Review Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: www.ijrpns.com

https://doi.org/10.36673/IJRPNS.2021.v10.i05.A34

FORMULATION AND CHARACTERISATION OF PASTES

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ABSTRACT

A dosage form has to be designed and formulated taking into account the physical, chemical, and biological characteristics of all the drug substances and pharmaceutical ingredients that will be utilized. Using materials that are compatible with each other will result in drug products that are stable, effective, attractive, easy to administer, and safe. Product quality control and container packaging should contribute to the product's stability. Product labels should provide guidance on how to use the product and storage conditions should promote shelf life. Various methods for the preparation of dosage forms and drug delivery systems are discussed in subsequent chapters. A few general considerations are presented within this chapter concerning ingredients and drug product formulations and good manufacturing practices.

KEYWORDS

Pastes, Pre-formulation, Evaluation and Stability.

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INTRODUCTION TO PASTES

Pastes are semisolid preparations containing a mixture of insoluble particulate solids and ointment intended for application to the skin. Types of paste include fatty Paste and non-greasy paste. The method of preparation of pastes includes the trituration method and fusion method. They are usually prepared by incorporating solids directly into a congealed system by levigation with a proportion of base to form paste like mass. Paste contains high percentage of insoluble solids that are finely dispersed in a suitable vehicle for treatment of chronic lesions.

Types of pastes

Pastes are classified according to the base used to formulate them:

Fatty Pastes

These formulations consist of fatty oleaginous bases. Eg: Zinc oxide paste.

Aqueous Gel Pastes

These are prepared with water miscible bases. Example: Titanium dioxide paste, sodium hydroxymethyl cellulose paste.

Hydrocolloid Pastes

These preparations consist of hydrocarbon bases. Eg: Tooth paste, Zinc oxide gelatin paste[1].

Advantages

Since pharmaceutical pastes are porous with a high solid content, moisture can evaporate from applied sites. In addition, pastes may be able to absorb moisture and other chemicals in exudates.

The opaque nature of pastes enables this formulation to be used as a sunblock.

The chemical stability of therapeutic agents that are prone to hydrolysis will be dramatically enhanced by formulation within pharmaceutical pastes.

Disadvantages

Staining of clothes is often associated with use of pharmaceutical pastes.

The viscosity of pharmaceutical pastes may be problematic in ensuring spreading of dosage form over the affected site.

Pharmaceutical pastes are generally not applied to hair due to difficulties associated with removal.

GMP REQUIREMENTS FOR PASTES

Good Manufacturing Practices (GMP) is a regulation to govern the manufacturing of drugs of consistent quality, purity and efficacy, provided under Schedule M of Drug and Cosmetics Rules, 1945.

Guidelines for GMP

Building and facilities, Equipment, Personnel, Raw materials, Production, Laboratory controls, Records, Labelling, Complaints

Buildings and facilities

The design of facilities is largely dependent upon the types of products manufactured and potential for cross contamination and microbiological contamination equipment. There must be appropriate facilities in the production area with proper supply of good quality of water.

Equipment

Equipment should be of sanitary design. This includes sanitary pumps, valves, flow meter which can be easily sanitized.

Raw material

The physical characteristics particularly the particles size of drug substances is very important for suspension. Should have provisions for separate extended area specially designed for sterile product. Manufacturing area must be airflow entry with restricted entry. Manufacturing area should be with adequate space and arranged to prevent cross contamination.

Quality control

Quality control is important step in the manufacturing of the drug substance includes the testing of bulk components, testing of finished products prior to sale, stability programmes. Finished products offer packaging should be stored in the finished goods store within an area marked and subjected to quality control test.

Records

Documentation of all GMP activities. Record must be readily available. The comfort of the personnel working and regular monitoring of temperature and humidity, particles count etc.

PART 1D

Specific requirements for the manufacture of topical products, i.e., external preparations

Topical products must be manufactured in an area protected by an airlock. A suitable airlock shall be installed outside the area.

The air to this manufacturing area shall be filtered through at least 20µ air filters and shall be air conditioned.

The area must be equipped with an exhaust system that is sufficiently powerful to remove vapours, fumes, smoke, or floating dust particles.

To prevent accidental contamination of the product with foreign matter or lubricant, the equipment used must be designed and maintained.

Cleansing or drying the equipment or accessories used in the process must use suitable cleaning equipment and materials.

Water used in compounding shall be Purified Water IP.

It is essential to sieve powders appropriately before using them in any application.

Heating vehicles and a base like petroleum jelly shall be done in a separate mixing area in suitable stainless-steel vessels, using steam, gas, electricity, solar energy etc.

A separate packing section may be provided for primary packaging of the products.

PART 2

Requirements of plant and equipment

External preparations should be made with the following equipment:

A mixing chamber and storage tank, preferably made from stainless steel or another appropriate material.

Jacketed Kettle stainless steel container (steam, gas or electrically heated).

Mixer (Electrically operated).

Planetary mixer.

Colloid mills or emulsifiers may be used.

It could also be an ointment mill.

Liquid filling equipment (Electrically operated).

Jar or tube filling equipment.

Area

The area for basic installation should be at least thirty square meters. The area for ancillary equipment should be at least ten square meters.

A separate area for formulations intended for external use and internal use should be provided.Units registered before 1st January 2002 are not subject to the ancillary area requirement in this part.

PRE-FORMULATION STUDIES

Discovering and developing new medicines is a long, complex and expensive process and the failure rate is high during the process. To minimize attrition, it is essential, therefore, to understand the physicochemical characteristics of compounds or biological entities that are candidates for development into final products.

Needs of pre-formulation

Pre-formulation provides and understands information related to:

Degradation process

Adverse condition relevant to drug

Bioavailability

Pharmacokinetics

Toxicity

Physicochemical parameters

Penetration

Solubility

Texture analysis

Effect of light

Salt formation

Partition coefficient

Hygroscopicity

Fine particle characterisation

Penetration

Measured by *in vivo* and *in vitro* studies. In *in vitro* techniques the permeation through skin is measured directly where sampling is carried out immediately below skin surface. Unlike many *in vivo* methods, this method measures systemic levels.

Solubility

The solubility of compound in the vehicle need to be determined because different solubility problems can be arise like crystal formation, precipitation and coagulation. In supersaturated systems, crystals grow. The methods used are shake flask method, computational screening method and miniature device[2].

Texture Analysis

Texture analysis used to evaluation of mechanical characteristic where a material is subjected to a controlled force from which a deformation curve of its response is generated. Primary mechanical characteristics includes hardness, springiness, adhesiveness, cohesiveness and secondary includes brittleness, gumminess, chewiness etc.

Effect of light

The stability of compound due to presence of light affected or not need to be check. E.g.: - Di ethanol shows a distinct instability in paraffin due to light but stable when protect from light[3].

Salt Formation

It improves the solubility of the drugs. A salt is a chemical combination of ionisable component, one is acidic and other is basic relative to each other. If pka of acid and base are close, stable salt may not form. When a salt formation is limited of molecule then need to synthesize pro drugs (eg: ester and amides). Some molecules are not form salt because it does not dissociate in solvent (eg: alcohol and steroid).

Partition coefficient

Influence permeation of a drug across biological membrane.

P(o/w) = C(oil) / C(water)

Drug with extremely high partition coefficient readily penetrate the membrane.

Hygroscopicity

When a drug molecule come in contact with moisture it retains water by capillary condensation or surface adsorption. Absorption and equilibrium moisture content depends on the atmospheric humidity, temperature and surface area. Other hygroscopic substance absorb water because of hydrate formation or specific site adsorption[4].

Fine particle characterisation

It is crucial to ensure that the new drug is homogenous in sample and has a large surface area for interaction during pre-formulation. Dissolution and chemical reactivity of compound is affected by size, particle size, shape and surface morphology of drug particle[3].

CRITERIA FOR EXCIPIENT SELECTION

Excipients are substances formulated with a medication's active ingredients in order to provide long-term stability, bulk up solid formulations containing active ingredients in small amounts, which facilitate drug absorption, reduce viscosity, or enhance solubility.

Bases

It is one of the most important ingredients used in the formulation of semi solid dosage form. Act as carrier of medicaments and control absorption of medicaments. Ideal properties:

Compatible with skin pH and drug,

Inert, non-irritating and non-sensitizing,

Good solvent,

Release medicaments easily at site of administration,

Possess good stability

Anti-oxidants

A highly reactive atom, oxygen is capable of forming potentially damaging molecules called free radicals. They are capable of attacking the healthy cells of the body, causing them to lose their structure and functions. To prevent this anti-oxidants are added.

Humectants

A humectant is a hygroscopic substance. It is often a molecule with several hydrophilic groups, most often hydroxyl group. They are used to -

Increase solubility of active ingredients.

To elevate its skin preparation.

Elevate the hydration of the skin.

Filters Abrasives

Provide polishing action in white toothpastes.

Rheology modifiers

Used to obtain easy flow of toothpaste from tube.

Detergents

Added to make product foam when brushing. This helps dispersion and retention of product in mouth.

Sweeteners, colorants and flavours

To mask unpleasant taste of drug and to improve palatability.

Preservatives

Some bases, although resist microbial attack but because of their high-water content, it requires an anti-microbial preservative[5].

METHOD OF PREPARATION

Pastes are prepared by two methods:

Trituration method

Fusion method

Pastes can be prepared in the same manner as ointments, by direct mixing or use of heat to soften the base prior to incorporating the solids, which have been comminuted and sieved.

Trituration method[7]

Used when base is liquid or semi solid.

Eg: Compound zinc paste.

Fusion method[8]

Used when base is semi solid or solid in nature.

Eg: Zinc and Coal tar paste BPC

EVALUATION OF PASTES

Organoleptic properties

Colour

A colour evaluation was conducted on the prepared toothpaste.This was done visually.

Odour

Odour was found by smelling the product.

Taste

The product was tasted manually.

Determination of pH

pH of ideal formulation was determined by 1% aqueous solution using digital pH meter (ELICO INDIA).

Determination of spreadability

Excess of sample was placed between two glass slides and compressed with a weight of 1000 grams for five minutes to determine spreadability. The time required to separate the two slides i.e., the time in which upper glass slide moves over the lower plate was taken as measure of spreadability(s).

S=m×l/t

Where; m=weight tide to upper slide, l=length moved on glass slide,

t=time taken.

Skin irritation test

Patches on the back of the rat were shaved and slightly abraded to make them more sensitive. For four hours, patches were covered with gauze and the herbal formulation applied. The skin was observed for signs of redness, inflammation, weeping or scabs.

Penetration test

The rabbits were taken and were divided into two groups, each of 2 rabbits, for assessing penetration. One-hour-long application of the formulated paste was applied to 2.5cm areas of the skin. Unabsorbed paste was then recovered and weighed.

Tube extrudability

An aluminum collapsible tube with a nasal tip opening of 5mm was filled with the composition under study and the tube was pressed down with a finger. When tube paste was applied to the tip, we measured how much paste extruded through the tip.

Viscosity

Brookfield digital viscometers were utilised to evaluate paste viscosity, with spindle number 3 using increasing values of shear rates in order to reveal possible fluid flow dynamics. All viscosities measurements were performed at controlled temperature of 30°C.

Foamability

Taking a small amount of preparation with water and shaking it for 10 times evaluated the foamable properties.

***In vitro* drug release study**

With the help of a permeation cell (a glass cylinder of 10cm in height, 3.7cm in the outer diameter and 3.1cm in the inner diameter with both the ends open), release study of dental pastes was done. A dialysis membrane (molecular cut off 10 K Da) taken and soaked distilled water for 24 h before use. The water-soaked dialysis membrane was attached to the last part of the cylinder with help of a strong glue. Prepared paste of 1g was placed in the permeation cell. A beaker containing phosphate buffer (pH 6.4) of 100ml was employed as the receptor compartment. Paste was dipped to depth of below surface of the receptor medium. The receptor compartment medium was agitated by a magnetic stirrer (Remi Motors, India) maintained at temperature of 37±0.5°C. 5ml of samples was withdrawn at regular time interval and then, the withdrawn samples were filtered through Whitman filter papers. Drug released from the pastes were assayed spectrophotometrically using UV–Visible spectrophotometer (Shimadzu, Japan) at 274.5nm wavelength (λmax) against the appropriate blank.

Antimicrobial activity study

Anti-bacterial activity

Anti-bacterial activity of formulated paste was studied by standard agar diffusion method. The sterilized Muller Hinton agar medium was poured into the sterile petridish and allow for solidification. The inoculation of selected bacterial suspension was done by spreading with sterile cotton swabs. Within 10 minutes, holes of about 4-5mm were bored into the medium with a sterile borer. The formulation and the standard paste were placed and kept for 4 hours at room temperature for diffusion and then kept in incubator at 37°C. After 18-24 hours of incubation, the diameter of zone of inhibition around each hole was observed.

Anti-fungal activity

Anti-fungal activity of formulated paste was studied by standard agar diffusion method. The sterilized Sabourand's dextrose agar medium was poured into the sterile petridish and allow for solidification. Sterile cotton swabs were used to spread selected fungal suspensions. Within 10 minutes, holes of about 4-5mm were bored into the medium with a sterile borer. The formulation and the standard paste was placed and kept for 4 hours at room temperature for diffusion and then kept in incubator at 37°C. After 18-24 hours of incubation, the diameter of zone of inhibition around each hole was observed[9].

STABILITY STUDIES

Pharmaceutical stability studies measure the duration of time during which a pharmaceutical product retains its physical, chemical, microbiological, pharmacokinetic properties and characteristics during its shelf life. Shelf life of the product can be defined as the substance reduces to 90% of its original concentration. Shelf life is a technical term used to denote the stability of the product and it is expressed as expiry date. Expiration varies for each pharmaceutical preparation. The expiry of the pharmaceutical dosage form depends on various environmental factors such as temperature, humidity, light, radiations etc. Literature data on the decomposition process and degradability of active substances are generally available together with adequate analytical methods. The most important steps during the developmental stages include pharmaceutical analysis and stability studies that are required to determine and assure the identity, potency and purity of ingredients, as well as those of the formulated products. Stability of a pharmaceutical product can also be affected because of important requirement for regulatory approval of any drug or formulation in preservative efficacy. Moreover, the data generated during the stability testing is an important requirement for regulatory approval of any drug or formulation.

Types of stability studies

A comprehensive pharmacopeial protocol (USP) prescribes the criteria for acceptable levels of physical, chemical, microbiological, therapeutic and toxicological stability studies.

Physical stability

The original physical properties such as appearance, colour, dissolution, palatability, suspendability are retained. The physical stability may affect the uniformity and release rate, hence it is important for the efficacy and safety of the product.

Chemical stability

It is the tendency to resist its change or decomposition due to the reactions that occur due to air, atmosphere, temperature, etc.

Microbiological stability

The microbiological stability of the drugs is the tendency to resistance to the sterility and microbial growth. The microbiological instability could be hazardous to the sterile drug product.

Therapeutic stability

The therapeutic effect (Drug Action) remains unchanged.

Toxicological stability

Toxicological stability has no significant increase in the toxicity occurs.

Types of stability studies

Drug products are tested for longer periods under different temperatures and relative humidities (RH) during stability tests. Long term stability studies are essential if the drug is to be distributed in different

parts of the world and shipping is required. By testing the sample at specific intervals and changing external parameters as required, long-term stability studies are performed. Main objective of this study is to determine shelf-life of the drug product. Stability studies are mainly four types, they are long term stability, Intermediate stability, Accelerated stability and In-use stability Studies. The type of stability studies and its storage conditions with respective time period were shown in Table No.2.

Stability testing methods

It is a procedure performed for pharmaceutical products at various stages of the product development. Inearly stages, the stability testing is performed by the accelerated stability studies which are mainly performed at higher temperature. The accelerated stability studies are easy to predict because of the degradation of the drug within short period of time. The stability testing procedures have been categorized into four types and they are:

Real-time stability testing
Accelerated stability testing
Retained sample stability testing
Cyclic temperature stress testing.

Real-Time stability testing

The real-time stability testing is normally performed for longer duration of period to allow significant product degradation under recommended storage conditions. The period of the test depends on the stability of product which should be long enough to indicate clearly that no measurable degradation occurs and it must permit one to distinguish degradation from inter-assay variation. During stability testing, data is collected at appropriate frequency such that a trend analysis is able to distinguish instability from day-to-day ambiguity.

Accelerated stability testing

In accelerated stability testing, the product is stressed at higher (warmer than ambient) temperatures and determine the amount of heat input required to cause product failure. This is done to make the product to a condition that accelerates degradation. The information is projected to predict shelf life and used to compare the relative stability of alternative formulations. This provides an early indication of product shelf life and thus shortening the development schedule. Apart from temperature, stress conditions applied during accelerated stability testing are moisture, light, agitation, gravity, pH and package.

Retained sample stability esting

The samples are tested at predetermined intervals i.e., if a product has shelf life of 5 years, it is conventional to test samples at 3, 6, 9, 12, 18, 24, 36, 48, and 60 months interval.

Cyclic temperature stress testing

This is not a routine testing method for marketed products. Cyclic temperature stress tests are designed on knowledge of the product to mimic likely conditions in market place storage. The period of cycle mostly considered is 24 hours since the diurnal rhythm on earth is 24 hours, which the marketed pharmaceuticals are most likely to experience during storage[10].

STORAGE

Active pharmaceutical ingredients are required to be stored under conditions which will preserve their quality. Storage conditions should be established on the basis of literature available and on the basis of stability studies carried out by the company. Active pharmaceutical ingredients should be stored under established conditions. Records of each batch of active pharmaceutical ingredient should be maintained in such form as will facilitate the recall of the ingredient in the case of complaint about its quality.

Pastes should be stored in an area shielded from extreme heat and cold. Ambient temperatures from 55°C. Ambient temperatures from 55°F (13°C to 24°C) are recommended.

Store in well closed container and in cool place so as to prevent evaporation of moisture content.

Pastes should not be stored near open flames or sources of high heat.

PACKAGING AND LABELLING

Pastes should be packed in well closed container in a cool place to prevent degradation of the product. They are packaged either in:

Pastes are dispensed in wide mouthed, glass or plastic bottles with tight screw cap with liner, to prevent evaporation of water, because evaporation of water hardens the paste, which is found very difficult to spread over a lint.

Dispensed in metallic or plastic collapsible tube, to prevent the microbial contamination and loss of water.

The labelling requirements for pastes are as follows:

The name of preparation
Strength
Quantity
Instructions for the use
Precautions and warnings
Storage conditions
Registration number
Batch number
Manufacturing and Expiry date
Price
The name and address of pharmaceutical industry.

In addition, it should contain auxiliary label.

For external use only

Store in a cool place

Documentation

It is the cornerstone of quality management system and it is an essential GMP requirement. It is defined as a system of information and control so that risks related to misinterpretation and error in oral communication can be minimized.

Each document should:

Have a clear title.
Have an identification number.
Be approved by authorized person.
Have the date of issue.
Have a due date of revision.
Have list to whom it has been issued.

Types of documents

Standard operating procedures (sops)

It is a set of written instructions that document a routine or repetitive activity which is followed by employees in an organization. The development and use of SOPs are an integral part of a successful quality system.

Master formula record

It is a master document for any pharmaceutical product. It contains all information regarding manufacturing process for the product and all other documents like BMR and BPR are prepared using MFR by the manufacturing units.

Batch formula record

It is a document designed to provide a complete record of the manufacturing history of a batch of product.

Quality audit plan and reports

The key element of a good quality system is conducting internal audits (self-inspections) and external audits of suppliers and outsourcing operations.

Specification and test methods

It is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It providesa set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use.

Distribution records

Since various persons and entities are often responsible for the handling storage and distribution of products, the guidelines are intended to apply to all steps in the entire distribution/supply chain[10].

Formulation of pastes[6]

Table No.1: Formulation of Paste

S.No	Ingredients	Examples
1	Active ingredient	Sodium fluoride, Zinc oxide
2	Base	Soft paraffin, Liquid paraffin, Glycerine, PEG
3	Abrasives	Calcium carbonate, Hydrated silica, Sodium bicarbonate, Dicalcium phosphate, Sodium meta phosphate
4	Rheology modifiers	Cellulose gum, CMC, Xanthan gum, Carrageenan
5	Anti-oxidants	Butylated hydroxy anisole, Butylated hydroxy toluene
6	Humectants	Glycerine
7	Detergents	Sodium Lauryl Sulphate
8	Flavour	Menthol, Cinnamon
9	Sweetener	Sodium saccharide
10	Colouring	Titanium dioxide
11	Preservative	Sodium benzoate, Ethyl paraben, Methyl paraben
12	Permeation enhancer	Methanol, Linalool, Oleic acid

Table No.2: Types of Stability Studies

S.No	Type of stability studies	Storage conditions	Minimum time period (Months)
1	Long term	25±2^{o}C and 60±5% RH or 30±2^{o}C and 65±5% RH	12
2	Intermediate	30±2^{o}C and 65±5% RH	6
3	Accelerated	40±2^{o}C and 75±5% RH	6

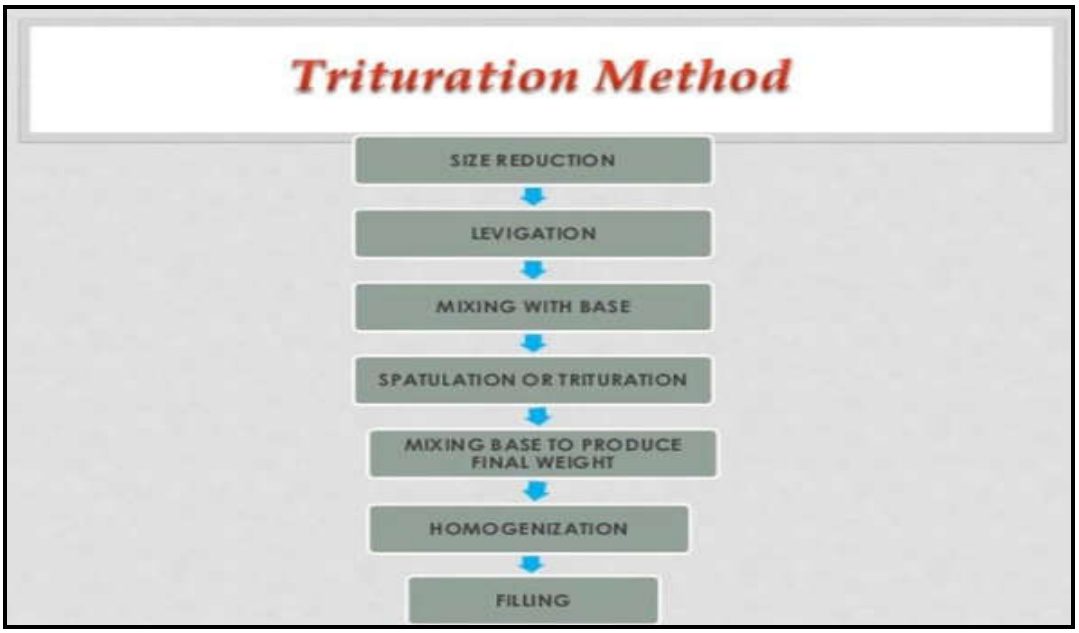

Figure No.1: Trituration Method

Figure No.2: Fusion Method

Figure No.3: Label of paste

CONCLUSION

Pastes are important category of pharmaceutical formulation and typically intended for external application to skin. They are usually thick and do not melt at physiologic temperature. The method of preparation of pastes includes the trituration methodand fusion method. They are usually prepared by incorporating solids directly into a congealed system by levigation with a proportion of base to form paste like mass. Paste contains high percentage of insoluble solids that are finely dispersed in a suitable vehicle for treatment of chronic lesions. Just as with GMPs, the goal of implementing compliance with GDPs will help pharmaceutical companies establish consistent practices that will minimize the risk of misinterpretation, errors in communication and ensure product quality. Different evaluation and stability studies should be performed to assess the quality of product and it is important for consumer health.

ACKNOWLEDGEMENT

The authors wish to express their sincere gratitude to Malik Deenar College of Pharmacy, Seethangoli, Bela, Kerala 671321, India for providing necessary facilities to carry out this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Moosan Basil Kallatra *et al*. Formulation and characterisation of pastes, *International Journal of Research in Pharmaceutical and Nano Sciences,* 10(5), 2021, 305-315.