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Review Article of Microsphere Based Orodispersible Tablets

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ABSTRACT

Orodispersible tablets (ODTs) are the novel dosage form which quickly disintegrates in the mouth (1-3 min) without chewing upon oral administration and without the need of water. The domain "Microsphere Based Orodispersible Tablets" comprises with 4 modules with different matters. Module one deals with Introduction, GMP and GLP requirements. The second Module illustrated with Preformulation, Identification and Characterization Methods for Drug, Excipient Drug Compatibility Studies, criteria for excipient selection, Formulation and Optimization Techniques, Formulation The third Module describes the Evaluation and Stability studies. The fourth Module includes SOP's, Packaging and Labelling.

INTRODUCTION

MICROSPHERES

Microspheres are solid, approximately spherical particles ranging 1-1000µm in size. They are made up of polymeric substances, in which the drug is dispersed throughout the microsphere matrix. The substances used in the formulation are biodegradable synthetic polymers and natural products. The natural polymers of choice are albumin and gelatin, the synthetic ones being poly lactic acid and poly glycolic acid.

ADVANTAGES OF MICROSPHERE

- Microspheres provide constant and prolonged therapeutic effect.
- Safe and convenient handling of toxic materials.
- Masking of odor or taste.
- Controlled and targeted drug delivery.
- To improve bioavailability & stability.
- Reduces the dosing frequency and thereby improve the patient compliance.

DISADVANTAGES OF MICROSPHERE

- The cost of materials & processing is high comparatively.
- The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
- Differences in the release rate from one dose to another.
- Change in process variables-temperature, pH, solvent addition & evaporation may influence the stability of core particles.
- Dosage forms of this kind should not be crushed or chewed.
- Reproducibility is less

TYPES OF MICROSPHERES

1. Bio adhesive Microspheres: These kinds of microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc. can be termed as bio adhesion.

2. Magnetic Microspheres: This kind of delivery system is very much important which localizes the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres.
3. Floating Microspheres: Gastro-retentive floating microspheres are low-density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. The drug is released slowly at the desired rate. It produces prolonged therapeutic effect and therefore reduces dosing frequencies.
4. Polymeric Microspheres: The different types of polymeric microspheres are biodegradable polymeric microspheres and synthetic polymeric microspheres. Biodegradable polymeric microspheres which contain biodegradable polymers which prolongs the residence time when contact with mucous membrane due to it's high degree of swelling property with aqueous medium. Synthetic polymeric microspheres are those which are made up of synthetic polymers and are used as used as bulking agent.
5. Radioactive Microspheres: Radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. They are injected to the arteries. The different kinds of radioactive microspheres are alpha emitters, beta emitters and gamma emitters.

METHODS OF PREPARATION OF MICROSPHERES

1. Emulsion Solvent Evaporation Technique

In this technique the drug is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0 .2 % sodium of PVP as emulsifying agent. The above mixture was agitated at 500 rpm then the drug and polymer was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralized water at room temperature for 24 hrs.

2. Solvent Extraction

This method is used for the preparation of the micro particles, involves removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. The process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, solubility profile of the polymer.

3. Spray Drying

The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone etc. The drug in the solid form is then dispersed in the polymer solution under high speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of microspheres.

APPLICATIONS OF MICROSPHERES:

1. Ophthalmic Drug Delivery
2. Oral drug delivery
3. Nasal drug delivery
4. Buccal drug delivery

ORODISPERSIBLE TABLETS(ODTs)

Oral dispersible tablets (ODTs) are the novel dosage form which quickly disintegrates in the mouth (1-3 min) without chewing upon oral administration and without the need of water. These are tablets which get dispersed or disintegrate when gets in contact with the saliva with the release of active drug.

ADVANTAGES OF ORODISPERSIBLE TABLETS

- Ease of administration to patients who cannot swallow.
- Improved compliance.
- No chewing needed.
- Suitable for controlled/sustained release actives.
- Cost effective.

DISADVANTAGES OF ORODISPERSIBLE TABLETS

- Sometimes may require more frequency of administration.
- For properly stabilization and safety of the stable product, ODT requires special packaging.
- Usually have insufficient mechanical strength. Hence, careful handling is required
- Leave unpleasant taste and/or grittiness in the mouth.

IDEAL PROPERTIES OF ODTS

- Easily dissolve or disperse in saliva within a few seconds.
- Have a pleasing taste.
- Leave no residue in the mouth when administered.
- Able to be manufactured in a simple conventional manner within low cost.
- Be less sensitive to environmental conditions like temperature, humidity etc.

GMP IN PHARMACEUTICAL PRODUCTS

Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use.

PART 1: FOR PREMISES AND MATERIALS

1. GENERAL REQUIREMENTS

Location and surroundings

The buildings for manufacturing of drugs shall be situated or shall have such measures as: -

- To avoid risk of contamination from external environment.
- Any factory, which produces obnoxious odors, fumes, dust, smoke, chemical or biological emissions.

Building and premises

The building should be designed in such a way that permits manufacturing operations in hygienic conditions.

- Adequately provided with working space.
- To avoid contamination.
- Designed to avoid entry of pests, birds, rodents etc.
- Interior surface should be smooth and free from crakes
- The production and dispensing area shall be well lightened, ventilated, and may have proper air handling system.
- Proper drainage system as specified for various categories of products.
- The walls and floors of manufacturing area shall be free from cracks.

Water system

- There shall be validated system for treatment of water.
- Potable water should be used to perform all the operations except cleaning and washing. The storage tanks shall be cleaned periodically and records maintained by the licensee.

2.WAREHOUSING AREA

- Adequate areas for proper warehousing of various categories of materials and products.
- Designed and adapted to ensure good storage conditions.
- Separate sampling area for active raw materials and excipients.

3.PRODUCTION AREA

- Separate manufacturing facilities shall be provided for the manufacturing of contamination causing and potent products such as;β-lactams.

4.ANCILLARY AREA

- Rest and refreshment rooms shall be separate from other areas.
- Facility for changing, storing clothes and for washing and toilet purpose shall be easily accessible and adequate.

5.QUALITY CONTROL AREA

- Quality control laboratories shall be independent of the production areas.seperate areas shall be provided each for physico-chemical, biological, microbiological analysis.
- Adequate space shall be provided to avoid mix-ups and cross contamination.
- The laboratory shall be provided with regular supply of water of appropriate quality for cleaning and testing purposes.

6.PERSONNEL

- The manufacture and testing shall be conducted under direct supervision of qualified technical staff.
- Personnel for QA & QC shall be qualified and experienced.
- Personnel in production and QC lab. shall receive training appropriate to the duties & responsibility assigned to them.

7.HEALTH , CLOTH AND SANITATION

- All personnel shall undergo medical examination including eye examination, and shall be free from skin and other communicable diseases
- To wash hands before entering a manufacturing area

Clothing:

- Need for special protective clothing.
- Personnel should not move between areas producing different products.
- Garments need to be cleaned.

Illness: -

- Staff with illness should not handle starting materials, intermediates or finished products.

8.RAW MATERIALS

- The licensee Keep an inventory of all raw materials to be used at any stage of production of drugs and maintain records as per Schedule U.
- Raw material from each batch checked for quality & appropriately labels the storage area.
- There shall be adequate separate area for materials “under test”, “approved “, and “rejected” with arrangement ands equipment .

PART 2: EQUIPMENTS AND LABELS.

1.EQUIPMENTS

- Equipments shall be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of the equipment shall aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross- contamination.

2.LABELS AND OTHER PRINTED MATERIALS

- Necessary for identification of the drugs and their use.
- Printed in bright colours and legible manner.
- All containers and equipment shall bear appropriate labels.
- Printed packaging materials & leaflets shall be stored separately to avoid mix-up.

3.DOCUMENTATION AND RECORDS

- It is the essential part of the Quality assurance system. as such related to all the aspect of GMP.
- Its aim is to define the specification for all materials, method of manufacturing, to ensure that all personnel concerned with manufacture know the information necessary to decide whether or not to release a batch of a drug for sale.
- Documents shall be approved, signed and dated by appropriate and authorized persons.

- The records shall be made or completed at the time of each operation in such a way that all significant activities concerning the manufacturing of pharmaceutical products.

GOOD LABORATORY PRACTICES (GLP)

Good Laboratory Practice is defined as "a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported."

PRINCIPLES

- The purpose of Good Laboratory Practice is to promote the development of quality test data and to ensure a sound approach to the management of laboratory studies.
- The Principles may be considered as a set of standards for ensuring the quality, reliability and integrity of studies, the reporting of verifiable conclusions and the traceability of data.
- The Principles require to assign roles and responsibilities to staff in order to ensure good operational management of each study.

PERSONNEL

- The GLP standards require that an adequate number of trained personnel are available for the study. Typical analytical laboratories keep minimal records on the training of personnel.
- Under GLP standards additional records must be kept and be available for audit. This includes at a minimum

1. The resume of the individual, documenting education, prior job history, publications, presentations, patents and memberships in technical organizations. The resume must be updated during the course of employment.
2. Training records in the organization. The personnel record should include documentation of training, including safety training, training in GLP regulations, and test-specific training. The records must include when the training was completed along with the signatures of the trainer and trainee.
3. A thorough job description for each employee and an organization chart showing the relationship of an individual to the rest of the staff must be documented.

FACILITIES: BUILDINGS

Test facilities should be of suitable size, construction and location to meet the requirements of the study and to minimize disturbances that could interfere with the study. They should be designed to provide an adequate degree of separation of the diverse elements of the study..

Separation ensures that disturbances are minimized and that different activities do not interfere with one another or adversely affect the study. They are achieved by:

• Physical Separation; e.g. walls, doors, filters or separate cabinets.

• Organisational Separation; e.g. carrying out different activities in the same area but at different times.

EQUIPMENT

• For the proper conduct of the study, appropriate equipment of adequate capacity must be available.

• All Equipments should be properly calibrated and maintained to ensure reliable and accurate performance.

• Records of repairs and routine maintenance and of any non-routine work should be retained.

1.Suitability

➢ Suitability can only be assessed by considering the tasks that the equipment is expected to perform.Deciding on the suitability of equipment is a scientific responsibility and is usually defined in SOPs.

2.Calibration

➢ All equipment, whether it is used to generate data, or to maintain standard conditions , should work to fixed specifications.

➢ Verifications should be performed at a frequency that allows action to be taken in time to prevent any adverse effect on the study should it be discovered that the equipment is not operating within specifications.

3.Maintenance

The requirement that equipment be properly maintained is based on the assertion that this ensures the constant performance of equipment to specifications and that it reduces the likelihood of an unexpected breakdown and consequent loss of data.

➢ Maintenance may be carried out in two quite distinct ways:

• Preventive maintenance; when parts are changed regularly based upon the expected life of the part concerned. Regular preventive maintenance therefore reduces the risk of breakdown.

• Curative maintenance; when repairs are made in the case of a fault being detected.

4.Documentation

➢ Routine maintenance should be documented in such a way that users of equipment can be assured that it is reliable.

➢ Records of equipment calibration, checking and maintenance demonstrate that the respective SOPs have been followed and that equipment used was adequate for the task and operating within its specifications.

TESTING FACILITIES

Standard operating procedures (SOP)

Standard operating procedures shall be established for

- Animal room preparation
- Animal care
- Receipt, identification, storage, handling, mixing and method of sampling of the test and control articles.
- Laboratory test
- Handling of animals found dead during study
- Data handling, storage and retrieval
- Maintenance and calibration of equipment

PREFORMULATION STUDIES

It is the study of physicochemical property of active pharmaceutical ingredient along with excipient before the formulation of dosage forms.

Needs for Preformulation:

Preformulation is to provide and understand information regarding:

- The degradation process
- Bioavailability.
- Pharmacokinetic and formulation of similar compounds.
- Toxicity.
- It forms physicochemically stable and bio pharmaceutically suitable dosage form.

A. IDENTIFICATION AND CHARACTERIZATION METHODS FOR DRUG.

1. Particle size and shape

The most widely used procedures to visualize micro particles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of micro particles. LM provides a control over coating parameters in case of double walled microspheres. The microspheres structures can be visualized before and after coating and the change can be measured microscopically. SEM allows investigations of the microspheres surfaces.

2. Swelling index:

Characterization of microspheres is performed with swelling index technique. Different solution (100mL) are taken such as (distilled water, buffer solution of pH (1.2, 4.5, 7.4) are taken and alginate microspheres (100mg) are to be placed in a wire basket and kept on the above solution and swelling is allowed at 37oC and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper.

Swelling Index = Initial weight – Final weight/ Initial weight × 100.

3. Solubility study

Solubility of the drug was determined by taking some quantity of drug (about 1-2 mg) in the test tube separately and added the 5 ml of the solvent (water, ethanol, methanol, 0.1 N HCl, 0.1 N NaOH and phosphate buffer pH 6.8). Shake vigorously and kept for some time. The solubility of the drug in various solvents was determined (at room temperature).

4. Determination of Angle of repose and bulk density

- Angle of repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation.

Tan θ= h/r , θ= tan-1 (h/r) , Where, θ is the angle of repose, h is the height, r is the radius.

- Bulk density and Tapped Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD an d TBD, calculated by using following formulas.

LBD = Powder weight/ Bulk volume.

TBD = Powder weight /tapped volume.

5. Void Volume:

The volume of the spaces is known as the void volume "v" and is given by the Formula,

V=Vb-Vt ,Where, Vb = Bulk volume (volume before tapping)

Vt = True volume (volume after tapping)

6. Porosity:

The porosity € of powder is defined as the ratio of void volume to the bulk volume of the packaging. Porosity is frequently expressed in percentage and is given as

%€ = (1 - Vt/ Vb) X 100.

EXCIPIENT-DRUG COMPATIBILITY STUDY

Pharmaceutical incompatibilities are generally referred to as changes in the physical, chemical and/or therapeutic properties of a dosage form resulting from the interaction of the API with excipients or other components of the drug product. The drug-excipient compatibility studies are carried out with an intent to identify, quantify and predict potential interactions (physical or chemical) along with the impact of these interactions on the manufacturability, quality and performance of the final drug product.

Analytical techniques used to detect Drug-Excipient Compatibility

1) Thermal methods of analysis

- Differential scanning calorimetry (DSC)

2) Spectroscopic techniques

- Powder X-ray diffraction (PXRD).
- Solid state nuclear magnetic resonance spectroscopy (ss NMR)

3) Microscopic technique

- Scanning electron microscopy (SEM)

Differential scanning calorimetry (DSC)

DSC represents a leading thermal analysis technique that has been increasingly used for active pharmaceutical ingredient screening of incompatibilities. In this technique, the DSC curves of pure components are compared to the curves obtained from 1:1 physical mixtures. It is assumed that the thermal properties (melting point, change in enthalpy, etc.) of blends are the sum of the individual components if the components are compatible with each other.

Powder X-ray diffraction (PXRD)

PXRD analysis is of immense help in case of incompatibilities which occur during processes like compression, wet granulation etc. and bring on change in crystallinity/amorphicity and polymorphic forms of API in the presence of excipients with/without adsorbed moisture.

Solid state nuclear magnetic resonance spectroscopy (ssNMR)

ssNMR has shown immense potential in the qualitative and quantitative analysis of pharmaceutical solids (APIs and drug formulations) throws light on the chemical bonding and composition of drug products.It has a unique advantage for detecting compatibility in crystalline as well as amorphous components.

Scanning electron microscopy (SEM)

This technique allows characterization of surface morphology of materials and is useful especially when there are distinctive differences in their crystal habits. It does not give any the chemical structure/thermal behaviour of drug materials.

CRITERIA FOR EXCIPIENT SELECTION

The selection of the excipients should take into account the API properties, process, target formulation and potential impact on the formulation .Some of those API properties can be

- ✓ **Dose**: Choose excipients that improves uniformity and the physical and chemical stability of your API.
- ✓ **Particle Size** : Choose glidants with controlled and narrow particle size distribution that improve tabletting properties and prevent segregation.
- ✓ **Flow Properties** : Choose glidants that do not decrease dissolution and compaction. This may require granulation techniques and micronized glidants
- ✓ **Bulk Density** : In general for a high density API, choose a diluent that has high density in order to avoid segregation in a directly compressible formulation.
- ✓ **Moisture Content** : Select the glidants or hydrophilic lubricants with the ability to absorb excessive moisture without diffusion to the surface.
- ✓ **Hygroscopicity** : Select excipient with dessicant properties(highly hygroscopic) and the functionality to improve the stability of your API under any relative humidity preventing degradation.
- ✓ **Excipient Compatibility** : Excipient/ API and excipient/ Excipient Compatibility testing help determine the best excipient considering API and other excipient used.

FORMULATION AND OPTIMIZATION TECHNIQUES

Optimization is selecting the most suitable element from available decisions in any resources considering all the factors in experiment. Various techniques of optimization Quality by Design enhances the assurance of safe and effective drugs to consumer and promise to improve manufacturing quality performance and also product free of contamination and gives the desired benefits to consumer. Optimization techniques to examine various problems that occur design are used during the research. If the experiments in the production are carried out randomly then results obtained will be random, so we need to plan the experimental process such that relevant information is obtained.

Optimization is necessary because:

- ➢ It reduces the cost
- ➢ It provides safety and reduces error
- ➢ It provides efficacy
- ➢ It saves the time

PARAMETERS OF OPTMIZATION

Parameters of optimization is divided into two main types:

1.Problem type

There are two general type are there in the problem type of optimization technique:

a) Constrained

These are the restrictions placed on the system by physical limitations.

Eg: Economical considerations

b) Unconstrained

In this system the problems involving uncomplicated or artless pharmaceutical preparations or processes.

2.Variables

Mathematically, they can be divided into two types:

a) Independent or primary variables

This type of variable comes under the composition of the selected ingredients i.e;Excipients and drugs

b) Dependent or secondary variables

The formulator has no direct control over this type of variable. They are reliant on an unrelated variable. These are responses like flow property etc..

FORMULATION.

METHODS.

1. Freeze drying/ Lyophilization

Lyophilization means drying at low temperature under condition that involves the removal of water by sublimation. Drug in a water soluble matrix which is then freeze dried to give highly porous structure. The tablets prepared by lyophilization disintegrate rapidly in less than 5 seconds due to quick penetration of saliva in pores when placed in the oral cavity. Lyophilization is useful for heat sensitive drugs i.e. thermo-labile substances.

2. Spray drying

This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This then mixed with active ingredients and compressed into tablets. The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate as disintegrating and an acidic material (e.g. citric acid) and / or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium.

3. Tablet Molding

Tablets produced by molding are solid dispersions. The physical form of the drug in the tablets can be determined by whether and to what extent it dissolves in the molten carrier. The drug can exist as discrete particles or micro particles dispersed in the matrix. The molded tablets shaped by compression molding are air-dried. As the molding process is employed usually with soluble ingredients (saccharides) which offer better mouthfeel and breakdown of the tablets. But, molded tablets have low mechanical strength, which results in erosion and flouting during handling.

4. Sublimation method

The slow dissolution of the compressed tablet containing even highly water-soluble ingredients is due to the low porosity of the tablets. This volatile material is then removed by sublimation separation to the behind as a highly porous matrix. Tablets manufactured by this method have generally disintegrated in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore-forming agents.

5. Direct compression

It is the simplest and most cost effective tablet manufacturing technique for ODTs as they can be fabricated using conventional tablet manufacturing and packaging machinery and also due to availability of tableting excipients with improved flow, compressibility and disintegration properties, especially tablet disintegrants, effervescent agents and sugar based excipients. There are number of factors which affect disintegration like particle size distribution, contact angle, pore size distribution, tablet hardness.

- Orodispersible tablets were prepared by direct compression method. The tablets were prepared using super disintegrant (sodium starch glycolate, avicel), mannitol as a diluent, lactose as a sweetening agent, talc with magnesium stearate as a flow promoter. The optimized microspheres and other ingredients were mixed together and then blended in a tumbling cylindrical blender with talc, and magnesium stearate and compressed into tablets.

INGREDIENTS	USE
Mannitol	Diluent
MCC (Avicel 102)	Disintegrant
Sodium starch glycolate (SSG)	Disintegrant
Lactose	Sweetening agent
Talc & Magnesium stearate	Flow promoters

EVALUATION OF MICROSPHERES

1. Percentage yield determination

The prepared microspheres were completely dried in an oven maintained at 37°C for 24 h and then weighed. The percentage yield was calculated by the following formula:

% Yield = Weight of microspheres ÷ Total weight of solid material × 100

2. Entrapment efficiency

Entrapment efficiency was calculated by digesting outer layer of 20 mg microspheres in 10 ml Chloroform and then 100 ml 0.1 N HCl was added. The suspension was then warmed for a few minutes, filtered & 1 ml of filtrate was made up to 10 ml with 0.1 N HCl. The solution was analysed using UV spectrophotometer at 294 nm. The entrapment efficiency was calculated by the formula.

EE = Practical drug content ÷ Theoretical drug content × 100

3. Evaluation of flow properties of microspheres

The prepared microspheres were evaluated for flow properties including bulk density, tapped density, angle of repose, carr's compressibility index and hausner ratio.

4. Particle size evaluation

Size distribution and average particle size of microspheres was calculated with optical microscopy. Optical microscope was fitted with eye piece micrometer which was then calibrated with a stage micrometer. Size of about 100 microspheres was calculated from each batch and then the average size was calculated.

5. Morphology

The morphology of the prepared batches of microspheres was evaluated by scanning electron microscopy. Samples were mounted on aluminium stubs and coated with gold using a vacuum evaporator. Samples were then examined with a SEM microscope at an accelerating voltage of 10 kV.

EVALUATION OF TABLETS.

1. Hardness

The hardness of the tablets was determined by using Monsanto hardness tester. A tablet hardness of about 4-5 kg/cm2 is considered adequate for mechanical stability.

Fig. No. 1 Monsanto Hardness Tester

2. Friability

As per USP, twenty six tablets were taken which corresponded to 6.5 g weight. The tablets were placed in a Roche friabilator and were rotated at 25 rpm for 4 minutes. The tablets were taken out,and reweighed. The percentage friability of the tablets was calculated by the formula,

Percentage friability = Initial weight – Final weight ÷ Initial weight × 100

3. Tablet thickness:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Thickness was recorded using vernier calliper.

4. Tablet tensile strength

The tablet tensile strength is the force required to break a tablet by compressing it in the radial direction. It is measured using a monsanto hardness tester. For measuring the hardness of the tablets, the plunger of the hardness tester is driven down at a speed of 20 mm/min. Tensile strength for crushing (T) is calculated using equation:

$T = 2F \div \pi dt \times 100$

Where F is the crushing load, and d and t signify the diameter and thickness of the tablet, respectively.

5. Weight variation test

20 tablets from each batch were subjected to weight variation test. As per Indian Pharmacopoeia standards, the tablets should be within the specified limits i.e. ± 5% of average weight.

6. Wetting Time

A piece of tissue paper (10.75×12 mm) folded twice was placed in a culture dish (d=6.5 cm) containing 6 ml of simulated saliva (phosphate buffer pH 6.8). A tablet was carefully placed on the surface of tissue paper and the time required for simulated saliva to reach the upper surface of the tablet was noted as the wetting time.

7. Moisture uptake studies

Due to high content of hydrophilic excipients, orodispersible tablets have increased chance of moisture uptake which greatly affects stability of moisture sensitive products, so there is a need for special attention towards storage and packaging of orodispersible tablets. Therefore, moisture uptake studies are strongly recommended for orodispersible tablets [27]. The test was performed by keeping ten tablets in a desiccator (containing calcium chloride) for 24 hours at 37 °C to assure complete drying. The tablets were then weighed and stored for 2 weeks at 75% humidity. To achieve this humidity conditions, a saturated solution of sodium chloride was kept at the bottom of the desiccator for three days. On the tenth day tablets were re-weighed and the percentage increase in tablet weight was recorded.

8. In-vitro disintegration time

Disintegration time for orodispersible tablets was determined using USP disintegration apparatus with 0.1 N Hcl (900 ml at 37±1 °C) as the disintegrating medium. To comply with the test all of the tablets should disintegrate within 3 minutes as per official requirements as given in European Pharmacopoeia.

9. In-vivo disintegration time

In vivo disintegration time was judged in five healthy male volunteers for each batch of tablets. Prior to the test the volunteers were instructed to rinse their oral cavity with distilled water. Each volunteer was asked to place one tablet on the tongue. Volunteers were strictly told not to chew or swallow the tablets, though licking was allowed. The end point for disintegration was taken when there was no lump left in the oral cavity. After the test was finished, volunteers were told to rinse there mouth properly.

STABILITY TESTING

Stability testing is the process by which drug manufacturers collect data on their product over predetermined lengths of time in specific environmental conditions to determine if there is any change in the quality of the Active Pharmaceutical Ingredient (API) or Final Product (FP).

STABILITY TESTING METHODS

1.Real time stability testing

It is normally performed for a long duration of time to allow significant degradation of the product under the storage conditions recommended. The period of time for the test of the product depends on the stability of the product.

2.Accelerated stability testing

The accelerated stability studies are carried out to predict the degradation that occurs over prolonged periods of storage, at normal conditions.

3.Retained sample stability testing

These studies are done under room temperature and at refrigerator temperatures. In this type of testing, the stability is done by selecting one batch for a year. If the number of samples exceeds more than 50 the they are divided into two batches.The samples stability studies help to predict the shelf life.The maximum shelf life of every product predicted could be 5 years which is conventional to the test samples at 3,,9,12,18,24,3,48 and 0 months.Thismethod of testing is also known as constant interval method.

4.Cyclic temperature stress testing

This method is not so much used to the sampling of the products. In this method, cyclic temperature stress tests are designed knowledge of the product so as to mimic likely conditions in the market place storage. In this testing the sampling is considered to be conducted by a cycle of 24 hours which is known as the rhythm of the earth is 24 hours.

- The prepared batches were evaluated for stability studies. In the accelerated stability test according to ICH guidelines, 20 tablets are packed in each 10 mLhigh-density polyethylene (HDPE) bottle and sealed thermally, then placed in a humidity chamber with temperature and relative humidity of about 40 ± 2 °C and 75% RH respectively were maintained. The formulations were analysed at 0 day, 1 and 3 month time interval for hardness, friability, taste evaluation score, drug content and in-vitro disintegration time.

SOP OF MULTI STATION TABLET COMPRESSION MACHINE

Purpose: For Tablet Compression.

Scope: This involves Standard Operating for working of tablet compression machine.

OPERATING CONTROLS

- WEIGHT ADJUSTMENT:
- Turn the drive wheel by hand in the direction of the arrow , so that the lower punch is at its lowest position.
- Add a quality of granulation equal to the required tablet weight into the die cavity.
- Press the spring loaded weight adjusting screw release pin and turn the weight adjusting screw to increase or decrease volume of die cavity so that the surface of the die.
- Release the pin to lock the weight adjusting screw after adjustment.
- HARDNESS ADJUSTMENT :
- Fill the hopper in the proper position and feed the granules to be compressed into it.
- Compress a few tablets by turning the drive wheel by hand, and check their hardness.
- To increase or decrease the hardness, turn the ball screw in either direction until the punched tablets have desired hardness (turn left to increase the hardness and right to decrease).
- EJECTION ADJUSTMENT
- Turn the drive wheel by hand in the direction of the arrow such that the lower punch reaches to the top most position.
- To bring the surface of the lower punch in level with the die table, turn the SB guide nut to desired degree.
- Rotate the machine by hand and compress a few sample tablets.
- Check their weight, hardness and thickness for consistency.
- Fit the dust box in proper position in front of the die table.

PACKAGING

- Packaging may be defined as the group of activities for designing and producing a container or a wrapper for a product.
- It is Science, art and technology for protecting products for distribution, storage, sale and use.

Fig. No.2

Fig .No. 3

- Packaging special care is required during manufacturing and storage to protect the dosage of other quick-dissolving route of administration. Fast-dispersing and/or dissolving oral route, the method can be packaged using various potential, such as single pouch, blister card with multiple units.
- ODTs are individually sealed in Alu-alu,blister packs to protect the tablets from damage, moisture, and oxidation. Because ODTs are soft in nature, the ability to successfully package an ODT in a bottle is difficult.

LABELLING

- Labelling is any written, printed or graphic communication upon the container or the wrapper of a drug package.
- Displays the information about the drug on its container, the packaging or the product itself.

Requirements

1. Proprietary name/Generic name, established name.
2. Strength and dosage form.
3. Manufacturing License number.
4. Quantity.
5. Instructions, precautions and warnings for their use.
6. Storage conditions.
7. Batch number.
8. Manufacturing and Expiry date.
9. The name and address of pharmaceutical industry.

a) Proprietary name/Generic name, established name.

The exclusive name of the drug substance or drug product owned by a company under trademark law.

b) Strength and dosage form.

It is the amount of active drug per unit dose.

c) Manufacturing License number.

In India, to manufacture a drug , it is required to get a manufacturing license number as per D&C Act, 1945, which is issued by state drug authorities.

d) Quantity

Quantity or volume present per packaging unit.

e) Storage conditions

- Store in a cool place
- Protect from sunlight.
- Keep out of reach of children.

f) Batch number.

A designation printed on the label of the drug that identifies the drug and permits the production history of the batch .

g) Manufacturing and Expiry date.

- In compliance with GMP, the manufacture date printed on the label represent the date the product was produced.
- Date stated on the label of a drug after which the drug is not expected to retain its claimed efficacy, safety, potency or after which it is not permissible to sell is called Expiry date.

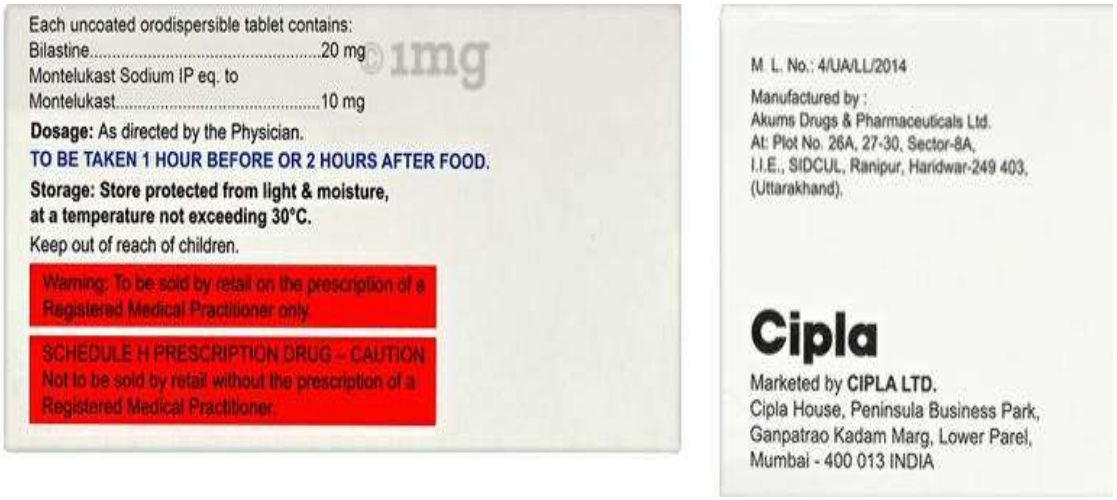

Fig No. 4

CONCLUSION

A detailed study was conducted on Microsphere Based Orodispersible Tablets. Orodispersible Tablets are those tablets which get dispersed or disintegrate(1-3min) when gets in contact with the saliva with the release of active drug. In this study we describe GMP and GLP requirements of Orodispersible Tablets. The Preformulation Studies Including Identification and Characterization Methods of Drug, Excipient Drug Compatibility Studies, Criteria for Excipient Selection, Formulation and Optimization Techniques and Formulation were also studied. The methods of preparation like Direct Compression, Freeze Drying, Spray Drying, Sublimation, Tablet Molding are studied. Evaluation of Microsphere Based Orodispersible Tablets were also studied. And also Stability Studies,SOP's,Packaging and Labelling of Microsphere Based Orodispersible Tablets are Studied.

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