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AlCOHOL DOSE DUMPING AND ITS CURE: A REVIEW

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ABSTRACT

Alcohol dose dumping is phenomena of sudden release of dose. This sudden release of dose is occurs due to the ingestion of drug with alcohol. Due to sudden release of dose so many side effects occur. Some of side effects are serious and some are not so serious. To solve this problem modified release of dosage form of drug is used. Modified release of drug prevents sudden release of drug the side effects of due to dose dumping can be avoided. Effect of the drug also gets maintained.

KEYWORDS: Alcohol Dose Dumping, Coating, MR Formulations, Oral Dosage Form, Drug.

INTRODUCTION

Oral drugs are ingested to provide therapeutic effect when administered. But sometimes the fluids with aid of which we ingest affect the absorption and distribution of the drug. Some drugs are fluid/meal sensitive and in presence of specific meals they deviate from their original ADME.[1] While ingesting drugs nature of fluid must be consider to avoid those deviations. The deviation can either retard or enhance drug delivery; this is totally based on types of meal we took either before, during or after administering drug. Sometimes these deviations can be fatal. Labels should be read properly to avoid these types of mishaps or drug should be prepared in manner that any meal does not affect its delivery.[2]

ALCOHOL – INDUCED DOSE DUMPING (ADD)

Dose dumping is an event in which environmental factors may cause exaggerated or premature release of a drug. This can significantly increase the concentration of a drug or excreted out without performing its therapeutic effect in the body and therefore produce adverse effects (sometimes can be severe) or even drug-induced toxicity and if the causative agent of Dose dumping is Alcohol then it is known as "Alcohol – Induced Dose Dumping" or "Alcohol Dose Dumping".

Dose dumping can also be defined as rapid release of whole dose or significant fraction of dose in short period of time. Side-effects can be critical or can cause even fatality, these completely depends on therapeutic effect, therapeutic indication and the pharmacokinetics of API.[3]

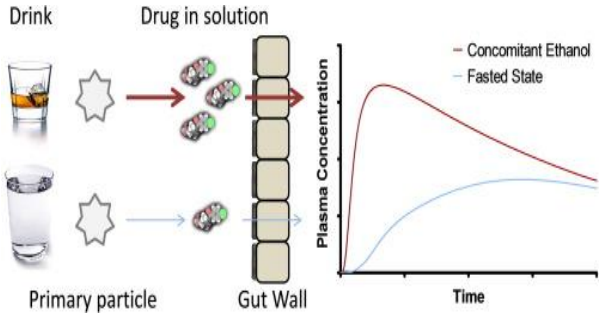

Fig. 1.1: Effect on Alcohol and Water on Drug Plasma Concentration-Time Profile.

Dose dumping is generally seen in drugs taken orally which digested in the GI tract. Dose dumping occurs when patients take their medication and around the same time, they can also ingest alcohol or fatty meal that can be altered delivery of drug. These substances may act on the outer layer of formulation (drug's capsule) to stimulate the absorptive surface of body to enhance the rate of drug uptake and speed up drug release, or Dose dumping is the common disadvantage found in a MR dosage form.[4]

Consumption of alcoholic beverages is widespread throughout the world. Specific patient populations, such as people suffering from depression or with chronic pain may tend to turn to alcohol as they think alcohol is best way to cope with their conditions as the physiological effects of alcohol are similar to those of anaesthetics. ADD may occur when patients consume alcoholic beverages with prescribed medication despite product warning to the contrary. Consumption of Alcohol should be avoided 30 minutes before and after administration of drug. Sometimes patient knowingly uses highly potent alcoholic beverages with medication to obtain more

effect (usually opioid analgesics) from SR formulations.[5]

However, there are certain patients who are vulnerable to overdose through ADD with MR medications due to concomitant consumption of alcoholic beverages. Release of drug in MR system is either controlled by polymer film coating or by a polymer matrix. Alcohol Dose dumping occur when the controlled release of drug is compromised through the dissolution of the controlling agent in hydro-alcoholic liquids.

As per CDC, Alcohol is used as the 2nd beverage after water in US by most of adults. Frequency of consumption of Alcohol is so normal that chances of co-administration of Drug with Alcohol are very much high. Data shows that about 51% of the total drinkers of US are regular drinkers (can be defined as who consume at least 12 drinks in the previous year), and about 13% are infrequent drinkers (who consume up to 11 drinks in the previous year).[6]

Also, large number of medications (available on prescription and OTC drugs) has the tendency to interact with Alcohol. So, the chances of Dose Dumping enhanced greatly which can results in serious medical problems.

Immediate Release (IR) of dosage form are modified into different dosages form like Controlled-Release (CR), Extended-Release (ER) or Modified-Release (MR) to attain sustained therapeutic blood levels of drug over a prolonged time interval (12–24 h) and ensuring convenience of dosing. In pain relief medication frequent dosing of IR formulation (every 4-6 hour) leads to patient in-compliance and breakthrough pain can easily be avoided by ingesting single tablet/capsule formulated as CR, MR or ER product (1-2/day). Due to these advantages large number of formulations are being developed and marketed as MR dosage form. To overcome frequent dosing, MR dosage forms contains significant amount of API and various excipient especially rate controlling polymers which allow drug to release in slow and moderate fashion. As the MR formulations remains for longer time in one's body, so the chances of ADD increased significantly so the patient should avoid consumption of Alcohol beverages during formulation remains in stomach. General time of Alcohol absorption in body is 30 minutes, this time should be avoided at least.[7]

Consumption of Alcohol with/during presence of medication in stomach can leads to Alcohol-Drug interaction which leads to various side effects like

- Drowsiness
- Headaches
- Dizziness
- Fainting
- Loss of coordination or
- Fluctuations in blood pressure
- Abnormality in behavior

Various Serious Complications like

- Various Heart problems
- Internal bleeding
- Liver damage
- Depression
- Impaired breathing

The Food and Drug Administration (FDA) and European Medical Agency (EMA) have certain requirements for ADD. Both agencies have certain requirements in common and some requirements to be fulfilled differently. The table below shows the conflicting requirements of following two agencies for 3 major topics.

Topic	FDA	EMA
Methodological requirements	Dissolution medium: 0.1N HCl Alcohol concentrations: 0%, 5%, 20%, and 40% Time: every 15 minutes until 2hrs	Dissolution medium: same as that proposed for routine testing Alcohol concentrations: 5%, 10%, and 20% Time: not defined
Products to be tested	At least all (generic) versions for modified-release opioid drug products; more preferably for (all) modified-release drug products with risk of alcohol-induced dose dumping	All oral modified-release applications
Acceptance criterion	Generic drug formulation should show rugged performance in alcohol If a generic drug formulation releases more rapidly in alcohol, the rate should be comparable to that of reference product.	If *in-vitro* alcohol incompatibility of the drug product is demonstrated, product should be reformulated. If alcohol effect cannot be avoided and is present also in the reference product, applicant should justify or demonstrate that it lacks clinical relevance.

Fig.1.4. Comparison of FDA and EMA requirements with regards to in-vitro testing formulations at risk of ADD.

MR dosage forms are developed with the aim to release drug in a controlled fashion for longer period of time, but care has to be taken that the drug should not release the rapidly. Several studies found that if MR preparations of theophylline are administered with food, concentration of drug in serum is higher (food-induced change) as compared to the fasted state. Due to deviation from the release line, MR dosage form of theophylline can be termed as dose dumping. This dose dumping results in safety issues, exposure levels adverse reactions chances were increased. Dose dumping situations are dangerous in drugs which have narrow therapeutic index or centrally acting drugs (CNS Drugs) and will impact efficacy of drug. Clinical study which shows effects of food on rate and extent of absorption and comparison between fed and fasted stated conditions have to be performed as per guidelines provided by CDER (Center for Drug Evaluation and Research).[8]

Dose dumping in MR dosage forms become a serious concerning issue for regulatory authorities, especially for the opioid class of drugs. The first case and very well-known case of ADD comes in lime light in 2005, where the drug Palladone XL™ (hydromorphone hydrochloride) an opioid class of drug was withdrawn from market because Palladone XL™ when ingested with Alcohol (Ethanol), the bioavailability of hydromorphone hydrochloride increase 6 time in blood than the drug taken with water. When drug comes in contact with ethanol the entire dose released at once due to interference of Alcohol in drug release mechanism of Palladone XL™ tablets. Due to the immediate release of drug in body, blood-plasma level also shows significant amount of drug in body as compared to blood-plasma level when drug is administered with water. The interference of release of drug by alcohol which leads to rapid unintended release of MR formulation in larger amount due to intentional or accidental use of alcohol with drug is known as ADD. Simultaneous consumption of drug and alcohol complicates things as it may influence ADME (Absorption, Distribution, Metabolism and Excretion of Drug).[9]

Need to Resist Alcohol Dose Dumping

- ADD leads to premature release of dose which can affect Drug action.
- ADD can also alter the bioavailability of drug (Conc. of drug in Blood-Plasma increased significantly).
- Increase in Blood-Plasma level conc. of drug causes more adverse effects due to ADD.
- ADME (Absorption, Distribution, Metabolism and Excretion) of Drugs are affected badly due to ADD.
- Exaggerated release of drug produce many adverse effect (can be severe sometimes) or even drug-induced toxicity.
- Sometimes Alcohol act on drug's capsule to activate, surface absorption of drug in body which causes increase in drug uptake.

Due to above following reasons ADD must be avoided. These can be done by:

- To make people aware about ADD and its adverse effects.
- Changes to be made in formulation to avoid interactions with Alcohol.
- By applying coating on formulation so that it can resist the attack of Alcohol.

Alcohol Resistive Coating

In this process, a layer of Alcohol Resistive material (like Salts of Alginic acid, pthalates, Ethylene Chlorotrifluoroethylene (ECTFE), Polytetrafluorethylene (PTEF) etc.) can be applied to formulations to avoid ADD.[10,11]

Advantages of Alcohol Resistive Coating

- Alcohol Resistive Coating is found to be effective with many formulations.
- This process is very cheap as compare to other options.
- Process of application of coating is not much time consuming.
- Out of Awaking people about ADD, development of new formulations and Alcohol Resistive Coating, Alcohol Resistive Coating is the best option.
- This process has lesser or no adverse effects on body.
- As Coating process is well known and currently used significantly, no special arrangements to be made to start the process on industrial scale.
- Materials like Salts of Alginic Acid worked as Enteric Coated as well as Alcohol Resistive Material.

Disadvantages of Alcohol Resistive Coating

- Researches are still under process as this process is still in developing phase.
- Options for Alcohol Resistive materials are still less.
- Process of additional coating increases the cost of drug.

COATING TECHNIQUE

Coating is a process in which a layer of coating material is applied to the dosage form to achieve specific objectives. Generally Coating is applied to a wide range of oral solid dosage form including tablets, capsules, drug crystals and multiparticulates. Application of Coating to Tablets is used as sugar coating, film coating or any functional coating.[12]

Advantages

- It can shield tablets from sun, moisture and oxidation to improve the shelf life of tablets.
- To boost product appearance and recognition.
- By making the tablets smoother its ease to swallow.
- To incorporate another drug which create incompatibility.
- To protect drug from the acidic pH (in stomach) and release later on (in gastric environment).

- The coating increases the mechanical resistance of the tablets.
- To mask the API-associated odors and to improve flavor.
- Coating of special material makes release of drug in various pH at different GI sites.
- With special coatings materials, continuous or prolonged release can be achieved.

Disadvantages

- The process may result in various defects in coating like cracking, chipping etc.
- The process is expensive and time consuming.
- Expertise of skillful technician is required as the process is complicated.

Types of Coating: Basically, there are 2 types of Coating-

✓ Functional Coating
✓ Non-Functional Coating

Non-Functional or Regular film coatings are for masking taste, masking odor, identification by color and Pearly appearance. Main examples of non-functional Coating are-

- Sugar Coating
- Film Coating

Controlled or Functional release coating makes release of drug in various gastro intestinal sites depending on pH. Few examples of functional coating are-

- Enteric Coating
- Prolonged or Sustained release Coating
- Drug Coating either same or different

CONCLUSION

Alcohol Resistive Coating is beneficial to avoid ADD as it blocks the attack of Alcohol to various formulations especially MR formulations. This technique is cost effective, efficient and viable. Various Researches are still going on to access the benefits of this technique. The technique (Coating) used to resolve the problem of ADD is widely used currently. This is the simplest process as widely known; no special equipment, manpower etc. are required. By reducing occurrence of ADD adverse events of drug therapy in cold climatic condition can also be reduced. This also helps in reducing other side effects of drugs that occurs due to sudden release of the drug. The efficacy of drug is much better than other form of drug.

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