diuretics are often administered intravenously because the ability to absorb oral diuretics may be impaired, when congestive heart failure is severe. Potential side effects of diuretics include: dehydration, abnormalities, particularly low potassium levels, hearing disturbances,and low blood pressure.It is important to prevent low potassium levels by taking supplements when appropriate. Such electrolyte disturbances may make patients susceptible to serious heart rhythm disturbances. Examples of various classes of diuretic include, furosemide, hydrochlorothiazide, torsemide, spironolactone, metalozone.Aldosterone has many theoretical detrimental effects on the heart and circulation in congestive heart failure. Its release is stimulated in part by angiotensin II. In patients taking ACE inhibitors, however, there is an "escape" phenomenon in which aldosterone levels can increase despite low levels of angiotensin II. Medical researchers have found that spironolactone (Aldactone) can improve the survival rate

of patients with congestive heart failure. In that the doses used in the study were relatively small, it has been theorized that the benefit of the drug was in its ability to block the effects of aldosterone rather than its relatively weak action as a diuretic (water pill). Possible side effects of this drug include elevated potassium levels and, in males, breast tissue growth.[12,13,].

 Aspirin: A daily aspirin regimen can lower your chance of having a heart attack. However, this kind of therapy isn't for everyone. Side effects of regular aspirin use include gastrointestinal bleeding and stroke due to broken blood vessels. Internal bleeding can also occur if you mix aspirin with ibuprofen.

 Statins: These cholesterol-lowing medications are meant to help lower your risk of a heart attack or stroke. But they can also cause muscle pain, increased blood sugar, and even liver damage. Statins can also cause mental fogginess, to the point that some patients suffer from memory loss.

 Nitrates: If you have heart disease, you have probably been prescribed nitrates for chest pain. While this medicine can help ease chest discomfort, it can also cause dizziness, headaches, and light-headedness. Some nitrates can also cause an allergic reaction, like skin tingling or itching and burning under the tongue.

 Anticoagulants: With heart disease, one of the main problems is plaque. A build-up of plaque in a blood vessel can lead to a blood clot, which can cause serious problems when it breaks free of the plaque. For instance, if the clot gets lodged in a heart vessel, it can partly or completely block blood flow to the heart and cause a heart attack. If the blood clot travels to the lungs, a pulmonary embolism could result. And if a clot lodges in the brain, a stroke could occur. Anticoagulants work by preventing blood clots from forming. Some do this by preventing your body from making substances called clotting factors. Examples of anticoagulant include: Warfarin,Heparin.[14].

Medication Which Cause

Heart Failure: Heart disease occurs when the blood vessels of your heart are damaged or diseased. This leads to fatty deposit build-up's called plaque, which can block the blood vessels or lead to blood clots. Heart disease can cause many serious health problems such as heart attack, congestive heart failure, or heart rhythm problems. All of these health issues can result in death, so treating heart disease is important

Nonsteroidal anti-inflammatory drugs (NSAIDs): NSAIDs include diclofenac, ibuprofen, indomethacin, and ketorolac. NSAIDs can boost heart failure odds because they make you retain water and salt, make it harder for your blood to flow, and make it tougher for diuretic drugs to work.

Diabetes medications: Thiazolidinedione (pioglitazone, rosiglitazone) cause fluid retention and weight gain in people with heart failure and make people who don't have it more likely to get it. , but dipeptidyl peptidase-4 inhibitors like alogliptin, linagliptin, saxagliptin, sitagliptin cause heart failure.

 Blood pressure medications

 Calcium channel blockers can worsen oedema or fluid that stays in your body's tissues.

 Central agonists such as clonidine, moxonidine cause changes in the way your body releases hormones that affect your heart.

 Antifungal medications

 Cancer medications

 Stimulants

 Antidepressant

 Tumor necrosis factor (TNF) inhibitor [15].

CONCLUSION

Excipient are included in dosage forms to aid manufacture, administration or absorption. Excipient is pharmacologically inert substances but it causes toxicity due to physical or chemical interaction with drug compound. They don't have active role in the prevention or treatment of particular aliments. Drug excipient interactions may take a long time to be manifested in conventional stability testing progammes.Deregulation in the cardiovascular system can lead to cardiovascular disease. Before targeting the cardiovascular system, it is important to understand the physiology and pharmacology of system, Otherwise it effects the target.Through drug-delivery and Nano formulation we can reduced the effects of excipient in heart failure . Great progress has been made in the development of different class of excipient into a drug-delivery system in cardiovascular disease.[16].

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