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PROSPECTIVE STUDY OF EXCIPIENTS & METHODS OF EVALUATION OF DRUG-EXCIPIENT INTERACTIONS

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ABSTRACT

Active pharmaceutical ingredient (API) that is nothing but drug is a chemical entity which is designed to treat or prevent any diseased condition. Excipients are the non-API natural or synthetic components that are added in pharmaceutical dosage form with API as functional or non-functional agents. A dosage form is said to be complete when these both components are present in it. It is impossible to make a formulation only with drug or without excipients. So, excipients have their own importance in formulating a dosage form. Different excipients have different functions and accordingly they are added in the formulation. The aim of a pharmaceutical company is to design and prepare an effective and safer dosage form. So, to fulfil this aim, compatibility should be taken in consideration while preparing a dosage form. API and the excipients must be compatible with each other. They should not cause any unwanted reaction which can cause deterioration of product. Hence, prior to formulate a dosage form the compatibility of API is tested with different excipients and accordingly the excipients are selected. For this prior study, different techniques and methods can be used. Accelerated

stability testing study can be performed. Apart from this, different methods like DSC, TGA, XRPD, FTIR, HPLC can be used. These methods will give an idea of compatibility between drug and excipients so that a proper, safer and effective formulation can be prepared.

KEYWORDS: API, Excipients, Preformulation.

INTRODUCTION

Active pharmaceutical ingredient and excipients are major components of a pharmaceutical formulation. So, for having a formulation with required pharmacological action and less side effects, it is very necessary that API and excipients are compatible with each other. It also helps to predict the shelf life of that formulation. That is why for testing the compatibility of API with different excipients, assessment is done with the help of different methods. So that, a prediction can be made that whether that excipient to be used with the API or not.

Introduction to excipients

Excipients are the natural or synthetic substances that are included in pharmaceutical dosage form along with API as either functional or non-functional agents. Examples of excipients include absorption enhancers, coloring agents, emulsifiers, extenders, diluents, fillers, flavors, preservatives, wetting agents, solvents, and sustained release matrices. An ideal excipient is the one that provides the volume, uniformity, and dose of the API in the medicine throughout the production process. Nowadays, pharmaceutical excipients are more than just simple substances added to complete a total volume formulation. These substances require numerous guarantees to the safety and efficacy of the medicine, such as ensure stability throughout the formulation process up to the administration of the medicine by the patient. They also may guarantee that the dose is administered and delivered with the same precision and accuracy. The addition of excipients with the API helps the formulation to function properly. Excipients must be added appropriately to a dosage form so that it can conveniently be administered enterally, parenterally or topically. Pharmaceutical excipients perform multiple functions, such as to complete the volume of the formulation, ensure stability by protecting the API, improve the precision and API dose accuracy in the product, improve bioavailability, facilitate the API administration by both improving the organoleptic characteristics or produce a final pharmaceutical formulation more pleasant, and, finally, to improve the acceptance of the treatment by the patient. The most important function of any excipient is to ensure the safety and efficacy of the medicine throughout the formulation, the storage period, and during and after its administration. Excipients can interact with the API and can cause

problems regarding formulation. They also can generate undesirable impurities or alter the absorption, distribution, metabolism and excretion (ADME) and ultimately reduce the bioavailability of the API.

Types of excipients

- ✓ Diluents
- ✓ Binders
- ✓ Disintegrating agents
- ✓ Antioxidants
- ✓ Preservatives
- ✓ Anti-adherents
- ✓ Glidants
- ✓ Lubricants
- ✓ Vehicles
- ✓ Sweeteners
- ✓ Coloring Agents
- ✓ Flavoring agents

Diluents:

Diluents act as fillers in pharmaceutical tablets to increase weight and improve content uniformity.

E.g., Lactose, Mannitol, Starch, etc.

Binders:

Tablet binder or binding agent are the substances which are added either dry or in liquid form during wet granulation to form granules or to promote cohesive compacts for directly compressed tablets.

E.g., Starch, Pregelatinized starch, Polyethylene glycol (PEG), Sorbitol, Hydroxy propyl methyl cellulose (HPMC), etc.

Disintegrating agents:

Disintegrants and super disintegrants are used in tablets and capsules to ensure the rapid break down into their primary particles, facilitating the dissolution or release of the active ingredients.

E.g. Starch, Sodium starch glycolate (SSG), Crospovidone, etc.

Antioxidants:

These are the substances that prevent oxidation by reducing the effect of free radicals which causes the deterioration of product.

E.g., Ascorbic acid, Butylated hydroxy toluene (BHT), Butylated hydroxy anisole (BHA), etc.

Preservatives:

These are the substances that prevent the microbial growth in the product and increase the shelf life of the same.

E.g., Benzalkonium chloride, Methyl paraben, Propyl paraben, etc.

Anti-adherents:

These are the substances that reduce sticking of tablet or powder or granules to punch or die cavity.

E.g., Talc, Magnesium stearate, Starch, etc.

Glidants:

Glidants are the substances that help to reduce the friction occurring between the particles.

E.g. Talc, Aerosil, Colloidal silica, etc.

Lubricants:

Lubricants are used to prevent the friction between tablet and die cavity.

E.g., Magnesium stearate, Stearic acid, Calcium stearate, etc.

Vehicles:

An inactive substance that is combined with an active medication to facilitate administration.

E.g., Polyethylene glycol (PEG), Propylene glycol, etc.

Sweeteners:

These are the substances that are used for the taste masking purpose in formulations.

E.g., Sucrose, Mannitol, Aspartame, etc.

Coloring agents:

Coloring agents are used to impart color to the formulation and to provide an elegant look to the formulation.

E.g., Dyes, Lakes, etc.

Flavoring agents:

These are the substances that provide a flavor to the formulation to increase the patient acceptance regarding that formulation.

E.g., Vanillin, Menthol, etc.

Ideal properties of excipients

- It should be physically, chemically and therapeutically inert.
- It should be compatible with API.
- It should be free from micro-organisms.
- It should be stable and should increase the stability of dosage form.
- It should not impart its organoleptic properties to formulation unless desired.

Preformulation

Preformulation is the study of different properties of the ingredients to be formulated prior to formulation. In a pharmaceutical dosage form the API and excipients are formulated together. So, due to this, interactions may occur between them. That interactions can be negative regarding the formulation. And this may cause degradation of the formulation, can affect pharmacological properties of API and can also affect patients' health. The main aim of the preformulation study is to design a much effective and safer dosage form. It will definitely help to avoid the circumstances occurring due to interactions between API and excipients. Hence, the study of physical, chemical and pharmaceutical properties is performed in preformulation study. For the study of these properties, different analytical methods are used or else the accelerated stability studies are also performed.

Need of Drug-Excipient compatibility

The preformulation studies are done with a purpose of making a stable and long expiry formulation. For getting pharmacological action, drug is considered as the major part of the formulation. A formulation is said to be stable when the drug present in formulation is stable. But, along with the drug excipients also have that much importance. Because, without excipients only drug cannot complete a formulation. So, for proper binding, proper delivery of dosage form excipients are must. But it is also necessary to test that whether those

excipients are compatible with the drug or not. If they are compatible with the drug then and then only a stable formulation can be done. If they are not compatible with the drug, it may arise problems before or after formulation. The excipients present in the formulation may hamper the properties or activity of drug. It may lead to loss of pharmacological action of that formulation. Sometimes, it may cause toxicity also. Hence, the choice of excipients must be in accordance with the drug i.e., they should be compatible with the drug so that a stable and safe formulation can be done.

Introduction to interactions of excipients

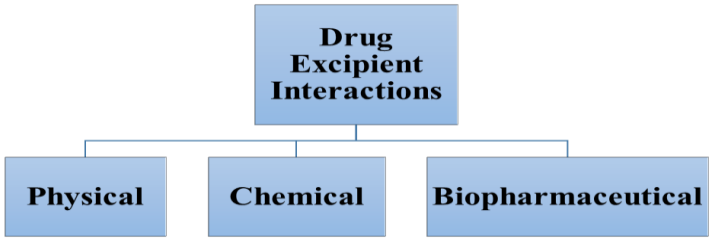
Interaction is a way through which two substances affect the properties of one another. In case of pharmaceutical dosage form, API and excipients are in close contact with each other during a formulation. As they both are present in same formulation, interaction may occur between drug and excipient. The interaction may affect properties of drug or properties of excipients. It may lead to cause problems in formulating a dosage form. Sometimes, a formulation may also get completed but the interaction may cause toxicity to the patient after administration of the dosage form. The interaction may cause degradation of the drug substance and hence no pharmacological action will be obtained. In short, the interactions become a reason behind deterioration of the formulation.

Examples of Drug-Excipient interactions

- Maillard Reaction - Amine drugs + Lactose = Discoloration.
- Tetracycline + Calcium filler = Reduces effect of Tetracycline and causes yellowing of teeth.
- Eutectic mixtures cause softening of tablet.
- Alkaloidal Drug + Ammonia = Precipitation.
- Salicylates + Ferric Chloride = Precipitation.
- Barbiturates + Ammonium Bromide = Precipitation.
- Sodium salicylate + Sodium Bicarbonate = Red brown coloration due to atmospheric oxygen.

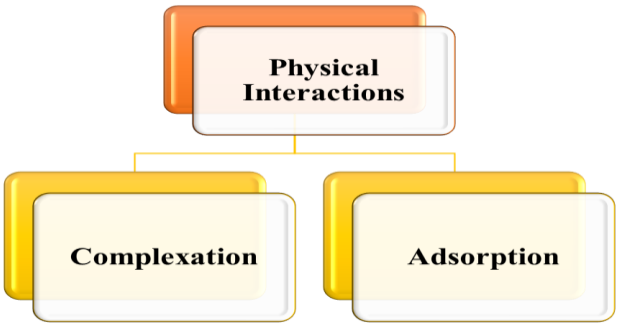
Types of Drug-Excipient interactions

Drug and excipients are in close contact with each other in a formulation. When two different components come in close contact with each other, any reaction can take place. That is how drug and excipients can also interact with other and an unwanted effect can be observed. Different types of Drug-Excipient interactions may occur and that are as follows:

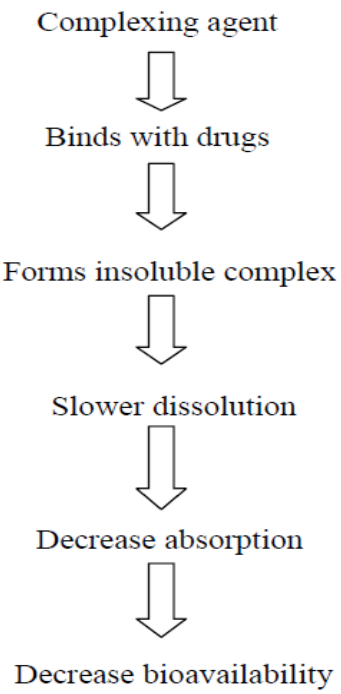


Physical interactions

Physical interactions are the interactions that do not involve any chemical changes. Physical interactions involve change in dissolution, solubility, sedimentation rate etc. Physical interactions are very common in dosage forms.



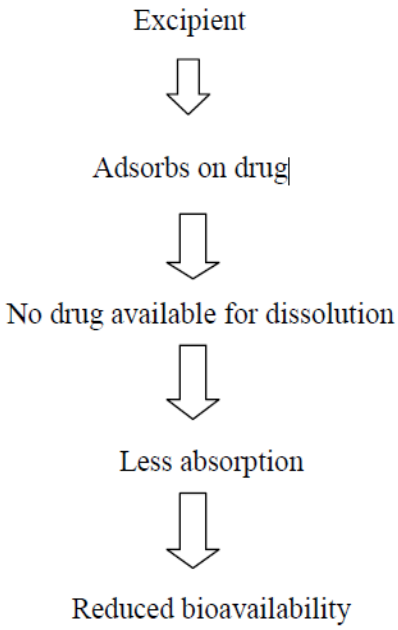
Complexation



When a complexing agent binds with drug, it forms insoluble complex. It further leads to lowering in dissolution. It results in decrease in absorption and ultimately decrease in

bioavailability. E.g., tetracycline forms insoluble complex with calcium carbonate leading to slower dissolution and decreased absorption.

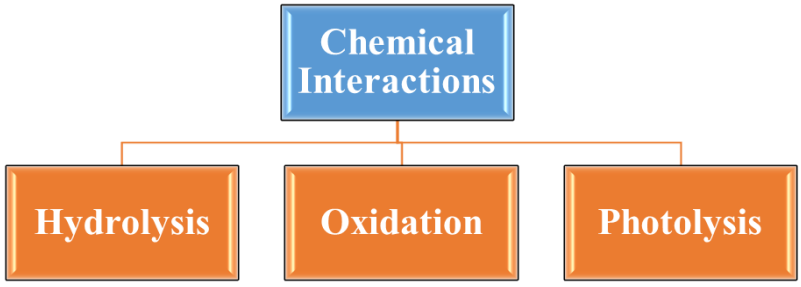
Adsorption



When an excipient gets adsorbed on to the surface of drug, it covers the surface of that drug. Hence, no drug remains available for dissolution. It further leads to less absorption and results in decreased bioavailability. E.g., Cetyl Pyridinium chloride cations get adsorbed on the surface of magnesium stearate which acts as a lubricant in tablet containing Cetyl Pyridinium chloride. This leads to marked reduction in the antibacterial activity of the drug.

Chemical interactions

A reaction between API and excipients that further leads to form unstable compounds. Generally, chemical interactions have deleterious effect on formulation. Hence, such kind of interactions must be avoided.



Hydrolysis

Hydrolysis is the breakdown in presence of water molecule. Drugs with functional groups such as esters, amides, lactones may be susceptible to hydrolytic degradation. It is probably the most commonly encountered mode of drug degradation because of the occurrence of such groups in medicinal agents and ubiquitous nature of water. Water can also act as a vehicle for interactions and facilitates microbial growth.

Oxidation

Oxidation is deterioration of product in presence of oxygen. Oxidative decomposition of drug products may cause many changes in the products such as drug degradation and discoloration. Some important factors accelerating oxidation are temperature, oxygen concentration and heavy metal ions. Several compounds particularly aldehydes, phenols, alkenes, alkynes, sugars, can undergo oxidative decomposition.

Photolysis

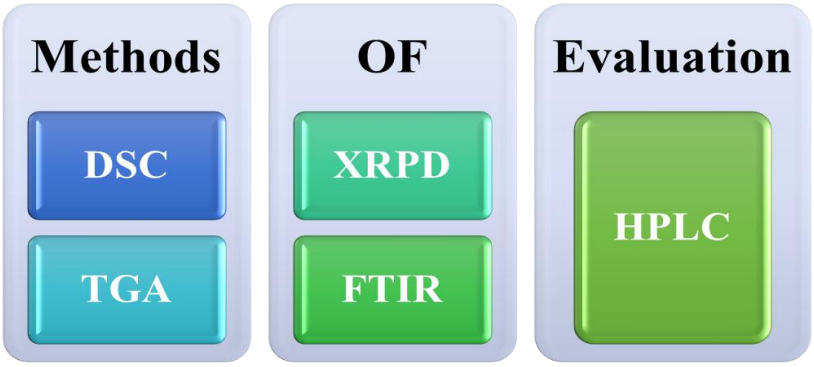
Photolysis is the degradation of product in presence of light. Light can cause photochemical decomposition of drugs. Energy absorption is greater at lower wavelengths and as many drugs absorb ultraviolet light, degradation by low-wavelength radiation is common. Exposure to light almost invariably leads to discoloration.

Biopharmaceutical interactions

These are the interactions which are observed after administration of the medication. Interaction of medicine with body fluid influences the rate of absorption. All excipients interact in physiological way when they are administered along with active pharmaceutical ingredients.

Methods of Evaluation of Drug-Excipient Interactions

While formulating a pharmaceutical dosage form, pre study of the interactions occurring between API and excipients is necessary. For that study, different analytical methods are used. These methods give idea about whether the excipients are compatible with the API or not.



Differential Scanning Calorimetry (DSC)

Principle

The sample and reference are maintained at the same temperature. During a thermal event in the sample, the system will transfer heat to and fro from the sample pan to maintain the same temperature in reference and sample pans. The energy required to maintain zero temperature difference is measured.

DSC measures the heat loss or gain resulting from physical or chemical changes within a sample as a function of temperature. Degradation and crystallization are exothermic processes. It is used to quantitate the solvated species present in a bulk drug sample. A plot of heat flow vs temperature is plotted

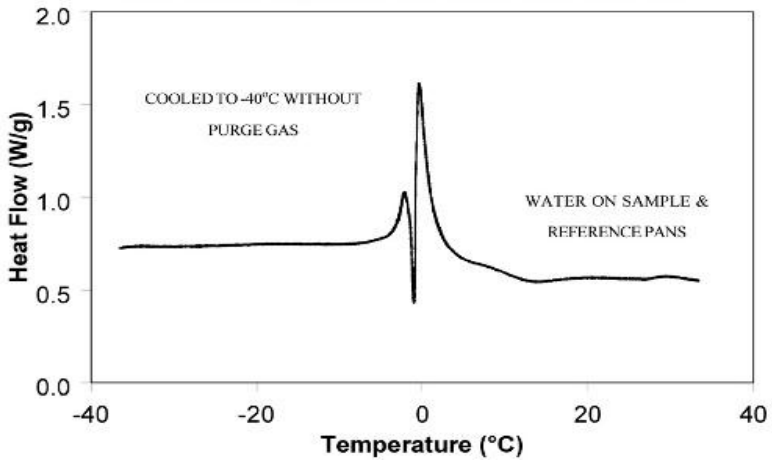


Figure 1: DSC Curve.

Thermo Gravimetric Analysis (TGA)

Principle

The sample is heated in a given environment at controlled rate. The change in weight of the substance is recorded as a function of temperature or time. The temperature is increased at

constant rate and the changes in weight are recorded at different time intervals. A plot of weight change against temperature is plotted.

Desolvation and decomposition processes are frequently monitored by TGA. It can also be used to quantitate the presence of solvated species within a bulk drug sample. A graph of weight loss vs temperature is plotted.

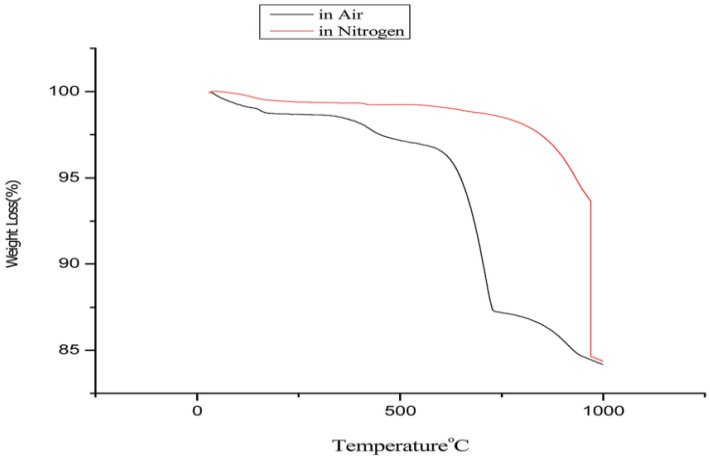


Figure 2: TGA Curve.

X-Ray Powder Diffraction (XRPD)

Principle

These X-rays are generated by a cathode ray tube, filtered to produce monochromatic radiation, collimated to concentrate, and directed towards the sample. Random orientation of a crystal lattice in a powder sample causes the x-rays to scatter at distinct angles relative to incident beam.

Each diffraction pattern is characteristic of a specific crystalline lattice for a given compound. Unknown crystalline materials can be analyzed by this method. A graph of intensity vs Ɵ is plotted.

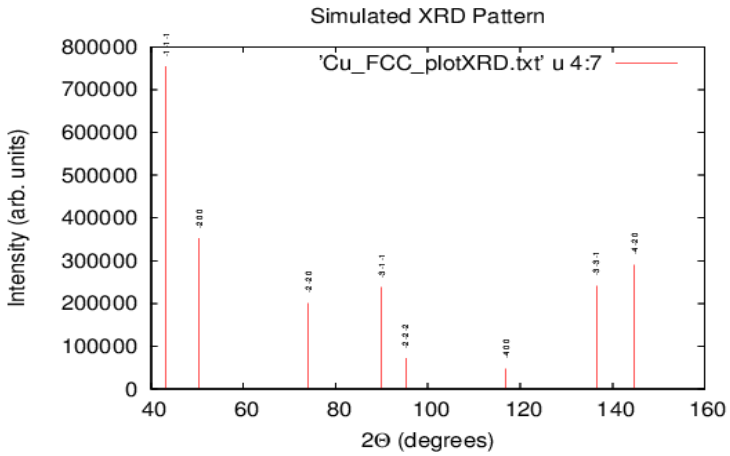


Figure 3: XRPD Pattern.

Fourier Transmission Infra-Red Spectroscopy (FTIR)

Principle

The IR spectroscopy theory utilizes the concept that molecules tend to absorb specific frequencies of light that are characteristic of the corresponding structure of the molecules.

FTIR is a simple methodology for the detection of variations within drug-excipient blends. The disappearance of an absorption peak, a reduction of the peak intensity, or the appearance of new peaks are indicative of the existence of interactions between the API and the excipient. A graph of % transmittance vs wavenumber is plotted.

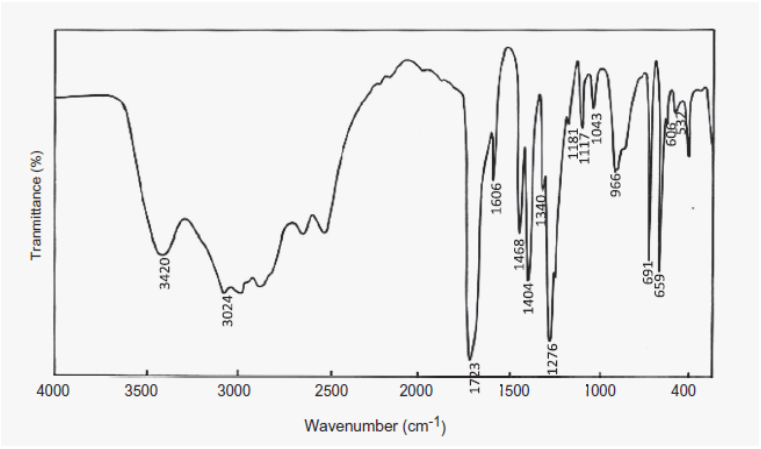


Figure 4: FTIR Spectrum.

High Performance Liquid Chromatography (HPLC)

Principle

The specific intermolecular interactions between the molecules of a sample and the packing material define their time on column. Hence, different constituents of a sample are eluted at different times. Thereby, the separation of the sample ingredients is achieved.

This chromatographic technique is widely employed for compatibility testing by quantitative estimation of drug excipient samples that have been subjected to isothermal stress testing (IST). IST involves the storage of drug alone and drug–excipient blends with or without moisture at high temperature for a specific period of time (about 3–4 weeks) to accelerate any drug–excipient interaction. HPLC results that exhibit a percentage loss similar to the drug considered individually indicate no interaction between drug and the excipients and vice versa. A chromatogram of intensity vs time is plotted.

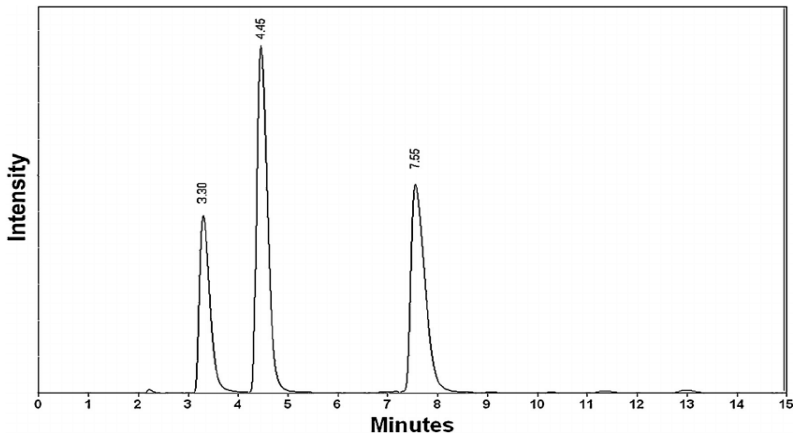


Figure 5: HPLC Chromatogram.

CONCLUSION

Excipients play a crucial role in a pharmaceutical formulation. Without excipients a formulation cannot be completed. Along with that the importance of study of interactions between drug and excipient is much more. It is very much important to predict the compatibility between API and excipients. This will help to formulate a much safer and effective dosage form. If any interaction is going to occur, it can be prevented by changing the excipients. Different methods help to predict the compatibility between drug and excipients. Thus, with the help of analytical methods, aim of formulating a proper dosage form is fulfilled.

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