A REVIEW ON:

"PHARMACEUTICAL PREFORMULATION STUDIES IN DEVELOPMENT OF NEW DOSAGE FORMS"

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Abstract: -

Immediate release dosage forms are new types of dosage forms that take effect shortly after being administered. Various superdisintegrants, such as croscarmellose, sodium starch glycolate, crospovidone, and others, are employed in immediate release dosage forms to promote rapid tablet breakage/disintegration following administration. The many advantages/benefits of immediate release dosage form, excipients utilised in immediate release dosage form, various technologies for immediate release tablets, and prospective therapeutical areas where immediate release dosage form is used are all discussed in this article. This page also includes a variety of commercially available immediate release dose forms. Preformulation is a set of studies that look at the physicochemical features of a novel drug candidate and how they might affect medication performance and dosage form creation. This could be useful information for formulation design or evidence for the necessity for molecular change. Every medicine has inherent chemical and physical qualities that must be considered prior to pharmaceutical formulation development. This property establishes the foundation for combining pharmaceuticals with pharmaceutical substances in the preparation of dosage forms. The goal of a preformulation study is to create a beautiful, stable, effective, and safe dosage form by determining the kinetic rate profile, compatibility with other ingredients, and Physico-chemical parameters of new therapeutic compounds. Drug solubility, partition coefficient, dissolving rate, polymorphic forms, and stability are among these qualities that are significant in preformulation studies. Polymorphism having crystal and amorphous forms shows different chemical physical and therapeutic description of the drug molecule. This article explains some properties for preformulation evaluation parameters of drug.

KEY WORDS: Immediate release, Superdisintegrants, Preformulation, Physio-chemical properties

INTRODUCTION

PREFORMULATION STUDIES

The initial step before developing final dosage forms is to conduct a preformulation study. The physical and chemical properties of the medicine and excipients are investigated in the preformulation study. The primary goal of the preformulation study is to get information that will aid in the creation of stable, effective, and bioavailable dosage forms. Various Preformulation studies were preformed like-:

1. PHYSICAL APPEARANCE:

Physical appearance is examined by its various organoleptic properties like colour, state, odour and taste.

2. MELTING POINT DETERMINATION:

Capillary fusion is used to determine the melting point. A little amount of medication was put into a capillary that was kept inverted, with the sealed end facing down into the melting point device. With the thermometer provided, the temperature at which the solid medication transforms into liquid was recorded.

3. PARTITION COEFFICIENT:

The partition coefficient is a metric for a drug's lipophilicity and ability to cross the cell membrane. In n-octanol: distilled water, the drug partition coefficient is measured. In a separating funnel, 50 mg of medication is precisely weighed and mixed with 50 ml of n-octanol: distilled water. Shake the mixture until it reaches a state of balance. The phases are separated in a separating funnel, and the distilled water is filtered through a Whatman filter no. 41 and filtered as needed. Using a UV spectrophotometer, the amount of medication dissolved in distilled water is determined. The partition coefficient is calculated and compared with literature value.

$$P_{o/w} = \frac{C(organiC)}{C(aqueous)} \quad \text{eq (1)}$$

4. DETERMINATION OF SOLUBILITY

Qualitative solubility of Ramipril in different solvents:

The solubility of drug is determined in different solvent systems. A small amount of the drug is mixed with 10 ml of each solvent in screw capped glass tubes and shaken on constant water bath shaker for 24 hrs. at 25^0C. The solutions are examined physically for the absence or presence of drug particles.

Quantitative solubility of Ramipril:

The solubility of drug is tested in distilled water and methanol. 10 mg of drug is dissolved in 10 ml of distilled water and methanol in 10 ml volumetric flasks. The mouth of flask is properly covered with aluminium foil and placed in water bath shaker maintained at 37^0C for 48 hrs, samples are taken manually and filtered. The UV absorbance of solutions after appropriate dilutions is determined by using UV

spectrophotometer and the amount of drug dissolved is calculated using calibration curve.

5. **ABSORPTION MAXIMA (λ_{max}) OF DRUG:**

UV absorption maxima of the drug is determined by scanning 20µg/ml solution with methanol, 0.1N HCI and phosphate buffer pH 6.8 between 200-400nm.

6. **CALIBRATION CURVE OF DRUG**

Calibration curve of drug is prepared in methanol, distilled water and in different buffers i.e., 0.1N Hydrochloric acid, phosphate buffer pH 6.8.

- **Preparation of calibration curve in 0.1N Hydrochloric acid:**
- *Preparation of 0.1N hydrochloric acid:* 0.1N hydrochloric acid is prepared by diluting 8.5ml of concentrated hydrochloric acid to 1000 ml with distilled water.

  50 mg of drug is taken and dissolved in 100 ml of 0.1N hydrochloric acid. From this 50 ml of sample is taken and volume is made up 100 ml with 0.1N hydrochloric acid to get 250µg/ml stock solution. From this stock solution, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1 ml are withdrawn and transferred to 10 ml volumetric flasks and volume is made up to 10 ml with 0.1N HCI to obtain different concentrations of 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 22.5 and 25 µg/ml. The absorbance is measured by UV spectrophotometer using 0.1N hydrochloric acid as blank.

- **Preparation of calibration curve in Phosphate Buffer pH 6.8:**
- *Preparation of phosphate buffer pH 6.8:* Disodium hydrogen phosphate of 28.80g and potassium dihydrogen phosphate of 11.45g are dissolved in sufficient water to produce 1000 ml.

  50 mg of drug is taken and dissolved in 100 ml of phosphate buffer. From this 50 ml of sample is taken and volume is made up 100 ml with phosphate buffer to get 250µg/ml stock solution. From this stock solution, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1 ml are withdrawn and transferred to 10 ml volumetric flasks and volume is made up to 10 ml with phosphate buffer to obtain different concentrations of 2.5, 5, 7.5, 10, 12.5, 15, 17.5, 20, 22.5 and 25µg/ml. The absorbance is measured by UV spectrophotometer using phosphate buffer pH 6.8 as blank.

7. **FOURIER TRANSFORM INFRARED ANALYSIS (FTIR STUDY):**

For qualitative compound identification, the sample's IR spectra is examined. On a Fourier converted IR spectrophotometer, drug IR spectra are measured. The sample is scanned at wavelength 4000cm^{-1} – 400 cm^{-1}.

8. **DRUG POLYMER INTERACTION STUDIES:**

Compatibility study of drug and polymers are performed to ensure that drug is not interacting with the polymer used under experimental conditions ($40^0C \pm 2^0C$ and 75±5% RH) for 4 weeks. Desired quantity of drug with excipients are taken and mixed thoroughly and filled in

dry vials. The vials are examined daily at regular interval for clumping, discoloration and liquefaction.

INTRODUCTION TO IMMEDIATE RELEASE DOSAGES FORMS

The quick release solid dosage form accelerates drug release, making it ideal for the delivery of poorly soluble medicines, high molecular weight proteins, and peptides. The majority of patients require a quick onset of effect; hence the medication must be released right away.

Immediate release dose forms are ones that dissolve and disintegrate quickly to release the active ingredients. Various carriers and diluents are used to provide immediate release, which does not extend or prolong medication absorption and release.

ADVANTAGES OF IMMEDIATE RELEASE SOLID DOSAGE FORMS

- Immediate release dosage form improves solubility of the pharmaceutical composition.
- Immediate release dosage form improves bioavailability and stability.
- Immediate release dosage forms reduce disintegration and dissolution timing.
- Immediate release dosage forms have the ability to provide effect of liquid preparation in the form of solid preparation.
- Immediate release dosage forms offer accurate dosing as compared to liquid dosage forms.
- High drug loading is possible in immediate release dosage form.

SUPER DISINTEGRANT

A disintegrant is an excipient, which is added to most tablet formulation to facilitate a breakup or disintegration of the tablet when it comes in contact with water in gastrointestinal tract. The disintegrating agent may be mixed at two stages -;

1) During the formation of granules (intragranular).

2) At the second mixing stage during compaction of granules into tablets (extragranular).

SUPER DISINTEGRANTS INCLUDES -:

Natural superdisintegrant

Synthetic superdisintegrant

NATURAL SUPER DISINTEGRANTS

Natural super disintegrating agents are natural in origin and mostly used over synthetic because of non-irritating, cheaper and non-toxic in nature. Natural superdisintegrant includes-;

- Gum karaya
- Mango Peel Pectin
- Dehydrated banana powder

- Plantago Ovata Seed Mucilage (Isapgula)
- Cassia fistula gum

SYNTHETIC SUPERDISINTEGRANTS

- Sodium starch glycolate (primogel), [2-8%]
- Cross – linked povidone or crospovidone (kollidone), [2-5%]
- Cross linked carboxy methyl cellulose sodium (Ac-Di-Sol) croscarmellose sodium, [1-3%]
- Low – substituted – hydroxyl propyl cellulose, [1-5%]
- Polacrilin potassium

MARKETED PRODUCTS OF IMMEDIATE RELEASE TABLETS

Table 1: List of marketed products

BRAND NAME	ACTIVE INGREDIENT	APPLICATIONS
Diltiazem	Diltiazem	Treating high blood pressure and chronic stable angina
Calan	Verapamil	Treating high blood pressure and chronic stable angina
Isoptin	Verapamil hydrochloride	Treating high blood pressure and angina
Cataflam	Diclofenac potassium	Treating pain and inflammation
Voltaren	Diclofenac potassium	Treating pain and inflammation
Nucynta	Tapentadol	Treating moderate and severe chronic pain

CURRENT SCENARIO /RECENT DEVELOPMENT IN IMMEDIATE RELEASE TABLETS

- Hot – melt extrusion and injection molding for continuous manufacturing of immediate release tablets.
- Novel hole technology
- A novel electrostatic dry powder coating process.
- Novel granulation technologies-;

❖ Pneumatic dry granulation (PDG)
❖ Freeze granulation technology (FGT)
❖ Foamed binder technologies (FBT)
❖ Melt granulation technology (MGT)
❖ Steam granulation technology (SGT)
❖ Moisture activated by dry granulation (MADG)
❖ Thermal adhesion granulation process (TAGP)

CONCLUSION

The instant release dosage form has a number of advantages, including ease of administration, painlessness, and patient comfort. The rate of drug release is increased when using an immediate release dose form. Because most patients seek rapid drug therapeutic action, traditional drug therapy results in poor patient compliance and diminished overall therapy effectiveness. The finest options for high-effective therapy are quick release dose forms. Most prescription medications, neutraceuticals, and over-the-counter (OTC) items can be combined into this novel immediate-release dose form. As a result, instant release dosage forms are a new improved oral product that can be used for a variety of medicinal agents. Following the completion of the preformulation evaluation of new drug candidates, a complete report emphasising the pharmaceutical issues associated with compounds is requested. It aids in the development of phase I formulations and regulatory documentation, as well as the development of following drug candidates. If the medicine is deemed to be satisfactory, enough is synthesised to do preliminary toxicity testing, analytical work, and preformulation. Phase I (clinical toxicology) commences for genuine formulations once initial toxicity has passed. Following that, phase II and III clinical testing commences, and an order of magnitude formula is finalised throughout this phase. After all of the above is completed, an NDA is submitted, and once approved, production can begin.

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