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PRE FORMULATION PARAMETERS AND CHARACTERIZATION STUDY FOR FELBAMATE ANTIEPILEPTIC DRUG

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Abstract: The goal of this study was to look at some of the major physicochemical properties study of Felbamate drug suitable for Nanoparticles in depth. Felbamate is used to control partial seizures (convulsions) in the treatment of epilepsy after other medications have failed or are not appropriate for the patient. It is also used to treat partial and generalized seizures induced by Lennox-Gastaut syndrome in children.. Prior to the development of these primary dosage forms, it is critical to identify the fundamental physical and chemical properties of the drug molecule, as well as other divided aspects of the drug powder. Many of the ensuing decisions are based on this knowledge.
Key words: nanoparticles, entrapment efficiency, Felbamate, Preformulation, Stability, Physico-Chemical properties, Preformulation evaluation

INTRODUCTION

Preformulation is the step of the research and development process during which the physical, chemical, and mechanical properties of a new pharmacological material are characterized both alone and when mixed with excipients in order to generate a stable, safe, and effective dosage form. A detailed study of physicochemical attributes may eventually provide a reason for formulation design or carry, the necessity for molecular change, or simply establish that no significant impediments to compound development exist. As a result, preformulation experiments were carried out on the resulting drug sample for solubility analysis, identification, and compatibility studies. Preformulation begins when a newly synthesized medication shows enough pharmacologic potential in animal models to warrant human testing. These investigations should concentrate on the new compound's physicochemical qualities that may affect medication performance and the creation of an effective dosage form. A comprehensive understanding of these features may eventually give a rationale for

formulation design or support the necessity for molecular change the goal of this study was to determine solubility, pKa, dissolution, melting point, and assay development, stability in solution, stability in solid state, microscopy, bulk density, flow characteristics, and excipient compatibility. Preformulation is a collection of studies that focuses on the physicochemical features of a novel drug candidate that may affect medication performance and dosage form development. This could be useful for formulation design or to justify the necessity for molecular change. Every medicine has inherent chemical and physical qualities that must be taken into account before developing a pharmaceutical formulation. This feature provides the basis for medication combination with medicinal components in dosage form production. The goal of preformulation research is to create an elegant, stable, effective, and safe dosage form by creating a kinetic rate profile, compatibility with other ingredients, and establishing physicochemical parameters of new therapeutic compounds. Drug solubility, partition coefficient, dissolution rate, polymorphic forms, and stability are among these qualities.

Felbamate is an anticonvulsant medication used to treat epilepsy. It is used to treat partial seizures in adults (with and without generalization) as well as partial and generalized seizures in children with Lennox-Gastaut syndrome. However, the drug's use is limited to severe refractory epilepsy due to an elevated risk of possibly deadly aplastic anemia and/or liver failure.

It has been proposed that Felbamate possesses a novel dual mode of action as a positive modulator of GABAA receptors and a blocker of NMDA receptors, particularly versions carrying the NR2B subunit. Although it is evident that Felbamate causes pharmacological inhibition of NMDA receptors, the utility of NMDA receptor blockage as a therapy method for human epilepsy has been called into question. As a result, the significance of felbamate's effects on NMDA receptors to its therapeutic efficacy in epilepsy is debatable.

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EXPERIMENTAL STUDIES:

Before beginning preformulation studies, we should be aware of the drug's properties, potency in comparison to competing products and dosage form, a literature search for stability and decay data, the proposed route of drug administration, a literature search for formulation approaches, bioavailability and pharmacokinetics of chemically related drugs. It also comprises preliminary research and molecular optimization by the drug (Step I), and if a deficiency is found, a molecular modification should be performed (Step II). To compensate for this shortcoming, molecular modification is used to create salts, pro drugs, solvates, polymorphs, and even novel analogues. The solubility rate of a medication salt differs significantly from that of the parent molecule. Potassium and sodium activity.

Physicochemical parameters:

1. Organoleptic properties:
2. Bulk characterization studies: a) Crystalline and polymorphism b) Hygroscopicity c) Fine particle characterization d) Bulk density e) Powder flow properties f) Compression properties) Physical description
3. Solubility analysis: a) Intrinsic solubility determination b) PKa determination) Partition coefficient d) Dissolution studies) Common ion effect 4. Stability analysis: a) In toxicology formulations b) Solution stability c) Solid state stability

Physical characters

Organoleptic properties:

Color:

It should be unappealing to the sight and should be determined by either instrumental or visible means that vary from batch to batch. Keeping track of early batches and developing "specs" is extremely beneficial for later production. If undesirable, the body can be coated in a variety of colors.

Odor and taste:

For disagreeable drugs, employ a less soluble chemical form or mask it with flavors, excipients, coating, and so on. Precautions should be used when handling drug compounds that are irritating to the skin. Flavors, colors, and excipients all have an

impact on stability and bioavailability. Colors include off-white, cream yellow, tan, and glossy. Pungent, sulfurous, fruity, fragrant, and odorless odors are all possible. Acidic, bitter, bland, strong, sweet, and tasteless flavors are all possible.

Crystalline and polymorphism:

Crystalline refers to the structure of a solid compound, and these features vanish in the liquid and vapor stages. Internal structures (cubic, tetragonal, hexagonal, rhombic, and so on) can be classified. Habits that are solid (platy, needle, tabular, prismatic, bladed, and so on), Changing the interior structures changes the crystal habits. Changing the chemical form (for example, salt production) changes both the internal structure and the crystal habit. Different polymorphs are formed via crystallization from various solvents and solidification following melting. It is referred to as "hydrates" when the incorporated solvent is water. The term "anhydrous" refers to a substance that does not include any water within its crystal structure. Atoms in crystalline materials are arranged in three dimensions in regular and recurring patterns. In amorphous materials, for example, metals and minerals, as well as atoms or molecules, are randomly arranged without a regular atomic configuration. Polymorphism refers to a compound's ability to crystallize as more than one distinct crystalline species with different internal lattices and diverse crystal shapes (at different free energy states). Their physicochemical properties differ (melting point, density, vapor pressure, X-ray, color, crystal structure, hardness, solubility, dissolution rate, and bioavailability). It is critical to determine the polymorph that is stable at room temperature during preformulation.

Solubility analysis:

One essential goal of the preformulation endeavor is to develop a method for creating medication solutions. For therapeutic efficacy, a medication must be soluble in water. A drug must first be in solution before it may penetrate the systemic circulation and exhibit a therapeutic effect. Incomplete absorption is common with somewhat insoluble substances. When a solute dissolves, the intermolecular forces of attraction of the material must be overcome by forces of attraction between solute and solvent molecules.

To create solute solvent attraction, the solute forces and the solvent-solvent forces must be broken. It focuses on drug solvent interactions that may arise during drug candidate delivery. For example, the solubility of an orally taken medication in simulated stomach medium should be investigated. We need to undertake solubility studies on a novel medicine to give a foundation for later formulation work and to determine how the drug will perform. Temperature, chemical and physical properties of both the solute and the solvent, are all factors that influence medication solubility. Pressure, acidity or basicity of the solution, solute and solvent state of subdivision, and physical agitation imparted to the solution during

Drugs with an aqueous solubility of less than 1% (10 mg/ml) will have bio absorption issues.

Determination of solubility:

Felbamate solubility was tested using a standard shaker agitator. Felbamate was mixed with 5 ml of methanol and agitated on a mechanical shaker for 48 hours at 370°C. After 48 hours, the saturated dispersion is filtered with a 0.45 filter followed by a 0.2 filter to remove the undisclosed particles. The filtrate was diluted adequately with a suitable solvent and the drug content was measured using a UV spectrophotometer/HPLC.

Bulk characterization studies:

All solid forms that may exist as a result of the synthetic step, such as the presence of polymorphs, must be identified. Bulk parameters such as particle size, bulk density, and surface morphology can be altered during the development process to avoid inaccurate predictions of solubility and stability that are dependent on crystalline structure.

Fine particle characterization:

The particle size distribution influences some physical and chemical aspects of therapeutic substances, such as drug dissolving rate, bioavailability, content homogeneity, taste,

texture color, and stability. Furthermore, particle size is affected by variables such as flow characteristics and sedimentation rates, among others. It is critical to determine how the particle size of the therapeutic component may affect formulation and product efficacy as early as possible. Light microscope with a calibrated grid, sedimentation techniques, stream scanning, Coulter counter, and surface area assessment by BET nitrogen adsorption method are examples of particle size and distribution evaluation methods.

Bulk density:

Knowing the actual and bulk densities of the drug material is very helpful in determining the size of the final dosage form. Obviously, this parameter is crucial for low-potency medicines, which may represent the majority of the final granulation or table. The bulk density of a product varies significantly depending on the method of crystallization, milling, or formulation. Once a density problem is found, it is frequently easily remedied through milling slugging or formulation. It can have an impact on powder flow characteristics. It has an impact on the size of a high dosage capsule product or the homogeneity of a low dose formulation with considerable variances in drug and excipient densities.

Determination of True density:

Felbamate true density was measured using the liquid displacement method. The volume of intrusion fluid (toluene) displaced in the pycnometer by a certain mass of powder is used to compute it. Where D denotes true density, Vp denotes total pycnometer volume, and Vi is the volume of incursion fluid in the pycnometer containing the quantity of powder (M). All estimations were done in triplicate, and the average is provided.

Compression qualities:

The compression properties (elasticity, plasticity, fragment ability, and punch filming tendency) of a potential drug candidate can be determined for small quantities. This feature is used in the optimal formulation ingredient selection.

Determination of compressibility index:

Felbamate bulk density was calculated using the three tap method [A 100 ml graduated cylinder was carefully filled with 10g of Felbamate powder. The cylinder was dropped three times from a height of one inch, each time for two seconds. The bulk density was calculated by dividing the sample's weight by the volume of the sample contained in the cylinder. The bulkiness was determined by the reciprocal of bulk density or the particular bulk volume. The percent compressibility index of Felbamate was computed using the formula below, and the results are shown in Table

$$\text{Compressibility Index} = 100(V_O - V_F)/V_O$$

V_O =Unsettled apparent Volume

V_F= Final Tapped Volume

Powder flow qualities:

Powder flow parameters are crucial for efficient tablet operation. Flow ability should be evaluated during the preformulation evaluation of the drug material, especially when the predicted dose of the medicine is substantial. Powders can be either free-flowing or cohesive (non-free-flowing).Changes in particle size; density, shape, electrostatic charges, and adsorbed moisture all have an impact on flow characteristics. It is distinguished by Carr's index and Hausner ratio, angle of repose, rheology and thixotropy, and so on.

Determination of repose

The fixed funnel and free standing cone method was used to calculate the static angle of repose, a. A funnel was tightened so that its tip was 2cm above graph paper on a flat horizontal surface. The granules were gently poured through the funnel until the apex of the cone created just touched the funnel's tip. The mean diameters (D) of the powder cone bases were measured, and the tangent of the angle of repose was calculated using the equation:

$$\text{Tan } \theta = 2h/D$$

Where h = height of pile; D = Dia of pile the data presented here is for triplicate determinations.

Determination of Partition Coefficient

The oil/water partition coefficient is a measure of a molecule's lipophilic properties, or preference for the hydrophilic or lipophilic phase. When developing a pharmacological substance into a dosage form, the partition coefficient should be taken into account. When a solute is given to an immiscible liquid combination, it will disperse between the two phases and attain equilibrium at a constant temperature. The ratio of the unionized drug dispersed between the organic (upper) and aqueous (lower) phases at equilibrium can be used to explain the distribution of the solute (unaggregated & undissociated) between the two immiscible layers.

10 mg medication was added to 50 ml of n-Octanol (pre saturated with water) and shaken, followed by 50 ml of distilled water (pre saturatd with n-Octanol) and mechanically shaken for 24 hours. Both stages are separated after 24 hours. The absorbance of both phases was measured, and the concentration in each phase was computed.

Partition Coefficient= Drug concentration in octanol/Drug concentration in water

Drug polymer interaction studies by FT-IR

FT-IR analysis of drug polymer interactions FT-IR spectroscopy was used to investigate drug-polymer interactions using the Shimadzu FT-IR-8400S device. The spectra for Felbamate PLGA, and a physical combination of Felbamate: PLGA (1:1) were recorded. For 3 minutes, samples were produced in KBr disks (2 mg sample in 200 mg KBr) using a hydrostatic press at 5.2 cm2 force. The scanning area was 400 - 4000 cm2 with a resolution of 4 cm-1.

pH Determination

This was accomplished by shaking a 1%w/v dispersion of the sample in water for 5 minutes and determining the pH with a digital pH meter (model 335, Systronics, India). The information supplied here is for triple determinations.

pKa determination:

The pH partition theory is based on the connection of the dissociation constant, lipid solubility, and pH at the absorption site, as well as the absorption characteristics of various medications. Potentiometric titration is commonly used to calculate the dissociation constant or pKa. The bulk of medications on the market today are weak organic acids or bases. It is critical to understand their particular ionization or dissociation characteristics since their absorption is heavily influenced by their degrees of ionization when they approach the membrane barriers. The degree of ionization of a drug is determined by both the pH of the solution in which it is delivered to the biologic membrane and the pKa, or dissociation constant, of the drug (whether acid or basic).The term pKa is taken

RESULTS AND DISCUSSION

Many bulk features of pharmaceutical importance, including as flow properties, packing, packing densities, compressibility segregation characteristics, and so on, are influenced by drug particle size distribution. As a result, pharmaceutical technologists must analyze particle size dispersion. The physical characteristic results given in table No.1

Physical Parameters	Results
Status	solid
colour	white
odour	odorless

The results of solubility, true density, bulk density, compressibility index, angle of repose, moisture content, pH, Partition Coefficient are given in Table No.2

Physical Parameters	Results
True density	1.51
Bulk density	0.41
Compressibility	17.32
Angle of repose	37.2
Partition Coefficient	1:2
pKa	13.12

Physical observation and assay demonstrate that no color change was seen during the drug-excipients accelerated compatibility study. Based on the chemical evaluation, no major changes were noticed, indicating that the medicine is compatible with the added substances.

CONCLUSION

The preformulation phase is crucial in determining the features of CDs that will enable for appropriate risk assessment for development. It usually starts during the lead optimization phase, then moves on to predomination and the early stages of development. Decisions taken based on the knowledge generated during this phase can have a significant impact on the development of those compounds in the future. As a result, it is critical that preformulation be done as thoroughly as possible in order to make rational conclusions. The number and quality of the medicines, as well as the technology available and the experience of the persons doing the examinations, can all have an impact on the results provided. We effectively completed the physicochemical characterization of Felbamate features such as shape, size, solubility, pH, and so on in this work.

Conflict of Interest:

The authors declare that they have no conflict of interest for this study.

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