FORMULATION, EVALUATION AND PROCESS VALIDATION STUDIES OF ACARBOSE TABLETS

Dissertation submitted to

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In

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Submitted by

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DEDICATED

TO

MY

BELOVED PARENTS

LIST OF ABBREVIATIONS USED

1. RMG - Rapid Mixer Granulator
2. QC - Quality Control
3. DQ - Design Qualification
4. IQ - Installation Qualification
5. OQ - Operational Qualification
6. PQ - Performance Qualification
7. USFDA - United States Food & Drug Administration
8. WHO - World Health Organization
9. MOC - Material Of Construction
10. cGMP - Current Good Manufacturing Practice
11. ICH - *International Conference on Harmonisation.*
12. SVC - Site Validation Committee
13. QA - Quality Assurance
14. VRA - Validation Risk Assessment
15. URS - User Requirement Specification.
16. VP - Validation Plans.
17. SOP - Standard Operating Procedure
18. MVP - Master Validation Plan.
19. API - Active Pharmaceutical Ingredient
20. CTD - Common Technical Document.
21. MedDRA - Medical Dictionary for Regulatory Activities.
22. ISPE - International Society for Pharmaceutical Engineering.
23. QbD - Quality By Design.
24. ASTM - American Society for Testing and Materials

25. CAQ - Critical Quality Attributes.

26. CDER - Centre For Drug Evaluation And Control.

27. EU - European Union.

28. EMA - European Medicines Agency.

29. FTIR - Fourier transform Infrared Spectroscopy.

30. HbA_{1c} - Glycated hemoglobin or glycosylated hemoglobin.

31. G.I.T - Gastro Intestinal Tract.

32. HDPE - High-density polyethylene (HDPE) or polyethylene high-density.

33. LOD - Loss On Drying.

34. R.P.M - Rotations Per Minute.

35. USP - United States Pharmacopeia.

36. HPLC - High Performance Liquid Chromatography.

37. M.S.D - Mean Standard Deviation,

38. R.S.D - Relative Standard Deviation.

39. NLT - Not Less Than.

40. NMT - Not More Than.

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INTRODUCTION

Oral solid dosage form [1,2]:-

The oral route of drug administration is the most important method of administering drug for systemic effects. Except in certain cases the parental route is not routinely used for self administration, e.g. insulin. The topical route of administration has only recently been employed to deliver drugs to the body for systemic effect. The parental route of administration is important in treating medical emergencies in which the subject is comatose or cannot swallow. Nevertheless it is probably that at least 90% of all drugs used to provide systemic effect are administered by oral route. When a new drug is discovered one of the first question a pharmaceutical company asks is if the drug can effectively administered for its intended effect by oral route. Drugs that are administered orally, solid oral dosage forms represent the preferred class of product. Tablets and capsules represent unit dosage forms in which usual dose of drug has been accurately placed.

Tablets and capsules represent unit dosage forms in which one usual dose of drug has been accurately placed. By comparison liquid forms such as syrups, suspensions, emulsions, solutions and elixirs are usually designated to contain one medication in 5-30 ml, such as dosage measurements are typically error by a factor ranging from 20-50%, when the drug is administered by patient.

Tablets [3,4]:-

In 1843, the first patent for a hand operated device used to form a tablet was granted. Tablets are defined as solid dosage forms each containing a single dose of one or more active ingredients, obtained by compressing uniform volumes of particles. They are intended for the oral administration, some are swallowed whole, some after being chewed. Some are dissolved or dispersed in aqueous phase before being administered and some are retained in the mouth, when the active ingredients are “liberated”.

Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use drug must be released form tablet that is dissolved in the fluids of mouth, stomach and intestine and then absorbed into systemic circulation by which it reaches its site of action.

The tablet is composed of the Active Pharmaceutical Ingredients (API) together with various excipients. These are biologically inert ingredients which either enhance the therapeutic effect or are necessary to construct the tablet. The filler or diluents (e.g. Lactose or sorbitol) area bulking agents, providing a quantity of materials which can accurately be formed into a tablet. Binders (e.g. methyl cellulose or gelatine) hold the ingredients together so that they can form a tablet. Lubricants (e.g. magnesium stearate or polyethylene glycol)are added to reduce the friction between the tablet and the punches and dies so that the tablet compression and ejection processes are smooth. Disintegrations (e.g. starch or cellulose) are used to promote wetting and swelling of the tablet so that it breaks up in the gastrointestinal tract;

this is necessary to ensure dissolution of the API. Superdisintegrants are sometimes used to greatly speed up the disintegration of the tablet. Additional ingredients may also be added such as colouring agents, flavouring agents and coating agents. Formulations are designed using small quantities in a laboratory machine called a powder compaction simulator. This can prove the manufacturing process and provide information.

Advantages[1] :

- They are unit dosage forms and they offer the greatest capabilities of all oral dosage forms for the greatest dose precision and the least content variability
- Their cost is lowest of all oral dosage forms.
- They are the lightest and most compact oral dosage forms.
- They are in general the easiest and cheapest to package.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They may provide the greatest ease of swallowing with the least tendency for "hang-up" above the stomach especially when coated provided the tablet disintegration is not excessively rapid.
- They lend themselves to certain special release profile products such as enteric or delayed release products.
- They are better suited to large scale production than other unit oral forms.

Disadvantages[1] :

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low density character.
- Drugs with poor wetting, dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract or any combination of these features may be difficult to impossible to formulate and manufacture as a tablet that will still provide adequate full drug bioavailability.
- Bitter tasting drugs, drugs with an objectionable odour or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation prior to compression or the tablets may require coating. In such cases the tablets may offer the offer the best and lowest coast approach.

Types of Tablets[1] :

The main reason behind formulation of different types of tablets are to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form that is convenient from patients perspective and utilize an approach that is unlikely to add complexity during regulatory approval process. To perceive each dosage form, tablets here are classified by their route of administration and by the type of drug the delivery system represent within that route.

Oral Tablets for ingestion:

- Standard compressed tablets
- Multiple compressed tablets
    - Compression coated tablets
    - Layered tablets
    - Inlay tablets
- Modified release tablets
- Delayed action tablets
- Targeted action tablets
    - Floating tablets
    - Colon targeting tablets
- Chewable tablets
- Dispersible tablets

Tablets used in oral cavity:

- Lozenges and troches
- Sublingual tablets
- Buccal tablets
- Dental cones
- Mouth dissolving tablets

Tablets administered by other routes:

- Vaginal tablets
- Implants

Tablets used to prepare solution:

- Effervescent tablets
- Hypodermic tablets
- Soluble tablets

METHODS INVOLVED IN FORMULATION OF TABLETS[5]:

- Direct compression
- Dry granulation
- Wet granulation

Direct Compression:

This method is used when a group of ingredients can be blended and placed in a tablet press to make a tablet without any of the ingredients having to be changed. This is not very frequent because many tablets have active pharmaceutical ingredients which will not allow for the direct compression due to their concentration or the excipients used in formulation are not conducive to direct compression.

Merits of direct compression:

- ❖ Cost Effective
- ❖ Stability
- ❖ Faster Dissolution
- ❖ Less wears and tears of punches
- ❖ Simplified Validation

Demerits of direct compression:

- ❖ Segregation
- ❖ Low dilution potential
- ❖ Re-workability
- ❖ Lubricant sensitivity
- ❖ Variation in functionality

GRANULATION:

Granulation is the process of collecting the particles together by creating bonds between them. There are several different methods of granulation. The most popular being the wet granulation which is used by over 70% in the formulation of tablets.

Dry Granulation:

In dry granulation process the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all the methods of granulation. The two basic procedures are to form a compact of materials by compression and then to mill the compact to obtain granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is recompressed and the resulting tablet or slug are milled to yield the granules. The other method is to pre compress the powder with pressure rolls using a machine as a Chilsonator.

Roller Compaction:

The compaction of powder by means of pressure roll can also be accomplished by a machine called Chilsonator. Unlike tablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral sugar to feed the powder into the compaction zones. Like slugs the aggregates are screened or milled for production into granules.

Use: use in the production of directly compressible ecipients, the compaction of drugs and drug formulations, the granulation of inorganic materials, the granulation of dry herbal materials and the production of immediate/sustained release formulations.

Processing Steps:

Weighing of raw materials, screening, mixing and compression to slugs-milling-mixing-compression to finished tablets.

Advantages:

The main advantage of dry granulation or slugging is that it uses less equipment and space.

It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation. Slugging can be used for advantages in the following situations

I. For moisture sensitive materials
II. For heat sensitive materials
III. For improved disintegration since powder particles are not bonded together by a binder.

Disadvantages:

I. It requires a specialized heavy duty tablet press to form slug
II. It does not permit uniform colour distribution which can be achieved by wet granulation where the de can be incorporated into binder liquid.
III. The process tends to create more dust than wet granulation, increasing the potential for contamination.

Wet Granulation:

The most broadly used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves the wet massing of the powder blend with a granulating liquid, wet sizing and drying. Important step involved in the wet granulations are

i. Mixing of the drug(s) and excipients.
ii. Preparation of binder solution
iii. Mixing of blend solution with powder mixture to form wet mass

iv. Drying of moist granules
v. Mixing of screened granules with disintegrant, glidant, and lubricant.

Merits:

a) Permits mechanical handling of powders without loss of mix quality.
b) Improves the flow of powders by increasing particle size.
c) Increases and improves the uniformity of powder density.
d) Improves cohesion during and after compaction.
e) Reduces air entrapment.
f) Reduces the level of dust and cross-contamination.
g) Allows for the addition of a liquid phase to powders (wet process only).
h) Makes hydrophobic surfaces hydrophilic.

Demerits:

a) The major limitation of wet granulation is its cost. It's expensive process because of labour, time, equipment, energy, space requirements
b) Loss of materials during various stages of processing
c) Stability may be major concern for moisture sensitive or thermolabile drugs.
d) Multiple processing steps add complexity and make validation and control difficult
e) An inherent limitation of wet granulation is that any compatibility between formulation components is aggravated.

TABLET COATING[6]:

The application of coating to tablets, which is an additional step in the manufacturing process, increases the coast of the product; therefore, the decision to coat a tablet is usually based on the following objectives:

1. To mask the taste, odour, or colour of the drug.
2. To provide physical and chemical protection for the drug.
3. To control the release of the drug from the tablet.
4. To protect the drug from the gastric environment of the stomach with an acid-resistant enteric coating.
5. To incorporate another drug adjuvant in the coating to avoid chemical incompatibilities or to provide sequential drug release.
6. To improve the pharmaceutical elegance by use of special colours.

There are two types of coatings they are

I. Sugar coating.
II. Film coating.

Introduction to Film Coating Materials

A film coating is a thin polymer-based coat applied to a solid dosage form such as a tablet. The thickness of such a coating is usually between 20-100 µm. Under close inspection the film structure can be seen to be relatively non- homogenous and quite distinct in appearance, from a film forming, from casting a polymer solution on a flat surface.

Film coating formulations usually contain the following components

Polymer,

Plasticizer,

Colourants / Opacifiers,

Solvent/Vehicle.

Polymers

Amongst the vast majority of the polymers used in film coating are cellulose derivatives or acrylic polymers and copolymers.

Non-enteric polymers

·Hypromellose

·Hydroxyethyl cellulose

·Hydroxyethylmethyl cellulose

·Carboxymethylcellulose sodium

·Hydroxypropyl cellulose

·Polyethylene glycol

·Ethylcellulose

Enteric polymers

Some examples of enteric coating polymers

·Hypromellose phthalate

·Polyvinyl acetate phthalate

·Cellulose acetate phthalate

·Polymethacrylates

·Shellac

Plasticizers

Plasticizers are simply relatively low molecular weight materials which have the capacity to alter the physical properties of the polymer to render it more useful in performing its function as a film-coating material. It is generally considered to be mechanism of plasticizer molecules to interpose themselves between individual polymer strands thus breaking down polymer-polymer interactions. Thus polymer is converted in to more pliable materials. Plastisizers are classify in three groups. Polyos type contain glycerol, propylene glycol, PEG(Polyethylene glycol). Organic esters contain phthalate esters, dibutyl sebacete, citrate esters, triacetin. Oils/glycerides contain castor oil, acetylated, monoglycerides and fractionated coconut oil.

Solvents/Vehicles

The key function of a solvent system is to dissolve or disperse the polymers and other additives. All major manufactures of polymers for coating give basic physicochemical data on their polymers. These data are usually helpful to a formulator. Some important considerations for solvent are as follows,

The major classes of solvents being used are

·Water

·Alcohols

·Ketones

·Esters

·Chlorinated hydrocarbons

Because of environmental and economic considerations, water is the solvent of choice; however organic coating is totally cannot be avoided.

Colourants / opacquants

These materials are generally used as ingredients in film-coating formulae to contribute to the visual appeal of the product, but they also improve the product in other ways

Identification of the product by the manufacturer and therefore act as an aid for existing GMP procedures.

- Reinforcement of brand imaging and reduction in product counterfeiting.
- Identification of the product by patients by using colourants.

Colourants for film coating are having, in more or less amount, property of opacifier. So they would give protection to active ingredients in presence of light. Colourants are mainly classified in to three part. Sunset yellow, tartrazine, erythrosine are examples of Organic dyes and their lakes. Iron oxide yellow, red and black, titanium dioxide, talc are the examples of Inorganic colours. Anthrocyanins, ribofloavine and carmine are the examples of natural colours.

Miscellaneous coating solution components

To provide a dosage form with a single characteristic, special materials may be incorporated into a solution·

Flavours and sweeteners are added to mask unpleasant odours or to develop the desired taste. For example, aspartame, various fruit spirits (organic solvent), water soluble pineapple flavour (aqueous solvent) etc.

Surfactants are supplementary to solubilize immiscible or insoluble ingredients in the coating. For example, Spans,Tweens etc.

Antioxidants are incorporated to stabilize a dye system to oxidation and colour change. For example oximes, phenols etc.

Antimicrobials are added to put off microbial growth in the coating composition. Some aqueous cellulosic coating solutions are mainly prone to microbial growth, and long-lasting storage of the coating composition should be avoided. For example alkylisothiazloinone, carbamates, benzothiazoles etc.

Coating Process

Film-coating of tablets is a multivariate process, with many different factors, such as coating equipment, coating liquid, and process parameters which affect the pharmaceutical quality of the final product.

Coating equipment

Before few years different types of coating pans are used for coating like conventional coating pans, manesty accelacota, driam (driacoater), butterfly coater etc. Now a days the side-vented, perforated pan-coater is the most commonly used coating device of tablets. In equipment spray nozzle, number of spray nozzle, pan size, etc may also affect the quality of final product. Its air flow system through a perforated pan ensures rapid and continuous drying conditions. The low evaporation capacity of water requires high drying efficiency of aqueous film-coating equipment.

Coating liquid

Coating liquid may affect the final quality of the tablets. Different film former have different chemical nature and different charesteristic. Viscosity may affect the spreading of coating liquid across surface of substrate. Surface tension may affect in wetting of surface. % Solid content generally affect the tablet surface and coating efficiency.

Process parameters

Spray rate

The spray rate is an significant parameter since it impacts the moisture content of the formed coating and, subsequently, the quality and uniformity of the film.A low coating liquid spray rate causes incomplete coalescence of polymer due to insufficient wetting, which could effect in brittle films. A high coating liquid spray rate may result in over wetting of the tablet surface and subsequent problems such as picking and sticking. If the spray rate is high and the tablet surface temperature is low, films are not formed during the spraying but the post drying phase, and rapid drying often produces cracks in the films.

Atomizing air pressure

In general, increasing the spraying air pressure decreases the surface roughness of coated tablets and produces denser and thinner films. If spraying air pressure is excessive, the spray loss is great, the formed droplets are very fine and could spray-dry before reaching the tablet bed, resulting in inadequate droplet spreading and coalescence. If spraying air pressure is inadequate, the film thickness and thickness variation are greater possibly due to change in the film density and smaller spray loss. In addition, with low spraying air pressure big droplets could locally over wet the tablet surface and cause tablets to stick to each other.

Inlet air temperature

The inlet air temperature affects the drying efficiency (i.e. water evaporation) of the coating pan and the uniformity of coatings. High inlet air temperature increases the drying efficiency of the aqueous film coating process and a decrease in the water penetration into the tablet core decreases the core tablet porosity, tensile strength and residual moisture content of coated tablets. Too much air temperature increases the premature drying of the spray during application and, subsequently, decreases the coating efficiency. Measuring the pan air temperature helps to manage the optimum conditions during the coating process and, consequently, enables predicting possible drying or over wetting problems which may result

in poor appearance of the film or may have unfavourable effects on the moisture and heat sensitive tablet cores.

Rotating speed of pan

It is well documented that increasing the rotating speed of the pan improves the mixing of tablets. The pan speed affects the time the tablets spend on the spraying zone and, subsequently, the homogeneous distribution of the coating solution on the surface of each tablet throughout the batch. Increasing the pan speed decreases the thickness variation and increase the uniformity of coatings. Too much rotating speed of the pan will cause the tablet to undergo unnecessary attrition and breakage.

Film coating technology is now a day's very important in the field of pharmacy particularly in formulation development. Process parameters and coating composition play an important in coating of tablets. So for getting good final quality of coated tablet it would be necessary to optimize the parameters.

VALIDATION: Validation is the documented act of demonstrating a procedure, process, and activity that will consistently lead to the expected results. It is a requirement for good manufacturing practices and other regulatory requirements. To ensure product quality, numerous features are required like chemical and physical stability, suitable preservation against microbial contamination (if appropriate), uniformity of dose of drug, acceptability to users including prescriber and patient, as well as suitable packing, labelling and validation[7]. To further enhance the effectiveness and safety of the drug product after approval many regulatory agencies such as the United States Food and Drug Administration (USFDA) also requires that the drug product be tested for its identity, strength, quality, purity and stability before it can be released for use. For this reason, pharmaceutical validation and process controls are important in spite of the problems that may be encountered[8]. Since a wide variety of procedures, processes, and activities need to be validated, the field of validation is divided into a number of subsections including the following:

- Cleaning validation
- Process validation
- Analytical method validation
- Computer system validation

Qualifying systems and equipment is divided into a number of subsections including the following:

- Design qualification (DQ)
- Component qualification (CQ)
- Installation qualification (IQ)
- Operational qualification (OQ)
- Performance qualification (PQ)

HISTORY[9,10]: The first validation activities were focused on the process involved in making these products but quickly spread to associated processes involving environmental control, media fill, equipment, and sanitization and purified water production. The concept of validation was first developed for equipment and processes and derived from the engineering practices used in delivery of large pieces of equipment that would be manufactured, tested, delivered and accepted according to a contract. The use of validation spread to other areas of industry after several large-scale problems highlighted the potential risks in the design of products.

REASONS FOR VALIDATION: Validation is "Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes." (FDA1987). A properly designed system will provide a high degree of assurance that every step, process and change has been properly evaluated before its implementation. Testing a sample of a final product is not considered sufficient evidence that every product within a batch meets the required specification.

NEED FOR VALIDATION [11,12,13]:

- It would be feasible to use the equipments without knowing whether it will produce the product we wanted or not.
- The pharmaceutical industry uses expensive materials, sophisticated facilities & equipments and highly qualified personnel.
- The efficient use of these resources is necessary for the continued success of the industry. The cost of product failures rejects reworks and recalls complaints are the significant parts of the total production cost.
- Detailed study and control of the manufacturing process validation is necessary if failure to be reduced and productivity improved.
- The Pharmaceutical industries are concerned about validation because of the following reasons:

a) Assurance of quality
b) Cost reduction
c) Government regulation.

DEPARTMENTS RESPONSIBLE[14]:

- SITE VALIDATION COMMITTEE (SVC): Develop site master validation plan, prepare or execute or approve validation studies.
- PRODUCTION DEPARTMENT: Prepares the batches as a routine production batch.
- QUALITY ASSURANCE: Ensure compliance, see that documentations, procedures are in place, approves protocols and reports.
- QUALITY CONTROL: Performs testing and reviews protocol and report as needed.

RESPONSIBLE AUTHORITIES FOR VALIDATION:

The working party would usually include the following staff members, preferably those with a good insight into the company's operations.

- Head of Quality Assurance
- Head of engineering.
- Validation manager
- Production manager
- Specialist validation discipline: all areas.

Table No 1: Authorities for Validation

DEPARTMENT/DESIGNATION	RESPONSIBILITY.
Manager production	Responsible for the manufacturing of batches and reviews of protocol and reports.
Manager QC	Responsible for analysis of sample collected.
Manager Maintenance	Providing utilities and engineering support.
Executive production	Responsible for preparation protocol and manufacturing of validation batches.
Manager QA	Responsible for protocol authorization and preparation of summary report.

ESSENTIALS OF PHAMACEUTICAL VALIDATION[15,16,17]:

Validation is the integral part of the quality assurance; it involves the systematic study of systems, facilities and processes aimed at determining whether they perform their intended functions adequately and consistently as specified. A validated process is one which has been demonstrated to provide a high degree of assurance that uniform batches will be produced that meet the required specifications and has therefore been formally approved. Validation in itself does not improve processes but confirms that the processes have been properly developed and are under control. Adequate validation is beneficial to the manufacturer in many ways:

1. It deepens the understanding of processes; decreases the risk of preventing problems and thus assures.
2. The smooth running of the process.
3. It decreases the risk of defect costs.
4. It decreases the risk of regulatory noncompliance.
5. A fully validated process may require less in- process controls and end product testing.

VALIDATION MASTER PLAN[18]:

Validation master plan is a document that describes how and when the validation program will be executed in a facility. Even though it is not mandatory, it is the document that outlines the principles involved in the qualification of a facility, defines the areas and systems to be validated and provides a written program for achieving and maintaining a qualified facility with validated processes. It is the foundation for the validation program and should include process validation, facility and utility qualification and validation, equipment qualification, cleaning and computer validation. The validation scope, boundaries and responsibilities for each process or groups of similar processes or similar equipment's must be documented and approved in a validation plan. These documents, terms and references for the protocol authors are for use in setting the scope of their protocols. It must be based on a Validation Risk Assessment (VRA) to ensure that the scope of validation being authorised is appropriate for the complexity and importance of the equipment or process under validation. Within the references given in the VP the protocol authors must ensure that all aspects of the process or

equipment under qualification; that may affect the efficacy, quality and or records of the product are properly qualified. Qualification includes the following steps:

- **DESIGN QUALIFICATION (DQ)** - Demonstrates that the proposed design (or the existing design for an off-the-shelf item) will satisfy all the requirements that are defined and detailed in the User Requirements Specification (URS). Satisfactory execution of the DQ is a mandatory requirement before construction (or procurement) of the new design can be authorised.
- **INSTALLATION QUALIFICATION (IQ)** – Demonstrates that the process or equipment meets all specifications, is installed correctly, and all required components and documentation needed for continued operation are installed and in place.
- **OPERATIONAL QUALIFICATION (OQ)** – Demonstrates that all facets of the process or equipment are operating correctly.
- **PERFORMANCE QUALIFICATION (PQ)** – Demonstrates that the process or equipment performs as intended in a consistent manner over time.
- **COMPONENT QUALIFICATION (CQ)** – is a relatively new term developed in 2005. This term refers to the manufacturing of auxiliary components to ensure that they are manufactured to the correct design criteria. This could include packaging components such as folding cartons, shipping cases, labels or even phase change material. All of these components must have some type of random inspection to ensure that the third party manufacturer's process is consistently producing components that are used in the world of GMP at drug or biologic manufacturer.

There are instances when it is more expedient and efficient to transfer some tests or inspections from the IQ to the OQ or from the OQ to the PQ. This is allowed for in the regulations, provided that a clear and approved justification is documented in the Validation Plan (VP)

PHASES OF VALIDATION:

PHASE 1:This is the pre –validation qualification phase which covers all activities relating to product research and development , formulation pilot batch studies, scale up studies, transfer of technology to commercial scale batches, establishing stability conditions and storage and handling of in process and finished dosage forms, equipment qualification

installation qualification , master production document, operational qualification and process capacity.

PHASE 2: This is the process validation phase .It is designed to verify that all established limits of the critical process parameters are valid and that satisfactory products can be produced even under the worst conditions.

PHASE 3:This is known as the maintenance phase .It requires frequent review of all process related documents, including validation of audit reports, to assure that there have been no changes , deviations , failures and modifications to the production process and that all standard operating procedures , have been followed, including the change control procedures. At this stage, the validation team comprising of individual representing all major departments also assures that there is no changes /deviations that should have resulted in requalification and revalidation. A careful design and validation of systems and process controls can establish a high degree of confidence that all lots or batches produced will meet their intended specifications. It is assumed that throughout manufacturing and control, operations are conducted in accordance with the principle of good manufacturing practice (GMP). Both in general and in specific references to sterile product manufacture. The validation steps recommended in GMP guidelines can be summarized as follows:

1. As a pre-requisite, all studies should be conducted in accordance with a detailed pre-established protocol or series of protocols, which in turn is subjected to formal-change control procedures.
2. Both the personnel conducting the studies and those running the process being studied should be appropriately trained and qualified and be suitable and competent to perform the task assigned to them.
3. All data generated during the course of studies should be formally reviewed and certified as evaluated against pre-determined criteria.
4. Suitable testing facilities, equipment instruments and methodology should be available.
5. Suitable clean room facilities should be available in both the local and background environment. There should be assurance that the clean room environment as specified as secured through initial commissioning (qualification) and subsequently through the

implemented of a program of re- testing –in process equipment should be properly installed, qualified and maintained.

6. When appropriate attention has been paid to the above, the process, if aseptic, may be validated by means of process stimulation studies.
7. The process should be revalidated at intervals
8. Comprehensive documentation should be available to define support and record the overall validation process.

PROCESS SHOULD SPECIFY THE FOLLOWING IN DETAILS:

1. The objective and scope of study – there should already be a definition of purpose.
2. A clear and precise definition of process equipment system or subsystem, which is to be the subject of study with details of performance characteristics.
3. Installation and qualification requirement for new equipment.
4. Any upgrading requirement for existing equipment with justification for change and statement of qualification requirements.
5. Detailed stepwise statement of actions to be taken in performing the study.
6. Assignment of responsibility for performing the study.
7. Statement on all the tests methodology to be employed with a precise statement of the test equipment and/or materials to be used.
8. Test equipment calibration requirements.
9. Requirements for the current format of the reports on the study.
10. References to any relevant standard operating procedures (SOP).
11. Acceptance criteria against which the success (or otherwise) of the study is to be evaluated.
12. The personnel responsible for evaluating and certifying the acceptability of each stage in the study and for the final evaluation and certification of the process as a whole as measured against the pre-defined criteria.
13. All personnel involved in conducting the studies should be properly trained and qualified because they can, and often, have a crucial effect on the quality of the end product. All the information or data generated as a result of the study protocol should be evaluated by qualified individuals against protocol criteria and judged as meeting or failing the requirements written evidences supporting the evaluation and conclusion should be considered as having failed to demonstrate acceptability and

documented. Any failure to follow the procedure as laid down in the protocol must be considered as potentially compromising the validity of the study itself and requires critical evaluation of all the impact on the study. The final certification of the validation study should specify the pre-determined acceptance criteria against which success or failure was evaluated.

COMPUTER SYSTEM VALIDATION[19]:

Validation (FDA 2002) defines verification as "Software verification provides objective evidence that the design outputs of a particular phase of the software development life cycle meet all of the specified requirements for that phase." It also defines Validation as "Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.

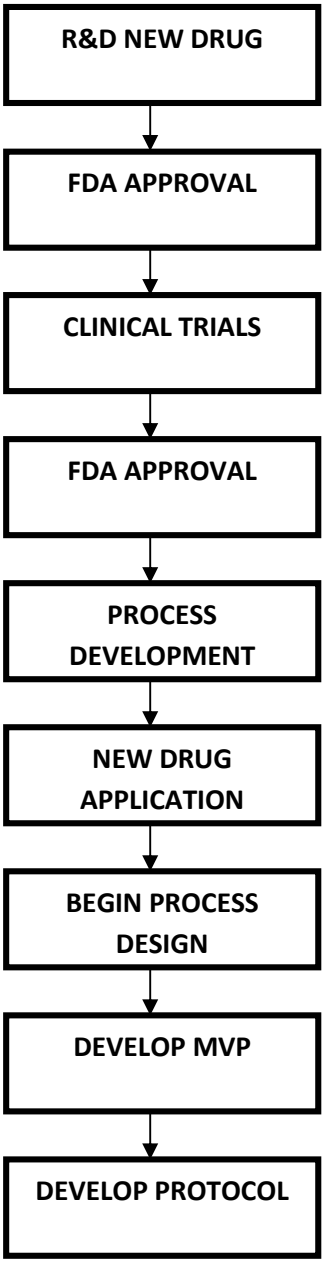
Weichel (2004) recently found that over twenty warning letters issued by the FDA to pharmaceutical companies specifically cited problems in Computer System Validation between 1997 and 2001.

SCOPE OF COMPUTER VALIDATION:

The main implications in this are that validation should cover all aspects of the process including the application, any hardware that the application uses, any interfaces to other systems, the users, training and documentation as well as the management of the system and the validation itself after the system is put into use. The PIC/S guideline (PIC/S 2004) defines this as a 'computer related system'. Much effort is expended within the industry upon validation activities, and several journals are dedicated to both the process and methodology around validation, and the science behind it.

A SIMPLIFIED DRUG/VALIDATION PATH

Figure no: 1 Simplified validation path



PROCESS VALIDATION:

INTRODUCTION[20,21]: This guidance outlines the general principles and approaches that FDA considers appropriate elements of process validation for the manufacture of human and animal drug and biological products, including active pharmaceutical ingredients (APIs or drug substances), collectively referred to in this guidance as drugs or products. This guidance incorporates principles and approaches that all manufacturers can use to validate manufacturing processes. This guidance aligns process validation activities with a product lifecycle concept and with existing FDA guidance, including the FDA/International Conference on Harmonization (ICH) guidance for industry, Q8(R2) Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System.2 Although this guidance does not repeat the concepts and principles explained in those guidance, FDA encourages the use of modern pharmaceutical development concepts, quality risk management, and quality systems at all stages of the manufacturing process lifecycle[20]. the lifecycle concept links product and process development, qualification of the commercial manufacturing process.

BACKGROUND: In the Federal Register of May 11, 1987, FDA issued a notice announcing the availability of a guidance entitled Guideline on General Principles of Process Validation (the 1987 guidance). Since then, we have obtained additional experience through our regulatory oversight that allows us to update our recommendations to industry on this topic. This revised guidance conveys FDA's current thinking on process validation and is consistent with basic principles first introduced in the 1987 guidance. The revised guidance also provides recommendations that reflect some of the goals of FDA's initiative entitled "Pharmaceutical CGMPs for the 21st Century. A Risk-Based Approach," particularly with regard to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality system tools and concepts[23]. This revised guidance replaces the 1987 guidance. FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The cGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess.

DEFINITION: Process validation is the collection and evaluation of data, from the process design stage throughout production, which establish scientific evidence that a process is

capable of consistently delivering quality products**.** Process validation involves a series of the activities taking place over the lifecycle of the product and process.

United States Food & Drug Administration: Process validation is establishing documented evidence which provide a high degree of assurance that a specific process consistently produces a product meeting its predetermined specification and quality attribute.

TYPES OF PROCESS VALIDATION:

Prospective process validation- where an experimental plan called the validation protocol is executed (following the completion of the qualification trials) before the process is put to commercial use. Most validation efforts require some degree of prospective experimentation in order to generate validation support data.

Concurrent Process validation- establishing documented evidence that the process is in a state of control during the actual implementation of the process .this is normally performed by the in-process testing and/ or monitoring of critical operations during the manufacture of each production batch.

Retrospective process validation-where historic data taken from the records of the completed production batches are used to provide documented evidence that the process has been in a state of control prior to the request for such evidence.

GENERAL CONSIDERATIONS FOR PROCESS VALIDATION:

In all stages of the product lifecycle, good project management and good archiving that capture scientific knowledge will make the process validation program more effective and efficient. The following practices should ensure uniform collection and assessment of information about the process and enhance the accessibility of such information later in the product lifecycle.

- Throughout the product lifecycle, various studies can be initiated to discover, observe, correlate, or confirm information about the product and process. All studies should be planned and conducted according to sound scientific principles, appropriately documented, and approved in accordance with the established procedure appropriate for the stage of the lifecycle.

- The terms attribute(s) (e.g., quality, product, component) and parameter(s) (e.g., process, operating, and equipment) are not categorized with respect to criticality in this guidance. With a lifecycle approach to process validation that employs risk based decision making throughout that lifecycle, the perception of criticality as a continuum rather than a binary state is more useful. All attributes and parameters should be evaluated in terms of their.
- Roles in the process and impact on the product or in-process material and reevaluated as new information become available. The degree of control over those attributes or parameters should be commensurate with their risk to the process and process output. In other words, a higher degree of control is appropriate for attributes or parameters that pose a higher risk. The Agency recognizes that terminology usage can vary and expects that each manufacturer will communicate the meaning and intent of its terminology and categorization to the Agency.
- Many products are single-source or involve complicated manufacturing processes. Homogeneity within a batch and consistency between batches are goals of process validation activities. Validation offers assurance that a process is reasonably protected against sources of variability that could affect production output, cause supply problems, and negatively affect public health.

Stage1. **PROCESS DESIGN**:

Process design is the activity of defining the commercial manufacturing process that will be reflected in planned master production and control records. The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its quality attributes.

Building and Capturing Process Knowledge and Understanding: Generally, early process design experiments do not need to be performed under the cGMP conditions required for drugs intended for commercial distribution that are manufactured during Stage 2 (process qualification) and Stage 3 (continued process verification). They should, however, be conducted in accordance with sound scientific methods and principles, including good documentation practices. This recommendation is consistent with ICH Q10 Pharmaceutical Quality System[21]. Decisions and justification of the controls should be sufficiently

documented and internally reviewed to verify and preserve their value for use or adaptation later in the lifecycle of the process and product.

Establishing a Strategy for Process Control:

Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall. Strategies for process control can be designed to reduce input variation, adjust for input variation during manufacturing (and so reduce its impact on the output), or combine both approaches. Process controls address variability to assure quality of the product. Controls can consist of material analysis and equipment monitoring at significant processing points. Decisions regarding the type and extent of process controls can be aided by earlier risk assessments, then enhanced and improved as process experience is gained. FDA expects controls to include both examination of material quality and equipment monitoring. Special attention to control the process through operational limits and in-process monitoring is essential in two possible scenarios:

1. When the product attribute is not readily measurable due to limitations of sampling or detectability (e.g., viral clearance or microbial contamination) or

2. When intermediates and products cannot be highly characterized and well-defined quality attributes cannot be identified.

Stage2. PROCESS QUALIFICATION:

During the process qualification (PQ) stage of process validation, the process design is evaluated to determine if it is capable of reproducible commercial manufacture. This stage has two elements:

(1) Design of the facility and qualification of the equipment and utilities and

(2) Process performance qualification (PPQ). During Stage 2, cGMP-compliant procedures must be followed. Successful completion of Stage 2 is necessary before commercial distribution. Products manufactured during this stage, if acceptable, can be released for distribution.

Design of a Facility and Qualification of Utilities and Equipment: Proper design of a manufacturing facility is required under part 211, subpart C, of the cGMP regulations on Buildings and Facilities. It is essential that activities performed to assure proper facility design and commissioning precede PPQ. Here, the term qualification refers to activities undertaken to demonstrate that utilities and equipment are suitable for their intended use and perform properly. These activities necessarily precede manufacturing products at the commercial scale.

Process Performance Qualification: The process performance qualification (PPQ) is the second element of Stage 2, process qualification. The PPQ combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches. A successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected. Success at this stage signals an important milestone in the product lifecycle. A manufacturer must successfully complete PPQ before commencing commercial distribution of the drug product. The decision to begin commercial distribution should be supported by data from commercial-scale batches. Data from laboratory and pilot studies can provide additional assurance that the commercial manufacturing process performs as expected.

PPQ Protocol: A written protocol that specifies the manufacturing conditions, controls, testing, and expected outcomes is essential for this stage of process validation. We recommend that the protocol discuss the following elements:

- The manufacturing conditions, including operating parameters, processing limits, and component (raw material) inputs.
- The data to be collected and when and how it will be evaluated.
- Tests to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step.
- The sampling plan, including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis as it

relates to the particular attribute under examination. Sampling during this stage should be more extensive than is typical during routine production.

The criteria should include for process performance indicators,

- A description of the statistical methods to be used in analyzing all collected data (e.g., statistical metrics defining both intra-batch and inter-batch variability).
- Provision for addressing deviations from expected conditions and handling of nonconforming data. Data should not be excluded from further consideration in terms of PPQ without a documented, science-based justification.

Design of facilities and the qualification of utilities and equipment, personnel training and qualification, and verification of material sources (components and container/closures), if not previously accomplished.

PPQ Protocol Execution and Report: Execution of the PPQ protocol should not begin until the protocol has been reviewed and approved by all appropriate departments, including the quality unit. Any departures from the protocol must be made according to established procedure or provisions in the protocol. Such departures must be justified and approved by all appropriate departments and the quality unit before implementation. The commercial manufacturing process and routine procedures must be followed during PPQ protocol execution. The PPQ lots should be manufactured under normal conditions by the personnel routinely expected to perform each step of each unit operation in the process. Normal operating conditions should include the utility systems (e.g., air handling and water purification), material, personnel, environment, and manufacturing procedures.

A report documenting and assessing adherence to the written PPQ protocol should be prepared in a timely manner after the completion of the protocol. This report should:

• Discuss and cross-reference all aspects of the protocol.

• Summarize data collected and analyze the data, as specified by the protocol.

• Evaluate any unexpected observations and additional data not specified in the protocol.

• Summarize and discuss all manufacturing nonconformances such as deviations, aberrant test results, or other information that has bearing on the validity of the process.

• Describe in sufficient detail any corrective actions or changes that should be made to existing procedures and controls.

• State a clear conclusion as to whether the data indicates the process met the conditions established in the protocol and whether the process is considered to be in a state of control. If not, the report should state what should be accomplished before such a conclusion can be reached. This conclusion should be based on a documented justification for the approval of the process, and release of lots produced by it to the market in consideration of the entire compilation of knowledge and information gained from the design stage through the process qualification stage.

• Include all appropriate department and quality unit review and approvals.

Stage 3. CONTINUED PROCESS VERIFICATION:

The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal. Adherence to the cGMP requirements, specifically, the collection and evaluation of information and data about the performance of the process, will allow detection of undesired process variability. Evaluating the performance of the process identifies problems and determines whether action must be taken to correct, anticipate, and prevent problems so that the process remains in control.

An ongoing program to collect and analyze product and process data that relate to product quality must be established. The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the quality attributes are being appropriately controlled throughout the process.

We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures

used in measuring and evaluating process stability and process capability. Procedures should describe how trending and calculations are to be performed and should guard against overreaction to individual events as well as against failure to detect unintended process variability. Production data should be collected to evaluate process stability and capability. The quality unit should review this information. If properly carried out, these efforts can identify variability in the process and/or signal potential process improvements.

Good process design and development should anticipate significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits. However, a process is likely to encounter sources of variation that were not previously detected or to which the process was not previously exposed. Many tools and techniques, some statistical and others more qualitative, can be used to detect variation, characterize it, and determine the root cause. We recommend that the manufacturer use quantitative, statistical methods whenever appropriate and feasible. Scrutiny of intra-batch as well as inter-batch variation is part of a comprehensive continued process verification program under.

We recommend continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until sufficient data are available to generate significant variability estimates. These estimates can provide the basis for establishing levels and frequency of routine sampling and monitoring for the particular product and process. Monitoring can then be adjusted to a statistically appropriate and representative level. Process variability should be periodically assessed and monitoring adjusted accordingly.

Variation can also be detected by the timely assessment of defect complaints, out-of-specification findings, process deviation reports, process yield variations, batch records, incoming raw material records, and adverse event reports. Production line operators and quality unit staff should be encouraged to provide feedback on process performance. We recommend that the quality unit meet periodically with production staff to evaluate data, discuss possible trends or undesirable process variation, and coordinate any correction or follow-up actions by production.

Data gathered during this stage might suggest ways to improve and/or optimize the process by altering some aspect of the process or product, such as the operating conditions (ranges

and set-points), process controls, component, or in-process material characteristics. A description of the planned change, a well-justified rationale for the change, an implementation plan, and quality unit approval before implementation must be documented. Depending on how the proposed change might affect product quality, additional process design and process qualification activities could be warranted.

Maintenance of the facility, utilities, and equipment is another important aspect of ensuring that a process remains in control. Once established, qualification status must be maintained through routine monitoring, maintenance, and calibration procedures and schedules.

CONCURRENT RELEASE OF PPQ BATCHES: In most cases, the PPQ study needs to be completed successfully and a high degree of assurance in the process achieved before commercial distribution of a product. In special situations, the PPQ protocol can be designed to release a PPQ batch for distribution before complete execution of the protocol steps and activities, i.e., concurrent release. FDA expects that concurrent release will be used rarely.

Concurrent release might be appropriate for processes used infrequently for various reasons, such as to manufacture drugs for which there is limited demand (e.g., orphan drugs, minor use and minor species veterinary drugs) or which have short half lives (e.g., radiopharmaceuticals, including positron emission tomography drugs). Concurrent release might also be appropriate for drugs that are medically necessary and are being manufactured in coordination with the Agency to alleviate a short supply.

A commercial manufacturing process can only be made after the PPQ protocol is fully executed and the data are fully evaluated. If Stage 2 qualification is not successful (i.e., does not demonstrate that the process as designed is capable of reproducible performance at commercial scale), then additional design studies and qualification may be necessary. The new product and process understanding obtained from the unsuccessful qualification study (ies) can have negative implications if any lot was already distributed. Full execution of Stages 1 and 2 of process validation is intended to preclude or minimize that outcome.

Circumstances and rationale for concurrent release should be fully described in the PPQ protocol. Even when process performance assessment based on the PPQ protocol is still outstanding, any lot released concurrently must comply with all CGMPs, regulatory approval

requirements, and PPQ protocol lot release criteria. Lot release under a PPQ protocol is based upon meeting confidence levels appropriate for each quality attribute of the drug.

When warranted and used, concurrent release should be accompanied by a system for careful oversight of the distributed batch to facilitate rapid customer feedback. For example, customer complaints and defect reports should be rapidly assessed to determine root cause and whether the process should be improved or changed. Concurrently released lots must also be assessed in light of any negative PPQ study finding or conclusions and appropriate corrective action must be taken .We recommend that each batch in a concurrent release program be evaluated for inclusion in the stability program. It is important that stability test data be promptly evaluated to ensure rapid detection and correction of any problems

DOCUMENTATION: Documentation at each stage of the process validation lifecycle is essential for effective communication in complex, lengthy, and multidisciplinary projects. Documentation is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each stage of the lifecycle. Information transparency and accessibility are fundamental tenets of the scientific method. They are also essential to enabling organizational units responsible and accountable for the process to make informed, science-based decisions that ultimately support the release of a product to commerce.

The degree and type of documentation required by cGMP vary during the validation lifecycle. Documentation requirements are greatest during Stage 2, process qualification, and Stage 3, continued process verification. Studies during these stages must conform to cGMPs and must be approved by the quality unit in accordance with the. Viral and impurity clearance studies, even when performed at small scale, also require quality unit oversight.

cGMP documents for commercial manufacturing (i.e., the initial commercial master batch production and control record and supporting procedures are key outputs of Stage 1, process design. We recommend that firms diagram the process flow for the full-scale process. Process flow diagrams should describe each unit operation, its placement in the overall process, monitoring and control points, and the component, as well as other processing material inputs (e.g., processing aids) and expected outputs (i.e., in-process materials and finished product). It is also useful to generate and preserve process flow diagrams of the various scales as the

process design progresses to facilitate comparison and decision making about their comparability.

ANALYTICAL METHODOLOGY: Process knowledge depends on accurate and precise measuring techniques used to test and examine the quality of drug components, in-process materials, and finished products. Validated analytical methods are not necessarily required during product- and process-development activities or when used in characterization studies. Nevertheless, analytical methods should be scientifically sound (e.g., specific, sensitive, and accurate) and provide results that are reliable. There should be assurance of proper equipment function for laboratory experiments. Procedures for analytical method and equipment maintenance, documentation practices, and calibration practices supporting process-development efforts should be documented or described. New analytical technology and modifications to existing technology are continually being developed and can be used to characterize the process or the product. Use of these methods is particularly appropriate when they reduce risk by providing greater understanding or control of product quality. However, analytical methods supporting commercial batch release must follow cGMPs. Clinical supply production should follow the cGMPs appropriate for the particular phase of clinical studies.

QUALITY BY DESIGN AND THE NEW PROCESS VALIDATION GUIDANCE[21]:

Pilot Program: The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together regulatory authorities and pharmaceutical companies from Europe, Japan, and the United States to discuss scientific and technical aspects of drug registration. Since its inception in 1990, ICH has worked through its global cooperation group to harmonize the increasingly global face of drug development. Its mission is to help ensure that safe, effective, and high-quality medicines are developed and registered with the most efficient use of resources. The organization focuses on four main subjects: quality, safety, efficacy, and multidisciplinary guidelines, which include the MedDRA standardized medical terminology guide and the common technical document (CTD), a format for submitting information for regulatory review in all participating countries. In relation to process validation, four ICH subtopics are most relevant: Q8, Q9, Q10, and Q11.

ICH Q8(R2): Pharmaceutical Development was adopted by the European Union in June 2009, by the United States in November 2009, and by Japan in June 2010, after having been finalized in November 2005. This document is intended to provide guidelines for drug products as defined in the scope of Module 3 of the common technical document (CTD), which is ICH topic M4. The guideline does not apply to contents of submissions for drug products in clinical research, but its principles are important to consider during that stage. An annex to the tripartite harmonized ICH text was finalized in November 2008 and incorporated into the core document, which was then, renamed Q8 (R1). That annex provided further clarification of key concepts and described the principles of QbD. It showed how concepts and tools (e.g., design space) outlined in the parent document could be put into practice. When a company applies QbD and quality risk management as part of a pharmaceutical quality system, opportunities arise to enhance science- and risk-based regulatory approaches The Q8 guideline was revised to (R2) in the summer of 2009 to reflect minor corrections.

ICH Q9: Quality Risk Management was adopted by the European Union in January 2006, by the United States in June 2006, and by Japan in September 2006 after the tripartite harmonized ICH guideline was finalized in November 2005. This guideline provides principles and examples of tools for quality risk management that can be applied to all aspects of pharmaceutical quality including development, manufacturing, distribution, and inspection and submission/review. It can be applied throughout the lifecycle of drug substances and medicinal products, biological, and biotechnological products and covers the use of raw materials, solvents, Excipients, packaging, and labeling materials.

ICH Q10: Pharmaceutical Quality System was adopted by the European Union in July 2008, by the United States in April 2009, and by Japan in February 2010 after the tripartite harmonized ICH guideline had been finalized in June 2008. This document applies to pharmaceutical drug substances and drug products (including biotechnology and biological products) throughout their lifecycles. Companies should apply its elements appropriately and proportionately to each stage.

Other Documents: Real-world experiences of companies and regulators with the Q8, Q9, and Q10 guidelines made ICH aware of a need for some clarification of key issues. The latest version of its resulting questions-and-answers document was finalized in

ISPE has published a guidance document that's free for its members and available to nonmembers at a nominal cost: ISPE Product Quality Lifecycle Implementation Guide: Overview of Product Design, Development and Realization — A Science- and Risk-Based Approach to Implementation International Society for Pharmaceutical Engineering.

According to ISPE:, the guide is "the first in a series of product quality lifecycle implementation good practice guides that will describe enhanced, QbD approaches to product realization and is an introduction to and an overview of the guides series." To address product and process development, transfer to and establishment of commercial manufacture using science- and risk-based approaches, the series will cover critical quality attributes (CQAs) and critical process parameters (Cops), design space, and control strategy.

In addition, ASTM International has published a standard that supports ICH Q8 and Q9 titled ASTM E2537-08: Standard Guide for Application of Continuous Quality Verification to Pharmaceutical and Biopharmaceutical Manufacturing. According to ASTM, "The accumulated product and process understanding used to identify critical quality attributes (CQAs), together with the knowledge that the risk-based monitoring and control strategy will enable their control, should provide confidence to show validation of each batch manufactured — as opposed to a conventional discrete process validation effort."

ICH Q11: Development and Manufacture of Drug Substances was endorsed as a topic by the ICH Steering Committee in April 2008. This new guidance is proposed for active pharmaceutical ingredients (APIs) harmonizing the scientific and technical principles relating to the description and justification of the development and manufacturing process (common technical document sections of drug substances including both chemical and biotechnological/biological entities. The document is only at stage 1 of the ICH process currently other Guidance Document molecules.

The pilot program has provided an opportunity for the biopharmaceutical industry and the FDA to evaluate and identify best practices for key QbD elements of target product profiles, critical quality attributes (CQA), risk assessment, process characterization for design-space definition, CQA-focused control strategies, and expanded change protocols. This builds on the concept of well-characterized biological (a.k.a. specified biologics), which came about in the late 1990s when it was recognized that analytical methods had improved to the point at which biologics could be analyzed and described well enough to separate their identities from

their processes. A few years later, CDER took over responsibility for those well-characterizable products from the Center for Biologics Evaluation and Research (CBER).

The OBP pilot program offers individualized examination of QbD initiatives submitted in market applications for biotech therapies for a number of original and supplemental biologic license and new drug applications. Manufacturers — such as Genentech, an early program participant — voluntarily provide chemistry, manufacturing, and controls (CMC) information in an expanded change protocol describing their implementation of QbD and risk management. Their candidate products are monitored by the OBP throughout product development and testing after early discussions with FDA reviewers about R&D issues.

For the pilot, the Office of Compliance (OC) will be part of review communication, so there is a need to transfer information among OBP, OC, and the field. Ideally, product reviewers should be present at initial QbD-type inspections. The Office of Compliance will play a key role in understanding the role of quality systems in QbD filings and their control strategies.

Continuous Verification: According to Swann, the new guidance describes three stages of process validation during the lifecycle of a drug product, which falls into line with ICH Q8 during early product and process development, process design builds criteria for testing, qualification, and setting specifications later on. “The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities” Process qualification encompasses many validation concepts familiar to those who have been working with the previous guidance document all along: Manufacturing equipment, tooling, and instrumentation, and utilities must be qualified using standard validation protocols along with an associated validation master plan, risk assessment, and requirements specifications. “During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

Continued process verification, the final stage, was the focus of Grace McNally’s presentation. “Ongoing assurance is gained during routine production that the process remains in a state of control” McNally emphasized the “life-cycle approach” that makes process validation an ongoing activity — not something a company can do and then move on.

“Criticality” (as of quality attributes) is a continuum, she pointed out, not an either–or question. McNally also pointed to several other sections of the Code of Federal Regulations

that can help those working to implement these concepts into their manufacturing process development

CURRENT TRENDS OF PROCESS VALIDATION[22,23,24]:

The significance of the process validation has taken on a new emphasis, since a series of new rules and regulations on this subject have been published, notably

- EU GMP Guide Annex 15: Qualification and Validation
- EMA Note for Guidance on Process Validation
- FDA Guidance for Industry -Process Validation: General Principles and Practices

Last but not least, EU GMP Guide, Part II covers the topic of validation more extensively than most other rules or regulations. For Excipients, the topic of validation is described in the IPEC Good Manufacturing Practices Guide for Bulk Pharmaceutical Excipients.

The objective of the EMA Note for Guidance on Process Validation is standardization of the validation documents that must be submitted with the submission file for marketing authorization. This guideline is directed at manufacturers of pharmaceutical products; to some extent, though, the procedure is also transferable to the manufacture of active pharmaceutical ingredients, Excipients, biotech or blood products.

The EMA Note for Guidance on Process Validation is to be revised in the course of 2011 in order to incorporate the concepts of ICH Q8, Q9 and Q10. The objective here is primarily to consolidate the various concepts and to clarify questions resulting from this -but not to introduce novel requirements. No additional requirements will result from this for products which have already been approved.

LITERATURE REVIEW

- Jyotsna godbole *et al*.,[25]designed the concept of bilayer matrix tablets containing Acarbose as immediate release component using sodium starch glycolate and cross croscarmellose sodium as super disintegrating agent and Metformin hydrochloride (HCl) for sustained release component by using hydroxyl propyl methyl cellulose (HPMC K 4M), (HPMC K 100) and sodium carboxyl methyl cellulose (SCMC) as the matrix forming polymer and PVPK-30 as binder. Matrix tablet are the type of controlled drug delivery systems, which release the drug in continuous manner. These release the drug by both as well as diffusion controlled mechanisms metformin HCl is 6.2 hrs, so an attempt was made in the direction of preparation and optimization of a combination of sustained release and immediate release in a single tablet. Tablets were prepared by wet granulation and direct compression method. Tablets were evaluated for post compression parameters. The tablets were evaluated for physico-chemical property. All the values were found to be satisfactory. Invitro release studies were carried as per USP in water and phosphate buffer of pH 6.8 using the apparatus I. The final preparation showed release of drug up hours. FTIR studies revealed that there is no interaction between the drug and other excipients used in the study.

- Kwabena ofori-kwakye *et al*.,[26] carried out study of the in vitro behaviour of tablet cores coated with novel films of albizia, albizia/khaya and albizia/HPMC. Diclofenac sodium tablet cores, 225 mg, were formulated and coated with aqueous film formulations consisting of albizia gum only, albizia/khaya (25:75), and albizia/HPMC (90:10). The thickness, breaking strength, disintegration time, swelling index and drug release properties of the uncoated and film coated tablets were evaluated. Tablet thickness increased with increase in coating time. The breaking strength of the film coated tablets was higher than that of the tablet cores and increased with increase in coating time. The disintegration time of the uncoated and film coated tablets in the media used was pH- dependent and followed the rank order: 0.1 M HCl > pH 6.8 phosphate buffer > distilled water. The extent of swelling (water absorption) of the film coated tablets in 0.1 M HCl was dependent on film composition and followed the order: albizia/HPMC > albizia > albizia/khaya. Drug release in pH 6.8 phosphate buffer was faster than in 0.1 M HCl solution. Albizia and albizia/HPMC film coated tablets exhibited the slowest drug release in the acidic and basic media, respectively.

The study shows the potential of albizia, albizia/khaya and albizia/HPMC films as coating materials for tablets.

- Vandana B. Patel *et al*,.[27] studied prospective process validation of Cimtidine 400mg tablet dosage form and investigated that Quality cannot be adequately assured by in-process and finished inspections and testing but it should be built in to the manufacturing process. These processes should be controlled in order that the finished product meets all quality specifications. Therefore building of quality requires careful attention to a number of factors, such as the selection of materials, product and process design, control variables, in process control and finished product testing. The critical process parameters were identified with the help of process capability and evaluated by challenging its lower and upper release specifications. Three initial process validation batches of same size, method, equipment & validation criteria were taken. The critical parameter involved in sifting, dry mixing, preparation of granulating agent, wet mixing, wet milling, drying, sizing, lubrication & compression stages were identified and evaluated as per validation plan. Film coating of tablet were evaluated for coating uniformity, coating process efficiency and surface roughness. The spry rate ,atomization air pressure, distance of nozzle from tablet bed, inlet air temperature, pan differential pressure ,pan speed and % solid content these affect the final film quality of coated tablets. The outcome indicated that this process validation data provides high degree of assurance that manufacturing process produces product meeting its predetermined specifications and quality attributes.

- Raveendranath Thaduvai *et al*.,[28] formulated Sodium Pantoprazole-Loaded Enteric Micro particles Prepared by Spray Drying and studied the effect of the Scale of Production and Process Validation. In this study investigation of the physical characteristics were carried out for enteric pantoprazoleloaded micro particles prepared by spray drying using a blend of Eudragit and HPMC. At pilot scale, among the four sets of micro particles prepared varying the atomization and the air pressure, in three of them free micro particles were obtained. The micro particles prepared with rotating disc atomizer or two fluid atomizer and mixed flow presented either crystals on the particle surface or very high polydispersity, respectively. Using two fluid nozzle and air pressure of 49 kPa (N1-microparticles) the product obtained was not adequate because it presented strings in the powder. Using the same atomizer but air

pressure of 196 kPa (N2-microparticles) the micro particles presented high encapsulation efficiency and the highest stabilization of formulation in acid medium. N2-microparticles were chosen for the pilot scale evaluation. The three batches of pantoprazole-loaded micro particles prepared to validate the process showed reproducible diameter, polydispersity, densities, encapsulation efficiency and gastro-resistance profile.

- Rahul Paruchuri *et al*.,[29] have studied that validation is one of the important steps in achieving and maintaining the quality of the final product. If each step of production process is validated, it can be assured that the final product is of the best quality and validation of the individual steps of the processes is called the process validation. Different dosage forms have different validation protocols. Here this article concentrates to provide assurance that the manufacturing procedure is suitable for intended purpose and consistently meet predetermined specifications and quality attributes, as per specified master formula record. It also provides a documented evidence for the operation sequence and schedule of manufacturing process and to determine the critical parameters and variables in the process of manufacturing of the tablets. It gives a higher degree of assurance that the manufacturing process consistently meet the pre-determined specifications and quality products output can be used to increase productivity, its consistent quality and decreasing the need for processing/market complaints.

- Jignakumari Manubhai Tandel etal.,[30] have studied that validation is best viewed as an impartment and integral part of cGMP, validation is therefore one element of quality assurance programs associated with a particular process. Then word validation simply means “assessment of validity” or action of proving effectiveness. This process involves addition of granulating agent to the dry mixed material and converting into granules. The goal of quality system is to consistently produce products that are suitable for their intended use. Process validation is a key element in assuring that these principles and goals are met. In this study concurrent process validation was carried out for pyrazinamide tablets IP 750 mg. In tablet dosage form, critical parameters like dry mixing, granulation, drying, sifting and milling, lubrication and compression were taken up for validation studies. In-process quality

monitoring of all critical processing steps was done for three production batches. LOD of the dried, milled and lubricated granules were checked and found within the limit. Assay after lubrication was within the specified limit, indicating blend uniformity. Physical parameters, dissolution and assay were checked and results found within the acceptance criteria. During packing operation, blisters were checked and found satisfactory. Thus process validation of pyrazinamide tablets IP 750 mg was successfully completed and found within the specifications.

- Ruchita.v.kumar *et al.*,[31] studied the potential of a novel combination of a galactomannan with acarbose (100 mg) that was evaluated for attaining a desired hypoglycaemic effect over a prolonged period of time. Three major antidiabetic galactomannans viz., fenugreek gum, boswellia gum, and locust bean gum were selected in order to achieve a synergistic effect in the treatment alongwith retardation in drug release. In vitro studies indicated that batches containing various proportions of fenugreek gum (AF40-60) were able to control drug release for a longer duration of approximately 10–12 h. In contrast, the matrices prepared using boswellia and locust bean gum were able to sustain the release for relatively shorter durations. Drug release mainly followed first-order release kinetics owing to the highly soluble nature of the drug. In vivo study depicted a significant reduction ($p < 0.001$) in the postprandial blood glucose and triglyceride levels in the diabetic rats on treatment with formulation AF40. Thus, the developed system provides a better control of the postprandial glycaemic levels and it also obviates the need of conventional multiple dosing of acarbose. Furthermore, it also reduces the occurrence of side effects like diarrhea and loss of appetite.

- F. A. Ibrahim *et al.*,[32] have studied a simple and sensitive kinetic spectrophotometric method for the determination of acarbose and miglitol in bulk and in their pharmaceutical preparations using alkaline potassium permanganate as an oxidizing agent. The method involves determination of acarbose and miglitol by kinetic studies of their oxidation at room temperature for a fixed time of 15 minutes for acarbose and 25 minutes for miglitol. The absorbance of the colored manganate ion was measured at 610 nm. Alternatively, the kinetic decrease in the absorbance of permanganate upon addition of the studied drugs at 525 nm was also used. The absorbance versus concentration plot was rectilinear over the concentration range of 4 - 20 and 1-10 µg/

ml for acarbose and miglitol, respectively. The detection limits were 0.189 and 0.089 µg/ ml at 610 nm and 0.081 and 0.179 µg/ ml at 525 nm for acarbose and miglitol respectively. The method was successfully applied for the determination of these drugs in their dosage forms. The results obtained were in good agreement with those obtained with the reference methods.

- Kumari G *et al*.,[33] Formulated and studied release kinetics of Hydrogel containing Acarbose using polymers as Hydroxypropylmethyl cellulose and Guar gum by Wet granulation technique. Hydrogel matrix tablets of Acarbose were formulated using these polymers which, slows the release of Acarbose over a period of 12 h and were suitable for maintenance portion of oral controlled release tablets. Acarbose release from these tablets was diffusion controlled and followed zero order kinetics after a lag time of 1 h and It was concluded that drug release rate was inversely proportional to the concentration of retardant polymer i.e., increase in concentration of retardant polymer resulted in a reduction in the drug release rate.

- Pradeep kumar T *et a.,l*[34] developed a pharmaceutically equivalent, stable, cost effective and quality improved formulation of film coated Ticlopidine Hcl tablets by direct compression method. The three superdisintegrants used in the study were crosscaramellose soudium(CCS), MCC, and native Starch. The formulation containg combination of ccs,mcc and native starch (6,44.73,554.75 mg) showed minimum DT and maximum drug realase.

- Nasiruddin Ahmad Farooqui *et al.,*[35] developed film coated tablets of senidazole which are designed to rupture and expose core tablets at the desired location in the gastro intestinal track the coating is done by film coating solutions which are polymers in nature, forming smooth coat over core tablets. The present study was aimed to formulate film coated tablets of senidazole by wet granulation and the granules are compressed for tablets and they are coated with polymers for getting film coated tablets at specified conditions and the evaluation for the following parameters as average weight, weight variation, thickness, dissolution, related substance, disintegration time and assay for compliance with acceptance criteria for formulation of secnidazole film coated tablets.

AIM AND OBJECTIVE OF WORK

- To formulate and evaluate the Pre-formulation and Pre-compression parameters of Acarbose core tablet.

- To formulate and evaluate Acarbose film coated tablets using various methods and various excipient.

- To carry out the process validation studies of the formulated Acarbose tablets.

- To carry out process validation studies for the three batches formulated.

  Batch A

  Batch B

  Batch C.

- To maintain the quality of the prepared product.

- The scope of this project is to minimize the errors in the process validation.

- To find out the uniformity in the batches.

- To check whether the Equipments that are used must justify the parameters that is in the specifications.

- To maintain the process validation control variables such as the analytical procedure, equipments, production process.

- To find out the results that are obtained is within the acceptance criteria.

PLAN OF WORK

The study was planned to carry out as follows,

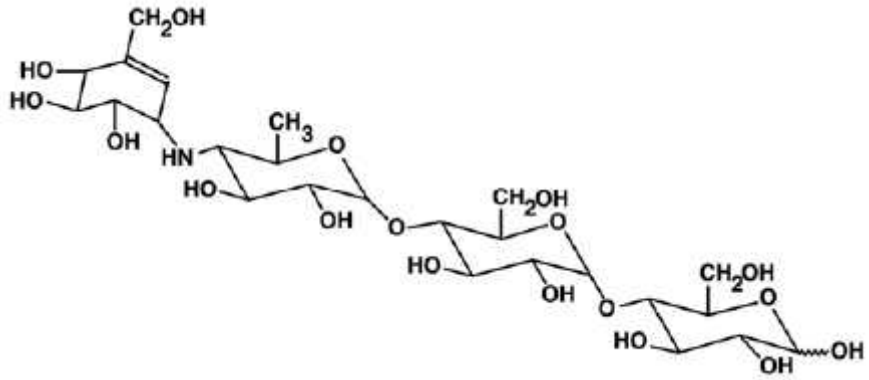
1. Literature survey.
2. Checking out for drug and excipient compatibility by FT-IR studies.
3. Preparation of blend of drug and excipients.
4. Pre compression studies which include,
    - **a)** Angle of Repose
    - **b)** Bulk Density
    - **c)** Tapped Density
    - **d)** Compressibility Index
    - **e)** Hausner's Ratio.
5. Preparation of Acarbose tablets by using the optimized formula.
6. Evaluation of the Acarbose core tablets.
    - i. Weight variation test
    - ii. Hardness test
    - iii. Thickness test
    - iv. Friability test
    - v. Disintegration time
7. Validation of the tablets and process.
8. Film coating of best Acarbose core tablets and packing.

DRUG PROFILE:

ACARBOSE[36]

Other Names:- Precose, Prandase.

STRUCTURE OF ACARBOSE



MOLECULAR FORMULA: $C_{25}H_{43}NO_{18}$.

MOLECULAR WEIGHT: 645.605

CHEMICAL NAME: 2*R*,3*R*,4*R*,5*S*,6*R*)-5-{[(2*R*,3*R*,4*R*,5*S*,6*R*)-5- {[(2*R*,3*R*,4*S*,5*S*,6*R*)-3,4-dihydroxy-6-methyl- 5-{[(1*S*,4*R*,5*S*,6*S*)-4,5,6-trihydroxy-3- (hydroxymethyl)cyclohex-2-en-1-yl]amino} tetrahydro-2*H*-pyran-2-yl]oxy}-3,4-dihydroxy- 6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl]oxy}- 6-(hydroxymethyl)tetrahydro-2*H*-pyran-2,3,4-triol.

APPEARANCE: White to yellowish, amorphous powder hygroscopic.

SOLUBILITY: Very soluble in water, Soluble in Methanol, Practically insoluble in Methylene chloride

CATEGORY OF DRUG:

- Hypoglycemic agent.
- Enzyme inhibitor.

MECHANISM OF ACTION:

Acarbose inhibits enzymes (glycoside hydrolases) needed to digest carbohydrates, specifically, alpha-glucosidase enzymes in the brush border of the small intestines and pancreatic alpha-amylase. Pancreatic alpha-amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine, whereas the membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine. Inhibition of these enzyme systems reduces the rate of digestion of complex carbohydrates. Less glucose is absorbed because the carbohydrates are not broken down into glucose molecules. In diabetic patients, the short-term effect of these drugs therapies is to decrease current blood glucose levels; the long-term effect is a reduction in Hb_{A1c} level. This reduction averages an absolute decrease of 0.7%, which is a decrease of about 10% in typical Hb_{A1c} values in diabetes studies.

PHARMACOKINETICS:

Absorption

Less than 2% of an oral dose of acarbose was absorbed as active drug, while approximately 35% of total radioactivity from a 14C-labeled oral dose was absorbed. An average of 51% of an oral dose was excreted in the feces as unabsorbed drug-related radioactivity within 96 hours of ingestion. Because acarbose acts locally within the gastrointestinal tract, this low systemic bioavailability of parent compound is therapeutically desired. Following oral dosing of healthy volunteers with 14C-labeled acarbose, peak plasma concentrations of radioactivity were attained 14 to 24 hours after dosing, while peak plasma concentrations of active drug were attained at approximately one hour. The delayed absorption of acarbose-related radioactivity reflects the absorption of metabolites that may be formed by either intestinal bacteria or intestinal enzymatic hydrolysis.

Metabolism

Acarbose is metabolized exclusively within the gastrointestinal tract, principally by intestinal bacteria, but also by digestive enzymes. A fraction of these metabolites (approximately 34% of the dose) was absorbed and subsequently excreted in the urine. The major metabolites have been identified as 4-methylpyrogallol derivatives .One metabolite (formed by cleavage of a glucose molecule from acarbose) also has alpha-glucosidase inhibitory activity. This metabolite, together with the parent compound, recovered from the urine, accounts for less than 2% of the total administered dose. Bioavailability is very low.

Excretion

The fraction of acarbose that is absorbed as intact drug is almost completely excreted by the kidneys. When acarbose was given *intravenously*, 89% of the dose was recovered in the urine as active drug within 48 hours. In contrast, less than 2% of an *oral dose* was recovered in the urine as active (i.e., parent compound and active metabolite) drug.This is consistent with the low bioavailability of the parent drug. The plasma elimination half-life of acarbose activity is approximately 2 hours in healthy volunteers. Consequently, drug accumulation does not occur with 3 times a day oral dosing.

CLINICAL PHARMACOLOGY

Acarbose is a complex oligosaccharide that delays the digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentration following meals. As a consequence of plasma glucose reduction, acarbose reduces levels of glycosylated hemoglobin in patients with type 2 diabetes mellitus. Systemic non-enzymatic protein glycosylation, as reflected by levels of glycosylated hemoglobin, is a function of average blood glucose concentration over time.

ADVERSE EFFECTS:

- Since Acarbose prevents the degradation of complex carbohydrates into glucose, some carbohydrate will remain in the intestine and be delivered to the colon.
- In the colon, bacteria digest the complex carbohydrates, causing gastrointestinal side-effects such as flatulence (78% of patients) and diarrhea (14% of patients).
- Since these effects are dose-related, in general it is advised to start with a low dose and gradually increase the dose to the desired amount.
- One study found that G.I. side effects decreased significantly (from 50% to 15%) over 24 weeks, even on constant dosing.
- Hepatitis has been reported with acarbose use. It usually goes away when the medicine is stopped.

EXCIPIENTS PROFILE[37-45]

MICROCRYSTALLINE CELLULOSE

Synonym	**:**	Cellulose gel, Crystalline Cellulose, Emocel, Fibrocel.
Chemical Name	**:**	Cellulose
Empirical formula	**:**	$(C_6H_{10}O_5)_n$ where n = 220
Molecular weight	**:**	36000
Description	**:**	MCC is purified, partially depolymerized cellulose that occur is as a white, odorless, crystalline powder composes of porous particle. It commercially available in different particle size and moisture grades that have different properties and application.
Functional category	**:**	Adsorbent, suspending agent, diluents, disintegrants.
Applications	**:**	Microcrystalline cellulose is widely used as a wet-binder/diluent in oral tablet and capsule formulations where it is used in both granulation and direct compression processes. In addition it is used as a microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

COLLOIDAL SILLICON DIOXIDE

Synonym	**:**	Aerosil 200; Amorphous Fumed Silica; Aerosil90
Chemical Formula	**:**	SIO_2
Molecular Weight	**:**	Not available.
Physical state and appearance	**:**	Solid. (Powdered solid.)
Odour	**:**	Odorless.
Taste	**:**	Tasteless.
Color	**:**	White.
Functional Category	**:**	Adsorbent. anticaking agent,emulsion thermal Stabilizer glidant, suspending agent, tablet disintegrant, stabilizer,viscosity-increasing agent.
Applications	**:**	It gives desirable flow characters and improves the flow properties of dry powders used in a number of processes such as tableting and capsule filling. It is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations.

MAGNESIUM STEARATE

Synonyms : Magnesium octadecananoate,Octadecanoic acid, Magnesiusalt, Stearic acid,magnesium salt.

Chemical name : Octadecanoic acid magnesium salt

Description : Magnesium stearate is a fine, white, precipitated or milled, Impalpable powder of low bulk density, having a faint odor or and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin

Empirical formula : $C_{36}H_7OMg0_4$

Molecular weight : 591.34

Functional Category : Tablet and capsule lubricant.

Application : Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacturing. It is also used in barrier creams

HYDROXY PROPYL METHYL CELLOLOSE

Synonyms	**:**	Benecel, HPMC, Methocel. ,Hypromellose
Chemical Name	**:**	Cellulose Hydroxy propyly methyl ether
Empirical formula	**:**	$CH_3\,CH_2\,(OH)\,CH_3$
Description	**:**	white or creamy white fibrous or granular, odorless, tasteless.
Melting point	**:**	Browns at 190-200 ^oC Chars at 225-230 ^oC
Applications	**:**	To retard the release of drugs from a matrix in tablets and capsules. Also used as binder and in tablet coating.
Functional Category	**:**	Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.
Applications	**:**	Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film coating, and as a matrix for use in extended release tablet formulations. High-viscosity grades may be used to retard the release of drugs from a matrix in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent.

TALC

Synonym : Kerolite, Magnesium Talc, Soapstone

Empirical formula : $Mg_3Si_4O_{10}(OH)_2$

Molecular weight : 379.27 Gm.

Category : Sillicate mineral.

Description : Talc is a very fine, white to grayish-white, odorless,

impalpable, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness

Applications : Talc was once widely used in oral solid dosage formulations as

a lubricant and diluents . It is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations in a novel powder coating for extended-release pellets and as an adsorbant In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves.

CORN STARCH

Synonyms : Amido,midon, amilo,amylum

Chemical Name : Starch

Empirical Formula : $C_6H_{10}O_5$

Functional Category : Diluent, disintegrant, binder,

Description : Starch occurs as an odorless and tasteless, fine, white to off

White powder. It consists of very small spherical or ovoid granules or grains whose size and shape are characteristic for each botanical variety.

Applications : Starch is a versatile excipient used primarily in oral solid-

dosage formulations where it is utilized as a binder, diluent,and

disintegrant. As a diluent, starch is used for the preparation of standardized triturates of colorants, potent drugs, and herbal extracts, facilitating subsequent mixing or blending processes in manufacturing operations. Starch is also used in dry-filled capsule formulations for volume adjustment of the fill matrix,and to improve powder flow, especially when using dried starches. Starch acts as an antiadherent and lubricant in tableting and capsule filling. In tablet formulations, freshly prepared starch paste used as a binder for wet granulation. Starch is one of the most commonly used tablet disintegrants.

TITANIUM DIOXIDE

Synonyms : Anatase titanium dioxide,brookite titanium dioxide, titanic Anhydride, titanii dioxidum, Tronox.

Chemical Name : Dioxotitanium

Empirical Formula : TiO_2

Molecular Weight : 79.88

Functional Category : Coating agent; opacifier; pigment.

Description : White, amorphous, odorless, and tasteless nonhygroscopic powder.Titanium dioxide may occur in several different crystalline forms

Applications : Titanium dioxide is widely used in topical and oral pharmaceutical formulations as a white pigment. Owing to its high refractive index, titanium dioxide has light scattering properties that may be exploited in its use as a white pigment and opacifier. In pharmaceutical formulations, titanium dioxide is used as a white pigment in film-coating suspensions, sugar-coated tablets, and gelatin capsules Titanium dioxide is also used in dermatological preparations and cosmetics, such as sunscreens.

PROPYLENE GLYCOL

Synonyms : 1,2-Dihydroxypropane,2-hydroxypropanol; methyl ethylene glycol; methyl glycol; propane-1,2-diol; propylenglycolum.

Chemical Name : 1,2-Propanediol

Empirical Formula : $C_3H_8O_2$

Molecular Weight : 76.09

Description : Propylene glycol is a clear, colorless, viscous, practically odourless liquid, with a sweet, slightly acrid.

Functional Category : Antimicrobial preservative; disinfectant; humectant; plasticizer; solvent; stabilizing agent; water-miscible cosolvent.

Applications : Propylene glycol has become widely used as a solvent, extractant, and preservative in a variety of parenteral and nonparenteral pharmaceutical formulations. Propylene glycol is commonly used as a plasticizer in aqueous film-coating formulations.

POLYETYLENE GLYCOL 6000

Synonyms : Carbowax,macrogola, PEG,

Chemical Name : a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl)

Empirical Formula : $HOCH_2(CH_2OCH_2)mCH_2OH$ where m represents the average number of oxyethylene groups.

Description : polyethylene glycol is being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures. Liquid grades (PEG 200–600) occur as clear, colourless or slightly yellow-coloured, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures. Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free flowing milled powders.

Applications : Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations. Polyethylene glycols are useful as ointment bases. Mixtures of polyethylene glycols can be used as suppository Bases.

Functional Category : Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

MATERIALS AND METHODS

LIST OF EQUIPMENTS

Table no :2 List of equipments

S.no	EQUIPMENT NAME	MODEL AND MAKE
1	Sifter	GANSONS, MUMBAI.
2	Rapid Mixer Granulator	GANSONS,MAHARASTRA.
3	Multimill	SAMS TECHNO, MUMBAI.
4	Tray Drier	SAMS TECHNO, MUMBAI.
5	Cage Blender	R.P.PRODUCTS, MUMBAI.
6	Tablet Compression Machine	CADMACH, AHAMADABAD.
7	Conventional Coating Machine	SAMS TECHNO, MUMBAI.
8	Strip Packing Machine	SATELLITE ENGINEERING, MAHARASTRA.
9	Weighing Balance	ESSAE TERA OKA, MUMBAI.
10	High performance liquid chromatography	WATERS.
11	IR Spectrophotometer	JASCO.

LIST OF RAW MATERIALS

Table No:3 List of Materials used:

S.NO	NAME OF RAW MATERIAL	SOURCE
1	ACARBOSE	BIOCON LABORATARY PVT LTD, INDIA.
2	CORN STARCH	B-PURA LABORATY,CHENNAI.
3	MICRO CRYSTALLINE CELLULOSE (COMPRECEL M 101)	DFE PHARMA,CUDDALORE.
4	ISOPROPYL ALCHOHOL #	RANBAXY FINE CHEMICALS,CHENNAI.
5	COLLOIDAL SILLICON DIOXIDE (AEROSIL 200)	CADSMAHAR,SALEM.
6	MAGNESIUM STEARATE	COVITIEN NALLIM CHRODIT GLOSA,INDIA.
7	CORN STARCH	BPURA LABORATY,CHENNAI.
8	CORN STARCH	BPURA LABORATY,CHENNAI.
9	HYDROXYPROPYL METHYLCELLULOSE E15	TAIAN RUITAL CELLULOSE,CO LTD,CHINA.
10	TALC	TAIAN RUITAL CELLULOSE,CO LTD,CHINA
11	TITANIUM DIOXIDE	ROHA DYE CHEMICAL,PVT LTD,DHABAR.
12	PROPYLENE GLYCOL	B-PURA LABORATRY, CHENNAI.
13	POLYETYLENE GLYCOL 6000	B-PURA LABORATRY, CHENNAI.

PREFORMULATION STUDIES

Drug-Excipient Compatibility Studies[46]

Fourier Transform Infrared Spectroscopy (FTIR):[47]

The Compatibility studies provide the scheme for the drug combination with excipients in the fabrication of dosage form. The study was carried out to establish that the therapeutically active drug has not undergone any changes after it has been subjected to processing steps during formulation of tablets. Compatibility studies are carried out by mixing a different proportion of Acarbose and Corn Starch, Micro Crystalline Cellulose, Colloidal Silica gel, Magnesium Stearate.

The FTIR analysis was conducted for the structure characterization. FTIR spectra of the pure drug, pure polymers and mixture of both were recorded. Formulations were taken in a Kbr pellet using **JASCO FTIR** instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade Kbr; samples were scanned in the IR range from 650 to 3800 cm^{-1}, with a resolution of $4cm^{-1}$.

Preparation of standard curve for Acarbose:

Accurately weigh and transfer 50mg of Acarbose working standard into 100ml clean, dry volumetric flask and add about 50ml of water and dissolve. Dilute to volume with water and mix.

Formulation of Acarbose tablets.

Table No: 4 Formula for Acarbose immediate release tablets.

INGREDIENTS	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Acarbose	50	50	50	50	50	50	50	50
Corn Starch	60	20	20	40	-	20	20	20
PVP K 30	-	-	-	-	40	20	-	-
Micro Crystalline Cellulose PH 101/Comprecel M 101	20	40	60	40	40	40	60	60
Colloidal Silicon Dioxide (Aerosil 200)	25	35	25	25	25	25	25	25
Magnesium Stearate	10	20	10	10	10	10	10	10
Purified Water #	-	-	-	-	-	-	qs	-
IsoPropyl Alcohol #	-	-	-	-	-	--	-	qs
Total	165	165	165	165	165	165	165	165

#does not appear in the final product.

FOR F1 & F2: DIRECT COMPRESSION

Formulation of Acarbose immediate release tablets was done by direct compression method.

➔ **Sifting:** Acarbose, Corn Starch and Micro Crystalline Cellulose are sifted through SS sieve #60 fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

Sift Aerosil 200, Corn Starch and magnesium stearate through SS sieve #40 in vibratory sifter and collect in double polythene lined HDPE/SS container.

Sift Micro Crystalline Cellulose, Corn Starch, Aerosil 200 through SS sieve #60 fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

Sift Magnesium Stearate through SS sieve #80 fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

➔ **Blending/Lubrication:** All the materials are blended for uniformity and then, lubricated with collided silicon dioxide and magnesium stearate.

➔ **Compression:** The lubricated blend is compressed into tablets.

The quantity of glidant and lubricant were increased in the formulation to improve the flow properties during compression and the next trial was done by direct compression.

Formulation of Acarbose immediate release tablets was done by direct compression method.

➔ **Sifting:** Acarbose, Corn Starch and Micro Crystalline Cellulose are sifted through SS sieve #60 fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

Sift Aerosil 200, Corn Starch and magnesium stearate through SS sieve #40 in vibratory sifter and collect in double polythene lined HDPE/SS container.

Sift Micro Crystalline Cellulose, Corn Starch, Aerosil 200 through SS sieve #60 fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

Sift Magnesium Stearate through SS sieve #80 fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

➔ **Blending/Lubrication:** All the materials are blended for uniformity and then, lubricated with collided silicon dioxide and magnesium stearate.

➔ **Compression:** The lubricated blend is compressed into tablets.

GRANULATION:

Comparatively, dry granulation is less expensive and cost effective and much preferred than wet granulation. So, dry granulation is chosen.

DRY GRANULATION:

- **Sifting:** Acarbose, Corn Starch and Micro Crystalline Cellulose are sifted through SS sieve #60 fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

  Sift Aerosil 200, Corn Starch and magnesium stearate through SS sieve #40 in vibratory sifter and collect in double polythene lined HDPE/SS container.

  Sift Micro Crystalline Cellulose, Corn Starch, Aerosil 200 through SS sieve #60 fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

  Sift Magnesium Stearate through SS sieve #80 fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

- **Granulation:** Load the sifted materials into RAPID MIXTURE GRANULATOR(RMG) with main impeller at slow speed and chopper kept off and dry mix for 20 minutes. Granulate the materials and the granule mass is formed.
  Unload the granules in double polythene lined tared HDPE drums.

- **Sifting and Milling:** Pass the granules through vibratory sifter fitted with #20

- **Blending/Lubrication:** All the materials are blended for uniformity and then, lubricated with collided silicon dioxide and magnesium stearate.

- **Compression:** The lubricated blend is compressed into tablets.

FOR F3-F6: DRY GRANULATION:

- **Sifting:** Acarbose, Corn Starch and Micro Crystalline Cellulose are sifted through SS sieve #60 fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

  Sift Aerosil 200, Corn Starch and magnesium stearate through SS sieve #40 in vibratory sifter and collect in double polythene lined HDPE/SS container.

  Sift Micro Crystalline Cellulose, Corn Starch, Aerosil 200 through SS sieve #60 fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

  Sift Magnesium Stearate through SS sieve #80 fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

- **Granulation:** Load the sifted materials into RAPID MIXTURE GRANULATOR(RMG) with main impeller at slow speed and chopper kept off and dry mix for 20 minutes. Granulate the materials and the granule mass is formed.
  Unload the granules in double polythene lined tared HDPE drums.

- **Sifting and Milling:** Pass the granules through vibratory sifter fitted with #20

- **Blending/Lubrication:** All the materials are blended for uniformity and then, lubricated with collided silicon dioxide and magnesium stearate.

Compression: The lubricated blend is compressed into tablets.

There was a reduction in the tablet compressibility and low granulation efficiency in dry granulation method. Hence, wet granulation method was tried which has better granulation efficiency and compressibility than dry granulation.

FOR F7 & F8: WET GRANULATION:

- **Sifting:** Acarbose, Corn Starch, and micro crystalline cellulose are weighed accurately and mixed thoroughly and sifted through #40 mesh fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

- **Sifting:** Aerosil 200 and Corn Starch and magnesium stearate are weighed accurately sifted through #40 mesh fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.

- **Sifting:** Micro Crystalline Cellulose, Corn Starch are sifted through #40 mesh with vibrator sifter and collected in double polythene lined HDPE/SS container

- **Sifting:** Magnesium stearate is sifted through #80 mesh fitted with vibratory sifter and collected in double polythene lined HDPE/SS container.
- **Granulation:** Load the sifted material in to RAPID MIXTURE GRANULATOR (RMG) with impeller at slow speed and chopper kept off and dry mix for 20 minutes. Add purified water to the contents with impeller at slow speed. Granulate the material and granular mass is formed. Unload the granules in double polythene lined tared HDPE drum
- **Drying:** Load the granular mass to the TRAY DRIER. Air dry the granular mass in TRAY DRIER for 30 minutes, switch on the heat button and set the temperature to 60ºC and continue at 60ºC, until LOSS ON DRYING(LOD) attains between 2 – 2.5% w/w.

- **Sifting and Milling:** Pass the dried granules through vibratory sifter fitted with mesh #20 and collect the sifted granules in double polythene lined HDPE/SS containers. Pass the oversized granules through multimill with 2.0mm screen with knives forward configuration at medium speed and collect the milled granules in double polythene lined HDPE/SS Containers.

➔ **Blending and Lubrication:** Load the dried granules into DOUBLE CONE BLENDER and blend for 15 min. And lubricated for 5 minutes. Unload the blended mass in double polythene tared HDPE drum.

➔ **Compression:** Then the blend is compressed into tablets using CADMACH compression machine.

PRE-COMPRESSION PARAMETERS:[48,49]

Angle of repose :

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and the horizontal plane. The granule mass should allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of granules on the paper. The results are show in Table no.8

$$\text{Tan } \theta = h/r$$

$$\theta = \tan^{-1} (h/r)$$

Where, h= height of the pile r= radius of the pile

Bulk density:

A given quantity of the powder is transferred to the measuring cylinder and it is tapped mechanically either manually or mechanical device till a constant volume is obtained. This volume is bulk volume (v) and it includes the true volume of the powder and void space among the powder particles. It is the ratio between a given mass of powder and its bulk volume. The results are show in Table no.8.

It is the ratio between a given mass of powder and its bulk volume.

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Total weight of powder}}$$

Tapped density :

Tapped density is defined as the ratio between weight of the sample powder taken and the tapped volume. The results obtained for tapped density are tabulated in Table 8.

Tapped density (P_t) = M/V_t

Where M = weight of sample powder taken

V_t = tapped volume

Compressibility index /Carr's index :

Based on the apparent bulk density and the tapped density, the percentage compressibility index of the powder was determined by using the following formula. The results are shown in Table no.8.

$$\text{Compressibility index} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped density}} \times 100$$

Hausner ratio:

By calculating tapped density and bulk density, the Hausner's ratio can be calculated. The results are shown in table no.8.

$$\text{Hausner ratio} = P_t / P_o$$

Where, P_t = tapped density

P_o = bulk density

Table No:5 Flow Properties and Corresponding Angle of Repose, Compressibility Index and Hausner's Ratio:

Flow Properties	Angle of Repose (θ)	Compressibility Index (%)	Hausner's Ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19.1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very Poor	56-65	32-37	1.46-1.59
Very Very Poor	>66	>38	>1.6

POST COMPRESSION PARAMETERS:

Thickness[50]:

The thickness of the tablets was determined by using micrometer screw gauge and the results were expressed in millimeter. ± 5% may be allowed depending on the size of the tablet.

Weight variation test[51] :

Ten tablets were selected at random, individually weighed in a single pan electronic balance and the average weight was calculated. The uniformity of weight was determined according to LP specification. As per I.P not more than two of individual weight would deviate from average weight by not more than 5% and none deviate by more than twice that percentage.

Table No:6 Limits of weight variation

S.No.	Average weight of tablet	Percentage
1.	80 mg or less	± 10%
2.	More than 80mg and less than 250mg	± 7.5%
3.	250 mg or more	± 5%

Hardness test[52]:

Tablets crushing load, which is the force required to break a tablet by compression in radial direction was determined by using Monsanto hardness tester. Ten tablets from the batch were used for hardness studies and results are expressed in Kg/cm $^{2.}$

Friability test[53]:

It was performed in Roche Friabilator apparatus where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of six inches with each revolution. Pre weighed samples of 20 tablets were placed in the Friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that loose less than 0.5 to 1% of their weight are generally considered acceptable.

$$\%\text{Friability} = \frac{\text{Weight loss}}{\text{Weight of tablets before operation}} \times 100$$

Disintegration[54] :

Disintegration time is the time required for a tablet to break up into granules of specified size(or smaller size),under carefully specified conditions. The is carried out by using USP device which consists of basket-racket assembly, a 1000-ml low beaker,138 to 160 mm in height and having an inside diameter of 97-115 mm for the immersion of fluid between 35º and 39 º and a device for raising and lowering the basket for immersion fluid at a constant frequency rate between 29-32 cycles per minute through a distance not less than 53mm and not more than 57 mm. The volume of the fluid in the vessel is such that the highest point of the upward stroke the mesh remains at least 15 mm below the surface of the fluid and descends to not less than 25mm from the bottom of the vessel on the downward stroke. The tablet is placed in each of the six tubes of the basket and a disk is added. Operate the apparatus using the water as immersion fluid maintained at 37±2 º.

***In vitro* dissolution studies[55]:**

Procedure :

Tablet dissolution was assessed using standard USP dissolution apparatus type II. The dissolution media used was 900ml of distilled water. The temperature was maintained at 37 ± 0.5°C. At predetermined time intervals, an aliquot of 5 ml sample was withdrawn, and made up to 10 ml with distilled water. Then these sample were measured in HPLC at 210 nm. A High Performance Liquid Chromatography system equipped with dual ƛ absorbent detector and data handling system is used.

Dissolution Parameters :

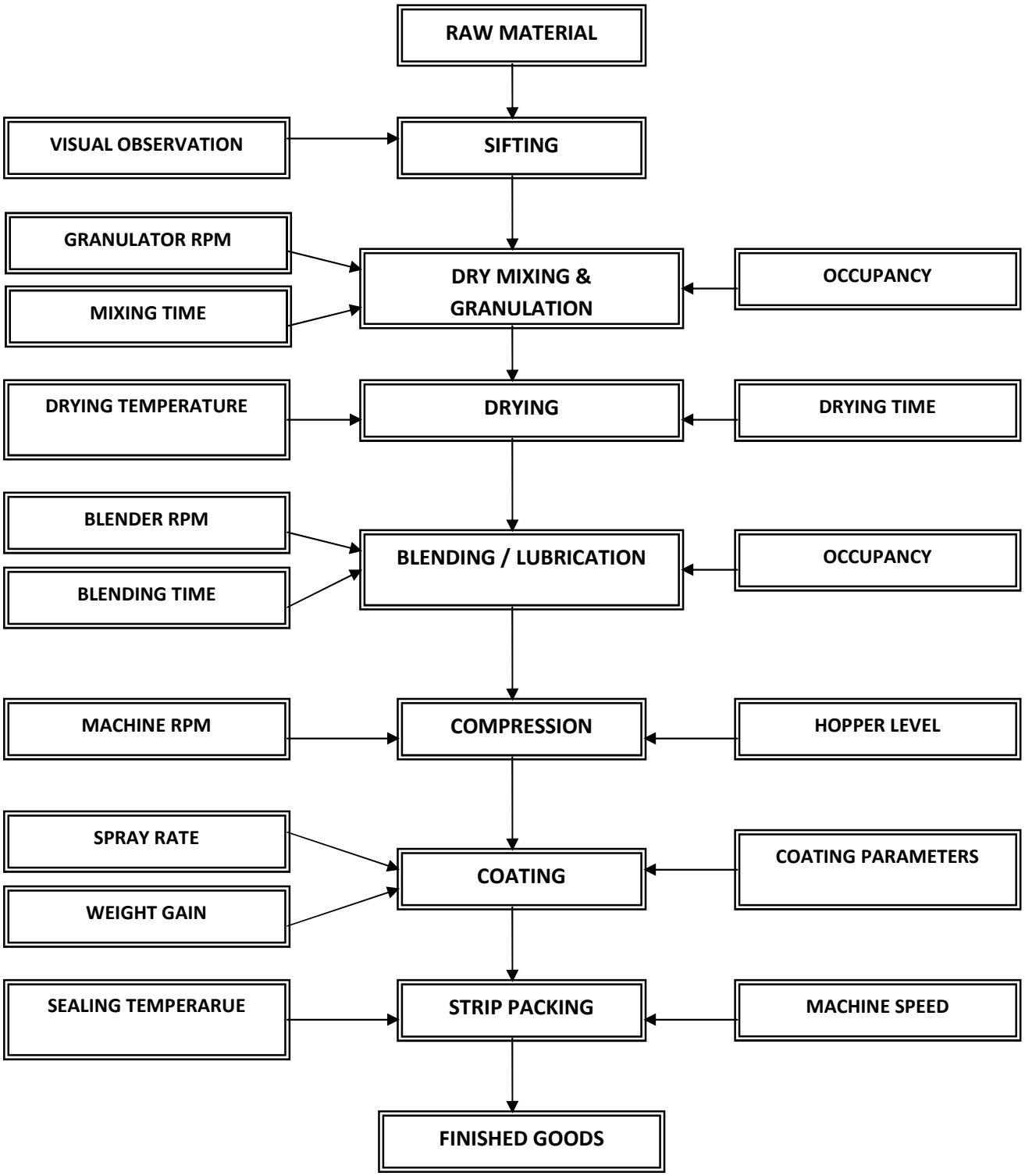
Apparatus	:	USP II, Basket
Medium	:	distilled water
Medium volume	:	900ml.
Medium Temp.	:	37±0.5^{o}C
Paddle speed	:	50 rpm
Sampling Time	:	60 min.
Sampling Volume	:	5ml.
Absorbance at	:	210nm.

Chromatographic conditions:

Column	:	Phenomenex,5µ (250mm x 4.mm)
Pump Mode	:	Isocratic
Flow Rate	:	1.5 ml/min
Detection	:	UV, 210 nm
Injection Volume	:	20 µL
Run Time	:	20 min.

PROCESS FLOW DIAGRAM OF ACARBOSE-50 mg ALONG WITH CONTROL VARIABLES:

Figure 2 Process flow diagram.



PROCESS STEPS, CONTROL VARIABLES AND MEASURING RESPONSES:

Table No:7 process steps, control variable and measuring responses

PROCESS	CONTROL VARIABLES	MEASURING RESPONSES
SIFTING	• VISUAL INSPECTION	• SIEVE INTEGRITY
DRY MIXING & GRANULATION	• OCCUPANCY • GRANULATOR RPM • MIXING TIME	• CONTENT UNIFORMITY
DRYING	• DRYING TEMPERATURE • DRYING TIME	• DRYING TIME • LOD
BLENDING / LUBRICATION	• OCCUPANCY • BLENDER TIME • BLENDER RPM	• CONTENT UNIFORMITY • BULK DENSITY • PARTICLE SIZE DISTRIBUTION
COMPRESSION	• MACHINE RPM • HOPPER LEVEL	• DESCRIPTION • UNIFORMITY OF WEIGHT • DISINTEGRATION TIME • HARDNESS • THICKNESS • DIAMETER • FRIABILITY • % ASSAY
COATING	• SPRAY RATE • COATING PAN RPM • BED TEMPERATURE	• DESCRIPTION • DISSOLUTION TEST • WEIGHT GAIN
STRIP PACKING	• SEALING TEMPERATURE • MACHINE SPEED	• DESCRIPTION • LEAK TEST

PROCESS VALIDATION OF ACARBOSE – 50 mg TABLETS:

DISPENSING OF RAW MATERIALS: The raw material that is received from the vendor is get approved by the quality assurance person, to check whether the product is meets its specifications in terms of its quality. These raw materials should be tested physically, chemically and biologically.

SIFTING:

EQUIPMENT USED: Vibratory Sifter- 2.

SIEVE SIZE: # 40, # 80.

WORKING PROCEDURE:

- Acarbose, Starch, Microcrystalline Cellulose PH 101 (Comprecel M101) are weighed and is sifted in #40 fitted in vibratory sifter and collected in the pre-labelled double polythene SS /HDPE containers and is labelled.
- Colloidal sillicon dioxide (Aerosil 200) and Corn starch are weighed and is sifted in #40 fitted in vibratory sifter and collected in pre-labelled double polythene SS/HDPE containers and is labelled.
- Corn starch (LOD compensation) is weighed and is sifted in #40 fitted in vibratory sifter and is collected in pre-labelled double polythene SS/HDPE containers and is labelled.
- Magnesium Stearate is weighed and is sifted in # 80 fitted to vibratory sifter and collected in the pre-labelled double polythene SS/HDPE containers and is labelled.
- Visual inspection is done after sifting of each ingredient**.**

DRY MIXING AND GRANULATION:

EQUIPMENT USED: Rapid Mixer Granulator.

SIZE/CAPACITY: 150 Lts.

MIXING TIME: 30minutes.

WORKING PROCEDURE:

- Ingredients after sifting is loaded into the Rapid Mixer Granulator and is dry mixed for 30 minutes.
- Sampling is done at 6 different places and is sent for Assaying at 10, 20 and 30 minutes from dry mixing of ingredients.
- Isopropyl alchohol is added during mixing of the ingredients till desired granular mass is obtained.

DRYING:

EQUIPMENT USED: Tray Drier.

DRYING TEMPERATURE: 60ºC

WORKING PROCEDURE:

- The granular mass is loaded in the tray drier.
- Dry the granules till LOD attains between 2-3.5% w/w.
- Sampling is done at 3 different time intervals each of 3 gms.

SIFTING:

EQUIPMENT USED: Vibratory sifter -2

SIEVE SIZE: #20

MILLING:

EQUIPMENT USED: Multimil

SCREEN SIZE: 1.5mm

WORKING PROCEDURE:

- The dried granular mass is passed through the vibratory sifter with sieve size #20 and collect the sifted granules in the pre-labelled double polythene SS/HDPE container .
- The oversized granules are passed through the multimill with screen size 1.5 mm with the knives forward configuration at medium speed and the milled granules are collected in the pre-labelled double polythene SS/ HDPE container and note down the weight.

BLENDING AND LUBRICATION:

EQUIPMENT USED: Cage blender.

LOAD SIZE: 33 KGS

BLENDER RPM: 25RPM.

BLENDING TIME: 15 minutes.

WORKING PROCEDURE:

- Load the dried granules into the cage blender and blend it for 15 minutes**.**
- Lubricate the above for 5 minutes.
- Sampling is done at 6 different places after the completion of the lubrication and the samples are analyzed for content uniformity, bulk density, particle size distribution.

TABLET COMPRESSION:

EQUIPMENT USED: 20 station compression machine.

TURRENT RPM: 25-33 RPM.

PUNCH SPECIFICATIONS:

SIZE: 7.9 mm

SHAPE: circular, shallow, concave**.**

DIES SPECIFICATION: Suitable for above.

WORKING PROCEDURE:

- Run the tablet compression machine at minimum speed (25 RPM) and sampling is done when the powder level in the hopper is maximum and minimum and is sent for the QC analysis.

[QUALITY TESTS: Description, Uniformity of Weight, Thickness, Diameter, Hardness, Friability, Disintegration Time.**]**

- Run the tablet compression machine at maximum speed (33RPM) and samplings is done, when the powder level in the hopper is maximum and minimum and samples are analyzed.

[QUALITY TESTS: Description, Thickness, Diameter, Hardness, Friability, Disintegration Time.**]**

- Sampling is done at various settings and speeds from the hopper at the compression stage.

SETTINGS/SPEEDS:

- **Minimum speed, maximum hopper level.**
- **Minimum speed, minimum hopper level.**
- **Maximum speed, maximum hopper level.**
- **Minimum speed, minimum hopper level.**

SAMPLING QUANTITY: 50 Tablets at each speed and each powder level.

COATING:

EQUIPMENT USED: Manual coating machine.

COATING PARAMETERS:

Atomising air pressure: 2.5-3.0 kg/cm².

Temperature of inlet air: 60-65 ºC

Distance between spray guns and tablet bed: 10 Inches.

Bed temperature: 40-45 ºC.

Coating pan RPM: 8.

WORKING PROCEDURE:

- Load the compressed tablets in the coating machine and start coating .
- Check the pan RPM while coating starts.
- Check the weight gain for every 15 minutes.
- Sampling is done after coating and the samples are analyzed (approximately 250 tablets)

[QUALITY TESTS: Description, Weight gain, Thickness, Diameter, Dissolution and Assay.**]**

PRIMARY PACKING:

EQUIPMENT USED: Strip Packing Machine**.**

SEALING HEATER TEMPERATURE: 120ºC-140º C.

WORKING PROCEDURE:

- Set the temperature of strip packing machine at 120º C and run the machine at high speed (60 cuts / minute) and pack the tablets and leak test is performed for the samples.
- Set the temperature of the strip packing machine and run the machine at low speed (40 cuts/ minute) and pack the tablets and leak test is performed for the samples.

SAMPLED QUANTITY: 6 strips at each temperature.

SECONDARY PACKING:

- The strips are packed in the carton which is labelled with the product name, batch number, manufacturer name, manufactured date, expiry date, and these are filled in cartons and put into the shipper and sealed and tapped.
- The shipper must have the identity label, tare weight, gross weight, net weight, batch number, manufacturing date and expiry date.

PROCESS VALIDATION DATA IN THE PRODUCTION OF ACARBOSE 50 mg TABLETS:

DRY MIXING/ GRANULATION:

EQUIPMENT NAME: Rapid mixer granulator

SPEED: Low speed: 80 Rpm.

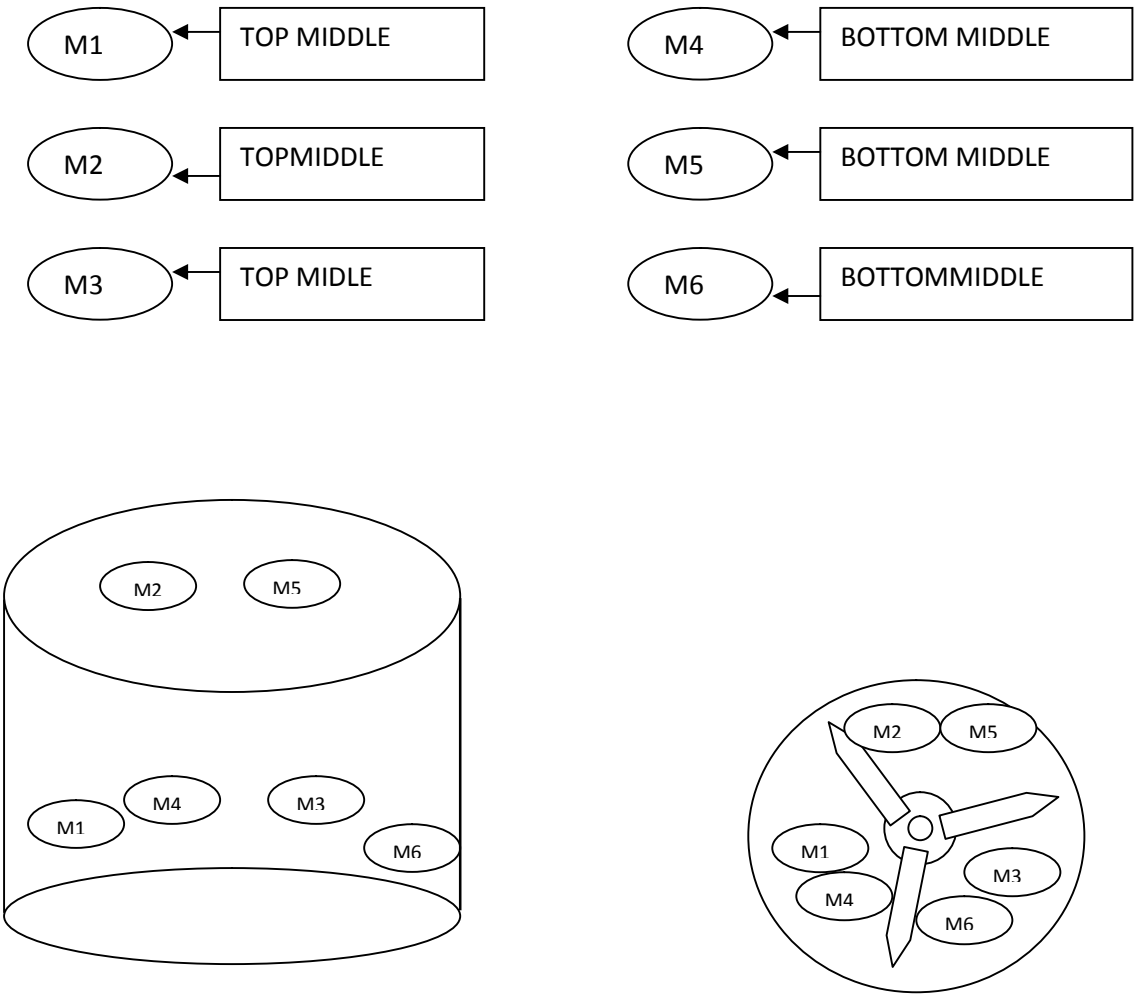
High speed: 155 Rpm.

TIME INTERVAL: 1 Hour.

BATCH SIZE: 2,00,000.

SAMPLING LOCATION DIAGRAM IN THE RMG

Figure no: 3 sampling location in R.M.G



DRYING:

EQUIPMENT NAME: TRAY DRIER.

TEMPERATURE: 60 ºC.

BATCH SIZE: 2,00,000.

BLENDING AND LUBRICATION:

EQUIPMENT NAME: Cage Blender.

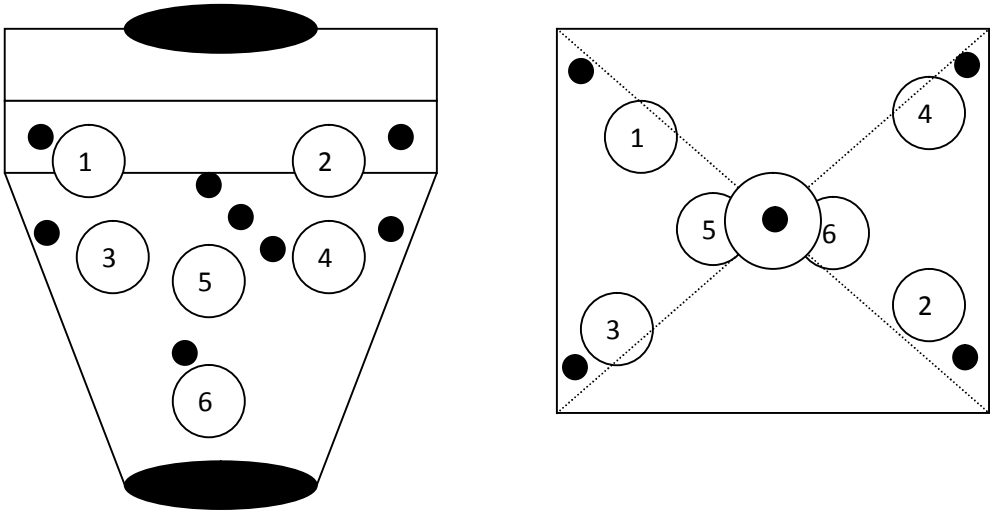
BLENDER RPM: 25 rpm

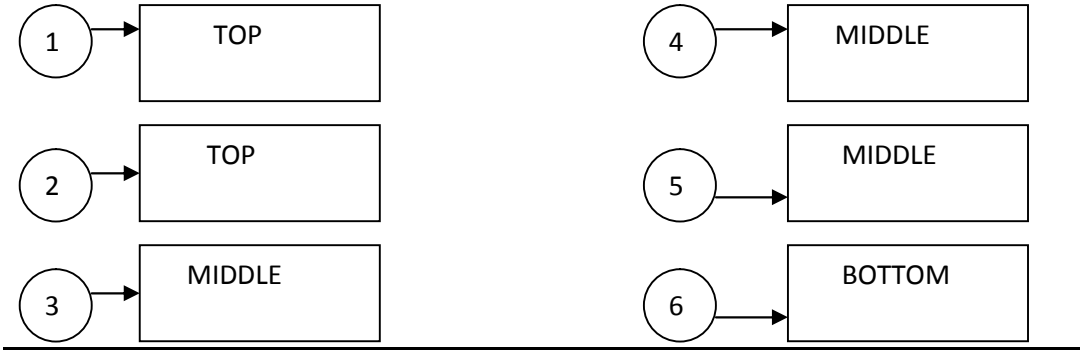
LOAD SIZE: 33 kg.

BATCH SIZE: 2,00,000.

SAMPLING LOCATION DIAGRAM

Figure no:4 Sampling location on Cage Blender





COMPRESSION:

EQUIPMENT NAME: 20 station compression machine.

RPM: 25 – 33.

BATCH SIZE: 2,00,000 Tablets

COATING:

EQUIPMENT NAME: Manual Coating Machine**.**

ATOMISING PRESSURE: 2.5-3.0 Kg/Cm²

TEMPERATURE OF INLET: 60-65 º C

DISTANCE BETWEEN SPRAY GUNS AND TABLET BED: 10 INCHES**.**

BED TEMPERATURE: 40-45 º C

COATING PAN RPM: 8 RPM**.**

SUMMARY:

DRY MIXING:

EQUIPMENT NAME: Rapid Mixer Granulator

BATCH SIZE: 2,00,000.

CAPACITY: 150 lts.

MIXING TIME: 30 minutes.

DRYING:

EQUIPMENT NAME : Tray Drier.

BATCH SIZE:2,00,000

DRYING TEMPERATURE: 60 ºC.

BLENDING / LUBRICATION:

EQUIPMENT NAME: Cage Blender**.**

BATCH SIZE: 2,00,000.

BLENDING RPM: 25 RPM

LOAD SIZE: 33 kgs.

BLENDING TIME: 20 minutes.

COMPRESSION:

EQUIPMENT NAME: Tablet Compression Machine (20 Stations).

BATCH SIZE: 2,00,000.

OPTIMUM SPEED: 25-33 Rpm

HARDNESS OF TABLET: 5.18 Kg/cm^2.

THICKNESS OF TABLET: 3.08mm**.**

TABLET DIAMETER: 7.95 mm

DISINTEGRATION TIME: 4 minutes 31 seconds.

COATING:

COATING SOLUTION: Opadry

EQUIPMENT USED: Manual Coating Machine**.**

BATCH SIZE: 2,00,000.

OPTIMUM SPEED: 8 Rpm.

ATOMISING AIR PRESSURE: 2.9kg/cm^2

INLET AIR TEMPERATURE: 62 ºC.

DISTANCE BETWEEN SPRAY GUNS AND TABLET BED: 10 inches.

BED TEMPERATURE: 42 ºC.

STRIP PACKING:

EQUIPMENT USED: Strip Packing Machine**.**

BATCH SIZE: 2,00,000**.**

SEALING TEMPERATURE: 136 ºC. **MACHINE SPEED:** 58 strips per minute.

POST-COATING PAARAMETERS

Weight gain:

20 uncoated core tablets were taken randomly and the average weight is noted. 20 film coated tablets are taken randomly and the average weight is noted. The film coating tablets show 3% coating weight gain which is acceptable as per the limit.

Evaluation of Packing:

Leak test[56]:

The required number of strips are taken and checked for the quality of strips for any damages. The collected strips are tied with a rubber band. All the strips must be dipped in water containing blue dye and the lid is closed. The opening of the dessicator is connected to a vacuum pump. A vacuum of 300 mm of Hg is applied and the knob of dessicator is closed. The vacuum is Kept for 30sec. The vacuum is released by opening the knob of the dessicator and the strips are removed. Water traces are removed by using the lint free duster. The strips are opened with scissors. The tablets are checked manually for traces of water inside the strips. Number of tablets, which have become wet, should not be more than 1%. If the leakage is more than the above percentage the leak test is repeated.

RESULTS AND DISCUSSION

PRE-FORMULATION STUDY:

FTIR drug-excipients compatibility

As a part of the pre-formulation studies drug-excipient compatibility was carried out to study the possible drug interactions between drug and excipients. The spectrum obtained for the drug excipients mixture was compared to that of the spectrum of drug alone. The spectrum for the drug alone and spectrum for the drug excipient are show in figure no:5 and figure no:6

PRE-COMPRESSION PARAMETERS:

Table No:8 Pre-compression parameters for formulation

Formula	Angle of Repose (θ)	Bulk Density	Tapped Density	Compressibility Index (%)	Hausner's Ratio
F1	47.01	0.53±0.005	0.62±0.02	32.65±1.06	1.36±0.02
F2	44.08	0.52±0.01	0.61±0.014	24.27±1.06	1.34±0.03
F3	35.36	0.526±0.005	0.61±0.014	14.78±0.18	1.16±0.01
F4	32.23	0.52±0	0.60	14.58±0	1.15±0
F5	29.42	0.526±0.01	0.605±0.01	27.51±0.02	1.163±0.02
F6	29.03	0.523±0.005	0.63±0.08	14.89±0	1.163±0.005
F7	26.71	0.54±0.03	0.64±0.05	15.10±0.51	1.17±0.10
F8	24.70	0.56±0.01	0.64±0.08	14.75±0.61	1.16±0.98

Mean±SD,(n=3)

DISSCUSSION:

The blend was analyzed for parameters such as Angle of Repose, Bulk Density, Tapped Density, Compressibility Index, Hausner's Ratio. **F1 and F2** showed poor flow ability.

POST COMPRESSION PARAMETERS:

Table No:9 post-compression parameters for formulation.

Formula	Weight Variation (Avg SD)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration Time
F1	188 ±0.30	3.07	2.88	1.12	2min 45 sec
F2	186 ±0.45	3.04	2.81	1.17	2min 40 sec
F3	166 ±0.23	3.02	2.56	1.16	2min 50 sec
F4	164 ±0.12	3.08	4.60	1.17	4min 43 sec
F5	168 ±.021	3.10	2.40	1.14	4min 46 sec
F6	167 ±0.18	3.15	4.56	1.10	4min 42 sec
F7	166 ±0.14	3.03	4.76	0.10	6min 36 sec
F8	165 ±0.28	3.01	5	0.09	4min 50 sec

Msd±n=3

Discussion

Post Compression Observations

- The formulation **F1** has shown weight variation problem up to ± 20 mg.
- There was no proper flow of powder into the die cavity.
- The formulation **F2** still show weight variation problem indicating poor flowability of the blend.
- There was a problem in the flow property during the compression

so, the ingredients must be granulated to improve flow properties to reduce the weight variation.

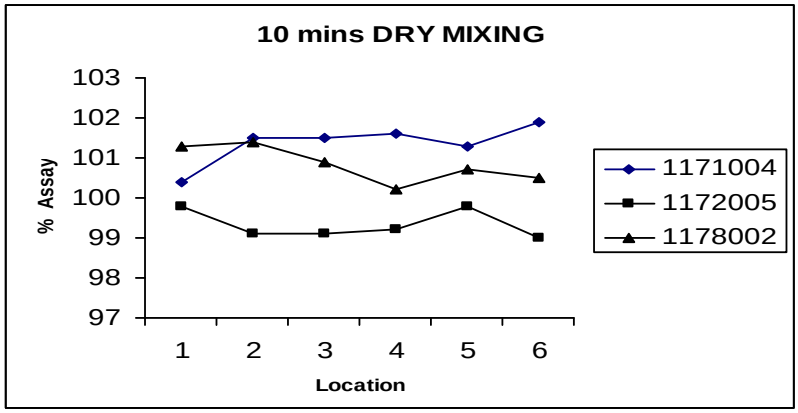
- The tablets **F3** obtained were too brittle.
- The tablets show very less hardness because of the too dry granules formed.
- The granulation in **F4** is done in the same manner as that of trial 3 and the granules are compressed.
- The tablets are shown friability greater than 1% which are not acceptable.

- The granules of **F5** were found to contain more number of coarse particles than fines and are too dry to form a compactable mass forming brittle granules with less compressibility.
- A mixture of binders has been used in the **F6** to improve the compressibility.
- The Granules formed have shown better compressibility and tablets have been evaluated for post compression parameters.
- The tablets formed have shown friability of more than 1% which is not acceptable as per the requirements.
- Disintegration time of the **F7** was slightly higher because the granules are well compacted and moisture in the granules holding them compactly.
- A non-polar solvent is used in the **F8** to reduce Disintegration Time because of the vaporization of the solvent forming much drier granules.
- The **F8** has good flow properties, the tablets have shown no weight variation and friability problems.
- The formulation 8 has show disintegration time within the range of 4 minutes.

ASSAY OF ACARBOSE DURING DRY MIXING

Table No:10 Assay of Acarbose during dry mixing

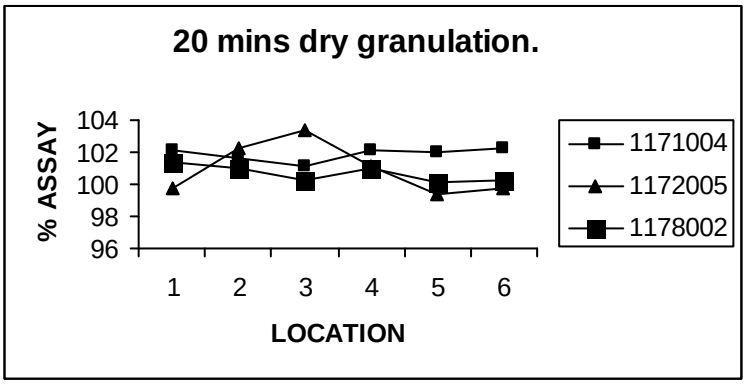
LOCATION	ASSAY OF ACARBOSE (%) (10 MINUTES DRY MIXING)			LIMIT
	BATCH A	BATCH B	BATCH C	
1	100.4	99.8	101.3	95.0-105.0% of input.
2	101.5	99.1	101.4	95.0-105.0% of input.
3	101.5	99.1	100.9	95.0-105.0% of input.
4	101.6	99.2	100.2	95.0-105.0% of input.
5	101.3	99.8	100.7	95.0-105.0% of input.
6	101.9	99.0	100.5	95.0-105.0% of input.
MINIMUM	100.4	99.0	100.2	---------
MAXIMUM	102.6	99.8	101.4	----------
AVERAGE	101.5	99.3	100.8	----------
%RSD	0.7%	0.4%	0.4%	NMT5%



ASSAY OF ACARBOSE DURING DRY MIXING

Table No:11 Assay of Acarbose during Dry mixing

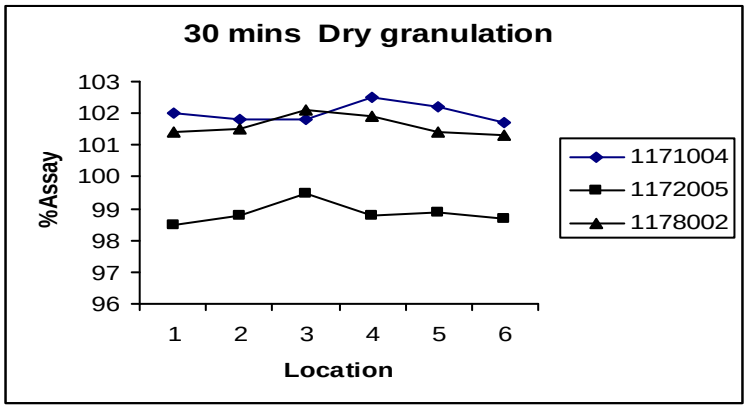
LOCATION	ASSAY OF ACARBOSE (%) (20 MINUTES DRY MIXING)			LIMIT
	BATCH A	BATCH B	BATCH C	
1	102.1	99.7	101.4	95.0-105.0% of input.
2	101.6	102.2	101.0	95.0-105.0% of input.
3	101.1	103.4	100.2	95.0-105.0% of input.
4	102.1	101.1	101.0	95.0-105.0% of input.
5	102.0	99.4	100.1	95.0-105.0% of input.
6	102.2	99.8	100.3	95.0-105.0% of input.
MINIMUM	101.1	99.4	100.2	---------
MAXIMUM	102.2	103.4	101.4	----------
AVERAGE	101.9	100.8	100.6	----------
%RSD	0.4%	1.4%	0.5%	NMT5%



ASSAY OF ACARBOSE DURING DRY MIXING

Table No:12 Assay of Acarbose during Dry mixing

LOCATION	ASSAY OF ACARBOSE (%) (30 MINUTES DRY MIXING)			LIMIT
	BATCH A	BATCH B	BATCH C	
1	102.0	98.5	101.4	95.0-105.0% of input.
2	101.8	98.8	101.5	95.0-105.0% of input.
3	101.8	99.5	102.1	95.0-105.0% of input.
4	102.5	98.8	101.9	95.0-105.0% of input.
5	102.2	98.9	101.4	95.0-105.0% of input.
6	101.7	98.7	101.3	95.0-105.0% of input.
MINIMUM	101.7	98.5	101.3	---------
MAXIMUM	102.5	98.5	102.1	----------
AVERAGE	102.0	98.9	101.6	----------
%RSD	0.3%	0.3%	0.3%	NMT5%



DRYING Table NO:13 LOD of Acarbose.

BATCH NUMBER	LOD AT DIFFERENT TIME INTERVALS			ACCEPTANCE CRITERIA
	INTERVAL 1	INTERVAL 2	INTERVAL3	
A	5.46	3.96	2.68	2-3.5%w/w
B	5.90	3.50	2.94	2-3.5%w/w
C	4.6	3.8	2.8	2-3.5%w/w

BLENDING AND LUBRICATION Table NO:14 Parcticle size disrtibution

BATCH NUMBER	PARTICLE SIZE DISTRIBUTION (IN %) (RETAINED ON)						BULK DENSITY
	#20	#40	#60	#80	#100	PASS THROUGH #100	
A	0.00	0.34	2.52	11.19	34.57	50.12	0.47
B	0.01	0.43	2.21	12.85	36.48	47.69	0.50
C	0.50	1.12	7.33	22.89	51.88	14.68	0.51

COMPRESSION DATA BATCH A

PARAMETER	SETTING/ SPEED				ACCEPTANCE CRITERIA
	1	2	3	4	
DESCRIPTION	*	*	*	*	White to off-white circular, shallow, concave, uncoated tablets plain on both the sides.
UNIFORMITY OF WEIGHT	169	169	170	169	165mg ± 7.5 % (153.0-177.0 mg)
	160	161	162	161	
THICKNESS	3.07	3.08	3.08	3.08	2.90-3.30mm
	3.04	3.02	3.04	3.02	
DIAMETER	7.93	7.93	7.93	7.93	7.8-8.0 mm
	7.89	7.89	7.89	7.89	
HARDNESS	4.80	4.81	4.81	4.86	NLT 3.0 kg/cm²
	4.56	4.56	4.52	4.60	
FRIABILITY	0.06%	0.07%	0.06%	0.07%	NLT 1.0 %w/w
DISINTEGRATION TIME	4 minutes 45seconds.	4 minutes 40 seconds.	4 minutes 45 seconds.	4 minutes 40 seconds.	NMT 15 minutes.
ASSAY	101.1	100.2	100.1	100.9	Assay of Acarbose should be 90.0-110.0% of label claim.

Table NO: 15 Compression Of Acarbose Batch A

PARAMETER	SETTING/ SPEED				ACCEPTANCE CRITERIA
	1	2	3	4	
DESCRIPTION	*	*	*	*	White to off-white circular, shallow, concave, uncoated tablets plain on both the sides.
UNIFORMITY OF WEIGHT	168	169	168	168	165mg ± 7.5 % (153.0-177.0 mg)
	162	163	162	163	
THICKNESS	3.08	3.08	3.08	3.08	2.90-3.30mm
	3.04	3.04	3.04	3.04	
DIAMETER	7.92	7.92	7.92	7.92	7.8-8.0 mm
	7.89	7.88	7.88	7.89	
HARDNESS	4.75	4.76	4.75	4.75	NLT 3.0 kg/cm²
	4.35	4.35	4.40	4.40	
FRIABILITY	0.08%	0.06%	0.06%	0.07%	NLT 1.0 %w/w
DISINTEGRATION TIME	3 minutes 45seconds.	3 minutes 50 seconds.	3minutes 50 seconds.	3minutes 45seconds.	NMT 15 minutes.
ASSAY	100.5	100.3	100.9	100.8	Assay of Acarbose should be 90.0-110.0% of label claim.

COMPRESSION BATCH B Table No:16 Compression Of Acarbose Batch B

COMPRESSION BATCH C:

Table No:17 Compression Of Acarbose Batch C

PARAMETER	SETTING/ SPEED				ACCEPTANCE CRITERIA
	1	2	3	4	
DESCRIPTION	*	*	*	*	White to off-white circular, shallow, concave, uncoated tablets plain on both the sides.
UNIFORMITY OF WEIGHT	166	166	167	166	165mg ± 7.5 % (153.0-177.0 mg)
	160	160	160	160	
THICKNESS	3.10	3.10	3.10	3.10	2.90-3.30mm
	3.05	3.05	3.05	3.05	
DIAMETER	8.00	8.00	7.94	7.94	7.8-8.0 mm
	7.82	7.86	7.91	7.89	
HARDNESS	6	6	6	6	NLT 3.0 kg/cm²
	5	5	5	5	
FRIABILITY	0.08%	0.09%	0.09%	0.10%	NLT 1.0 %w/w
DISINTEGRATION TIME	4 minutes 42 seconds.	4 minutes 46 seconds.	5 minutes	4 minutes 46 seconds.	NMT 15 minutes.
ASSAY	99.6	101.1	99.4	99.7	Assay of Acarbose should be 90.0-110.0% of label claim.

COATING: Table No:18 Coating Of Acarbose Tablets

TIME	% WEIGHT BUILD UP		
	BATCH A	**BATCH B**	**BATCH C**
	Average weight of core tablets: 165.	**Average weight of core tablets: 164.**	**Average weight of core tablets:164**
15 minutes.	0.23%	0.21%	0.32%
30 minutes.	0.49%	0.35%	0.46%
45 minutes.	0.70%	0.72%	0.51%
60 minutes.	0.91%	0.89%	0.69%
75 minutes.	1.14%	1.19%	0.89%
90 minutes.	1.37%	1.35%	1.22%
105 minutes.	1.60%	1.56%	1.52%
120 minutes.	1.82%	1.85%	1.79%
135 minutes.	1.97%	1.95%	1.83%
150 minutes.	2.12%	2.10%	2.01%
165 minutes.	2.27%	2.25%	2.06%
180 minutes.	2.42%	2.40%	2.29%
195 minutes.	2.57%	2.55%	2.48%
210 minutes.	2.72%	2.70%	2.52%
225 minutes.	2.90%	2.80%	2.74%
240 minutes.	3.03%	2.92%	3.03%
3.05%			

COATING: Table No:19 Coating of Acarbose Tablets

PARAMETER	OBSERVATION			ACCEPTANCE CRITERIA.
	Batch A	Batch B	Batch C	
Description	*	*	*	White to off white circular, shallow, concave, coated tablets, plain on both sides.
Weight gain	3.03	3.05.	3.03	2.8-3.2% weight gain from average weight of core tablets.
Thickness	3.16.	3.18	3.17	3.0- 3.4 mm
Diameter	8.02.	7.99	8.01	7.9-8.1 mm
Dissolution	99.5	100.1	94	NLT 80% of labelled amount of Acarbose in the tablets is dissolved in 30 minutes.
Assay	99.2%	100.6%	99.7%	Assay of Acarbose should be 90.0-110.0%of label claim.

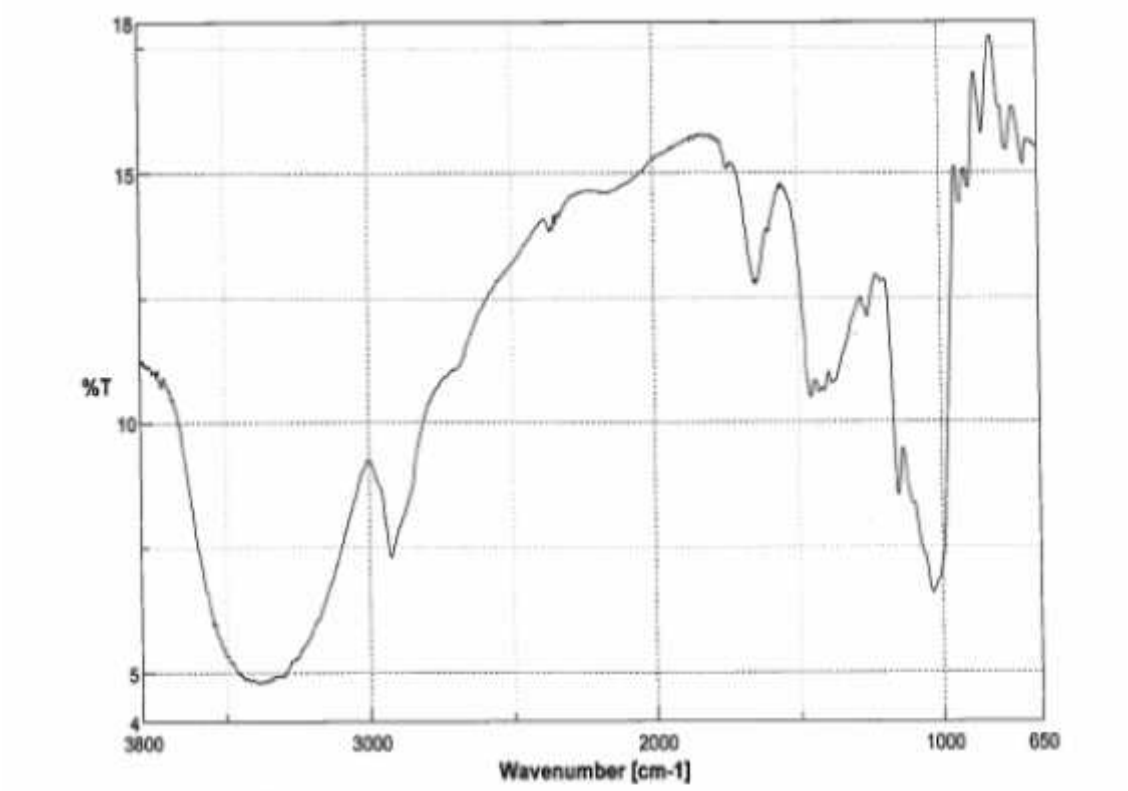
PACKING

Table No:20 Packing of Acarbose

PARAMETER	OBSERVATION			SPECIFICATION
	BATCH A	BATCH B	BATCH C	
Description	White, circular, biconvex, film coated tablets plain on both the sides.	White, circular, biconvex, film coated tablets plain on both the sides.	White, circular, biconvex, film coated tablets plain on both the sides.	White, circular, biconvex, film coated tablets plain on both the sides.
Leak test	Ok	Ok	Ok	Not a single strip should fail.

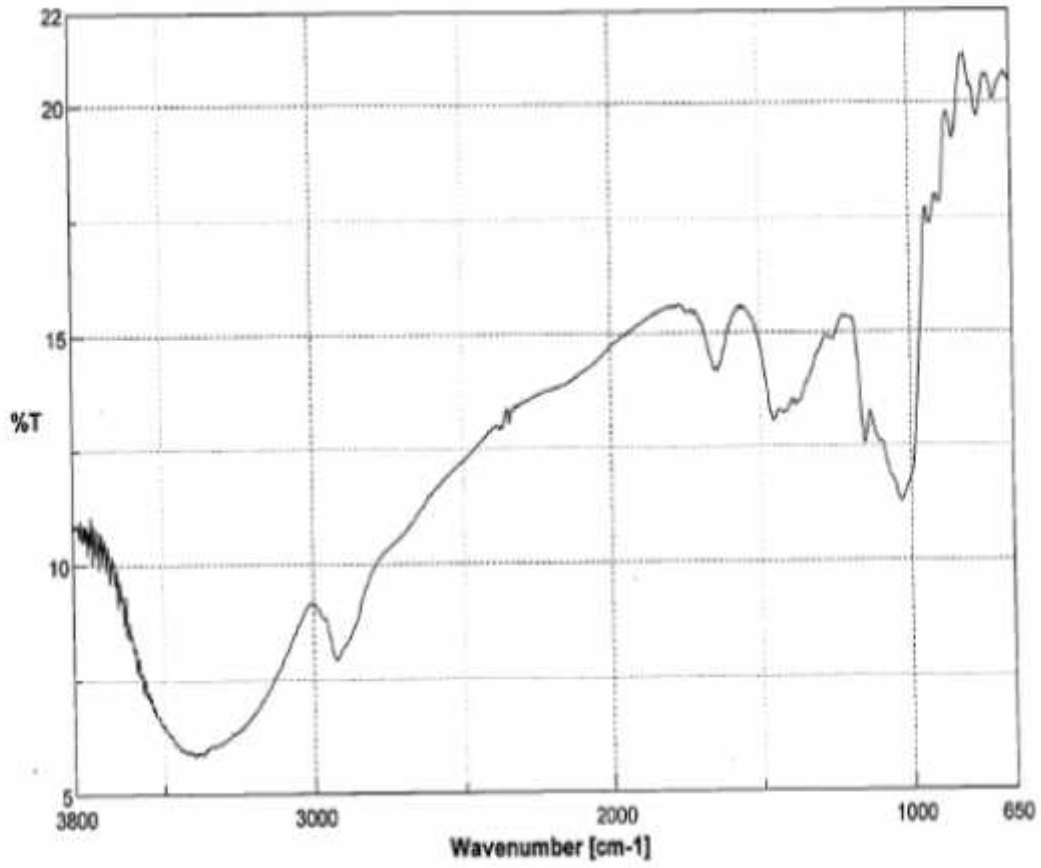
ANNEXURES

Figure No 5: FTIR GRAPH OF ACARBOSE (STANDARD)



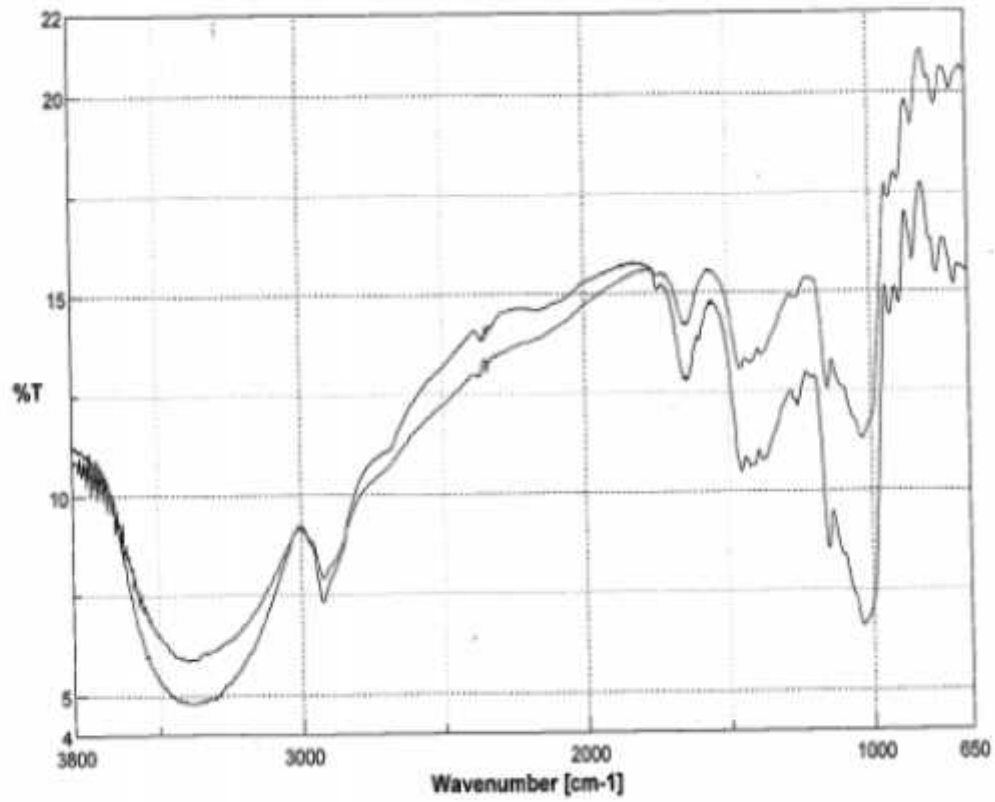
Accumulation	16
Resolution	4 cm-1
Zero Filling	OFF
Apodization	Cosine
Gain	16
Scanning Speed	2 mm/sec
Date/Time	27/11/2012 4:32PM
Operator	R.N.MAHESH
File Name	ACARBOSE-STD-WSJ023.jws
Sample Name	ACARBOSE-STD-WSJ023
Comment	NA

Figure No:6 FT IR GRAPH OF ACARBOSE SAMPLE



Accumulation	16
Resolution	4 cm-1
Zero Filling	OFF
Apodization	Cosine
Gain	16
Scanning Speed	2 mm/sec
Date/Time	27/11/2012 4:44PM
Operator	R.N.MAHESH
File Name	ACARBOSE-SPL-WSJ023.jws
Sample Name	ACARBOSE-SPL-WSJ023
Comment	NA

Figure No:7 FTIR OF COMPARISON OF SAMPLE WITH STANDARD



Accumulation	16
Resolution	4 cm-1
Zero Filling	OFF
Apodization	Cosine
Gain	16
Scanning Speed	2 mm/sec
Date/Time	27/11/2012 4:44PM
Operator	R.N.MAHESH
File Name	ACARBOSE-SPL-WSJ023.jws
Sample Name	ACARBOSE-SPL-WSJ023
Comment	SAMPLE MATCHES WITH STANDARD

Figure No:8

HPLC CHROMATOGRAM OF F3

STD-1 **STD-2**

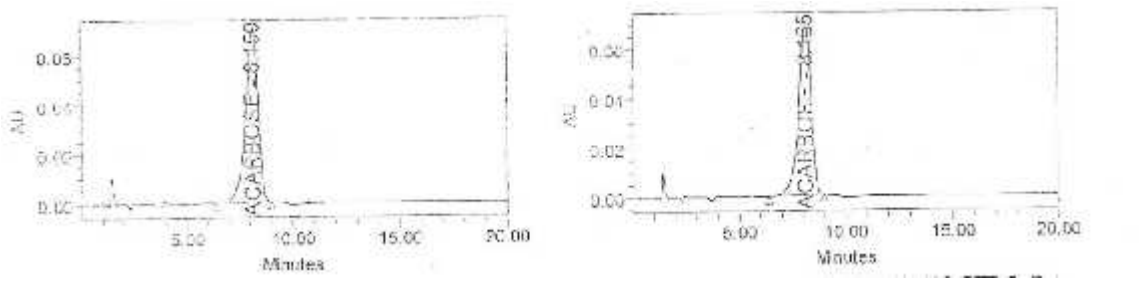


Figure No:9

HPLC CHROMATOGRAM OF F4

STD-1 **STD-2**

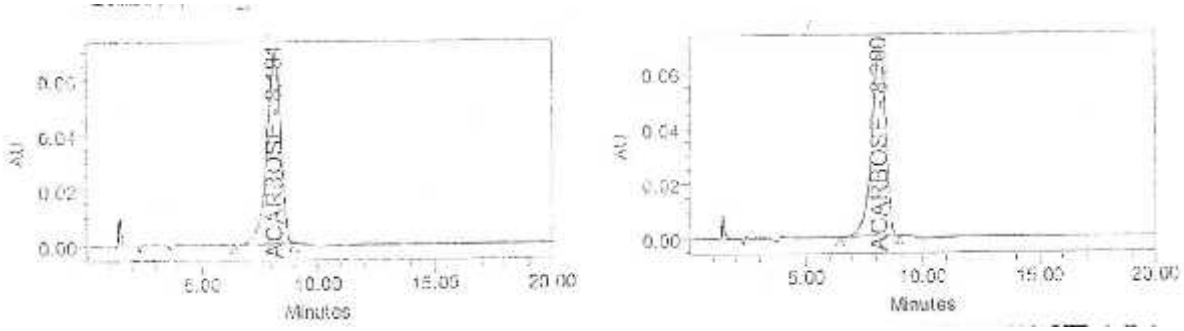


Figure No: 10

HPLC CHROMATOGRAM OF F 3

SPL-1 **SPL-2**

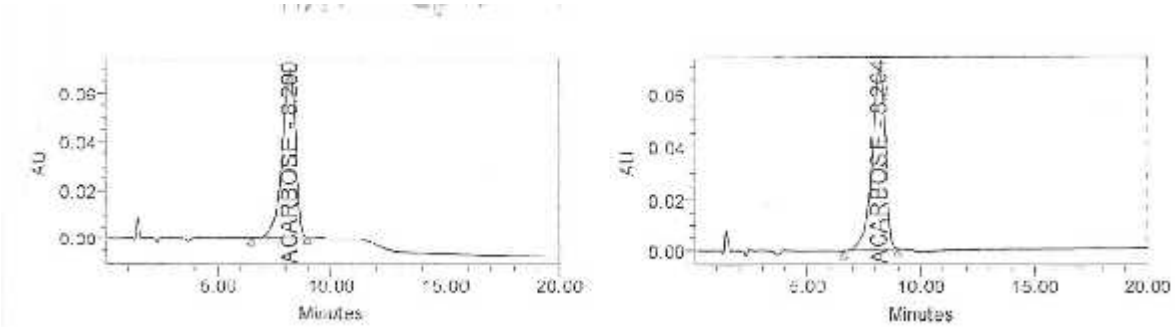
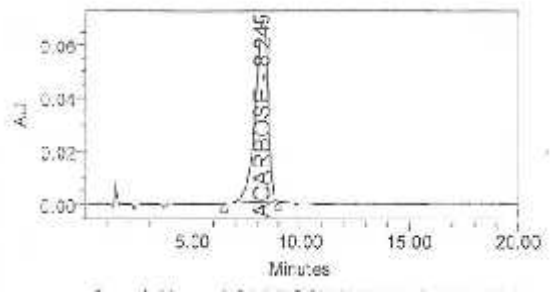
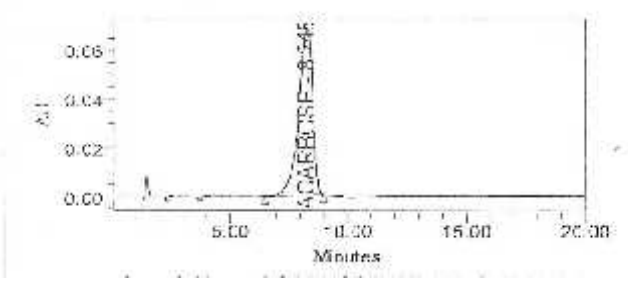


Figure No:11

HPLC CHROMATOGRAM OF F 4

SPL-1 **SPL-2**





Name : ACARBOSE

	Vial	Retention Time	Name	Area	% Area	USP Tailing	USP Plate Count
1	1	8.150	ACARBOSE	2822639	100.00	0.8	986
2	1	8.165	ACARBOSE	2815825	100.00	0.8	992
3	1	8.191	ACARBOSE	2810580	100.00	0.8	986
4	1	8.200	ACARBOSE	2802262	100.00	0.8	989
5	1	8.200	ACARBOSE	2805905	100.00	0.8	988
6	1	8.204	ACARBOSE	2806002	100.00	0.8	987
Mean		8.185		2810535		0.8	988
% RSD				0.3			

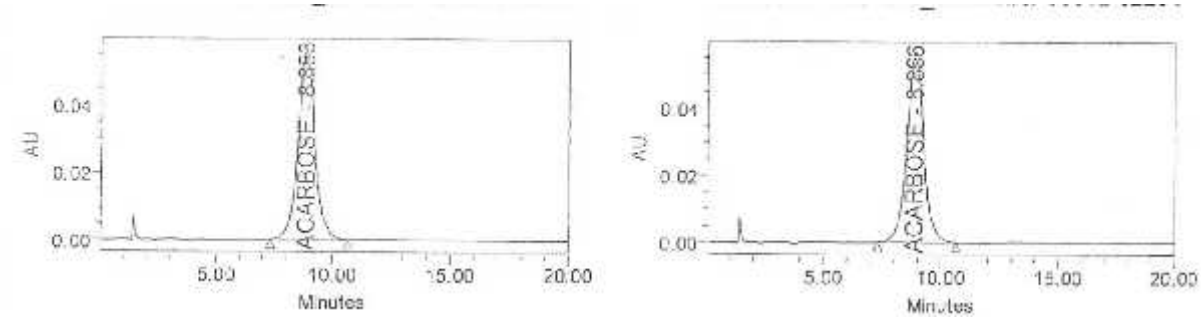
Name : ACARBOSE

	Vial	Retention Time	Name	Area	% Area
1	1	8.245	ACARBOSE	2804954	100.00
Mean				2804954	
% RSD					

Figure No:12

HPLC CHROMATOGRAM OF F 5

STD-1 **STD-2**



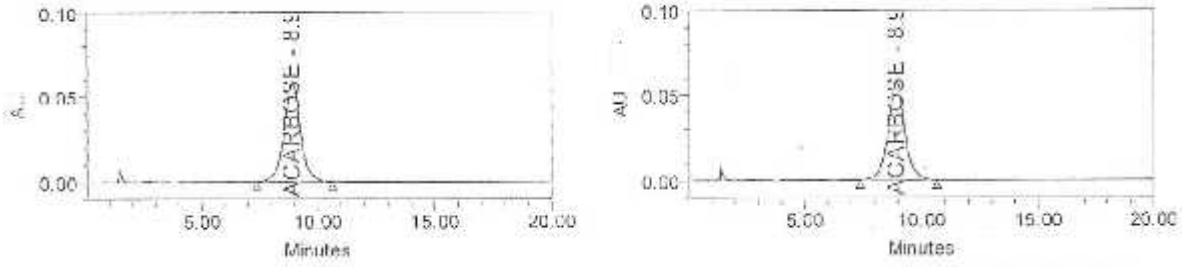
Name : ACARBOSE

	Vial	Retention Time	Name	Area	% Area	USP Tailing	USP Plate Count
1	1	8.867	ACARBOSE	2779301	100.00	1.0	820
2	1	8.869	ACARBOSE	2782130	100.00	1.0	826
3	1	8.883	ACARBOSE	2791706	100.00	1.0	830
4	1	8.896	ACARBOSE	2788952	100.00	1.0	834
5	1	8.888	ACARBOSE	2784341	100.00	1.0	833
6	1	8.888	ACARBOSE	2784114	100.00	1.0	829
Mean		8.882		2785090		1.0	829
% RSD				0.2			

Figure No:13

HPLC CHROMATOGRAM OF F 4

SPL-1 **SPL-2**



Name : ACARBOSE

	Vial	Retention Time	Name	Area	% Area
1	2	8.918	ACARBOSE	2829456	100.00
2	2	8.946	ACARBOSE	2830389	100.00
Mean				2829923	
% RSD				0.0	

Figure No:14

HPLC CHROMATOGRAM OF F 6

STD-1 **STD-2**

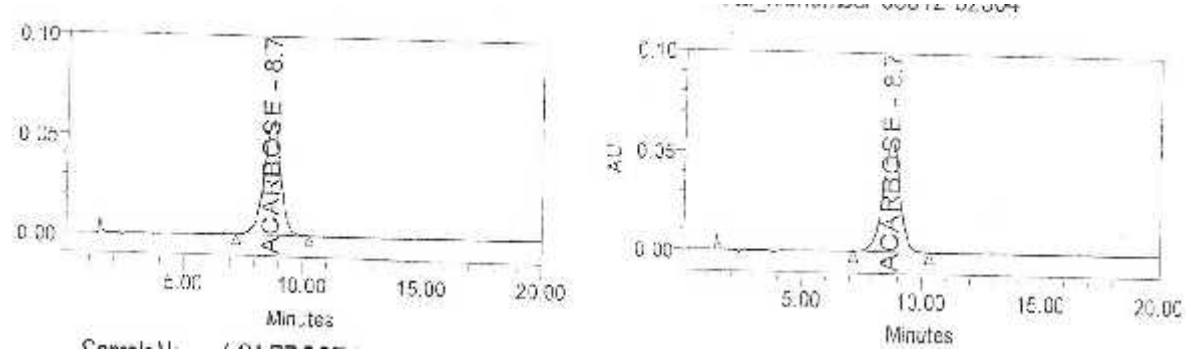


Figure No:15

HPLC CHROMATOGRAM OF F 5

SPL-1 **SPL-2**

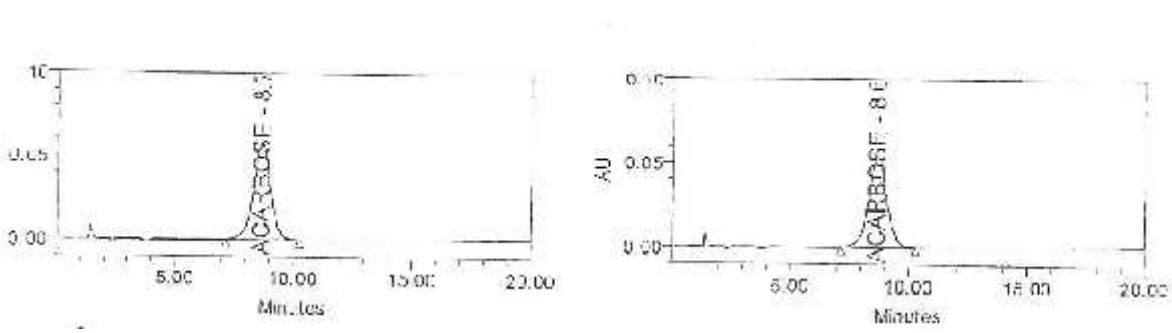
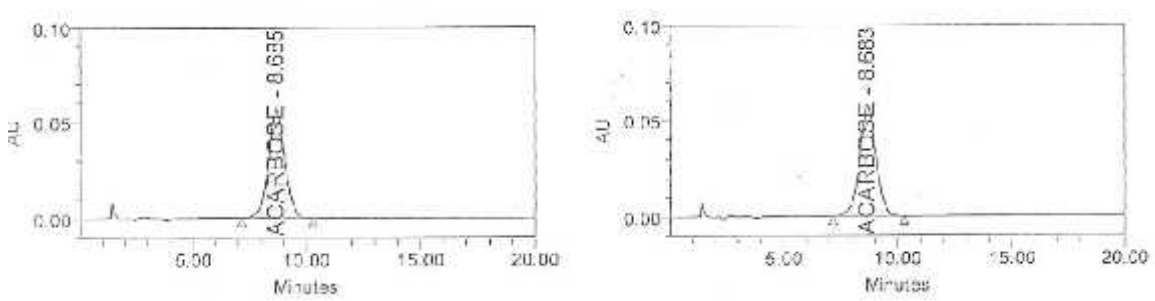


Figure No:16

HPLC CHROMATOGRAM OF F 6

SPL-1 **SPL-2**



Name : ACARBOSE

	Vial	Retention Tme	Name	Area	% Area	USP Tailing	USP Plate Count
1	1	8.708	ACARBOSE	2792188	100.00	1.0	777
2	1	8.707	ACARBOSE	2789902	100.00	1.0	779
3	1	8.706	ACARBOSE	2793193	100.00	1.0	778
4	1	8.701	ACARBOSE	2799294	100.00	1.0	779
5	1	8.712	ACARBOSE	2796018	100.00	1.0	784
6	1	8.685	ACARBOSE	2798822	100.00	1.0	679
Mean		8.703		2791903		1.0	763
RSD				0.1			

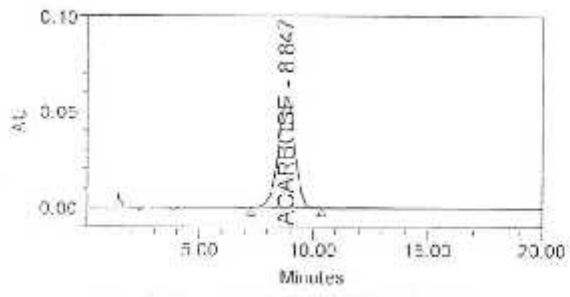
Name : ACARBOSE

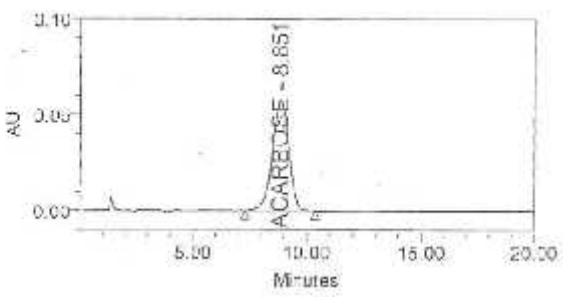
	Vial	Retention Time	Name	Area	% Area
1	2	8.685	ACARBOSE	2860693	100.00
2	2	8.683	ACARBOSE	2866997	100.00
Mean				2863845	
% RSD				0.2	

Figure No:17

HPLC CHROMATOGRAM OF F 7

STD-1 **STD-2**





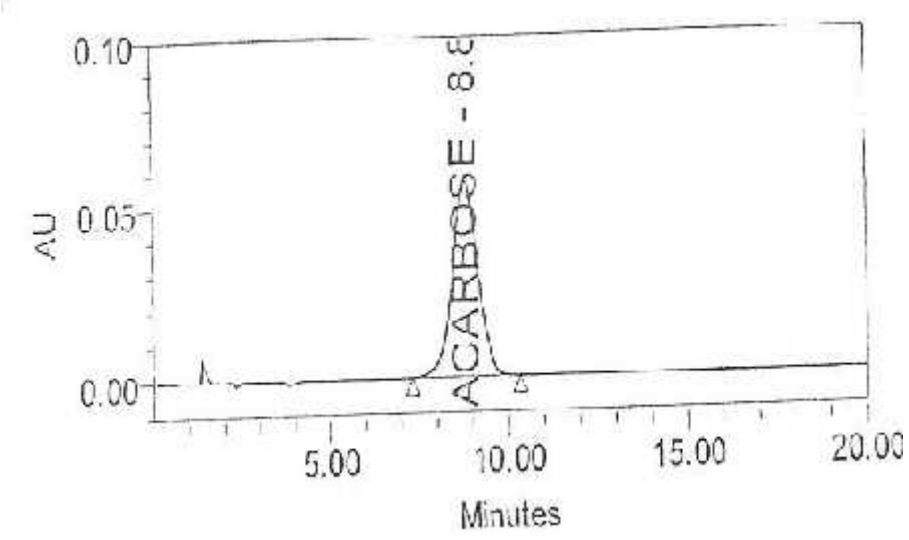
Name : ACARBOSE

	Vial	Retention Time	Name	Area	% Area
1	16	8.847	ACARBOSE	2851700	100.00
2	16	8.851	ACARBOSE	2855208	100.00
Mean				2853454	
% RSD				0.1	

Figure No:18

HPLC CHROMATOGRAM OF F 7

SPL-1



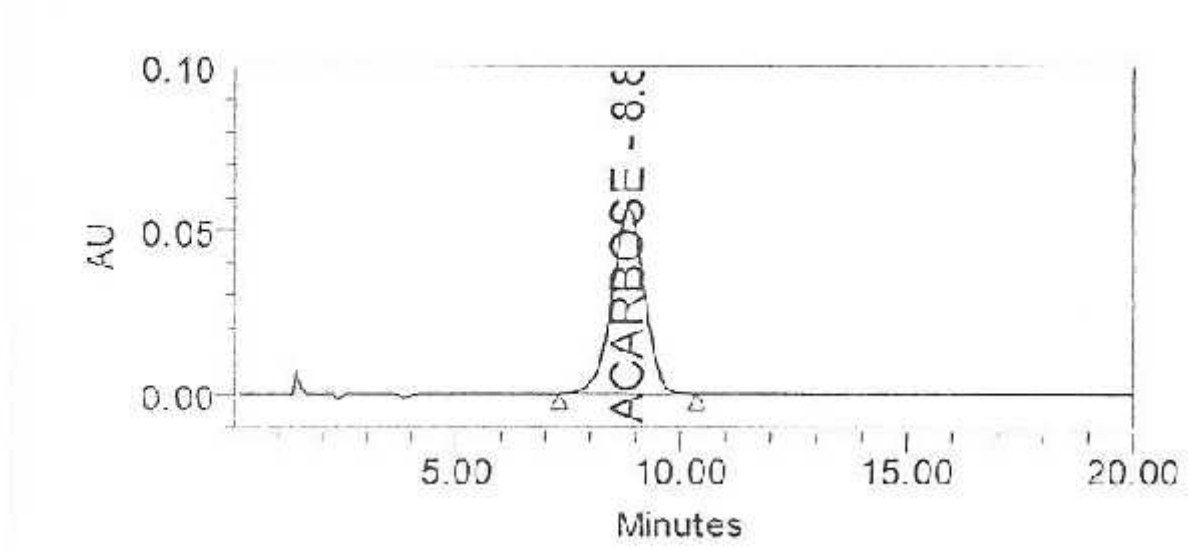
Name : ACARBOSE

	Vial	Retention Time	Name	Area	% Area
1	1	8.847	ACARBOSE	2797297	100.00
Mean				2797297	
% RSD					

Figure No:19

HPLC CHROMATOGRAM OF F 7

SPL-2



Name : ACARBOSE

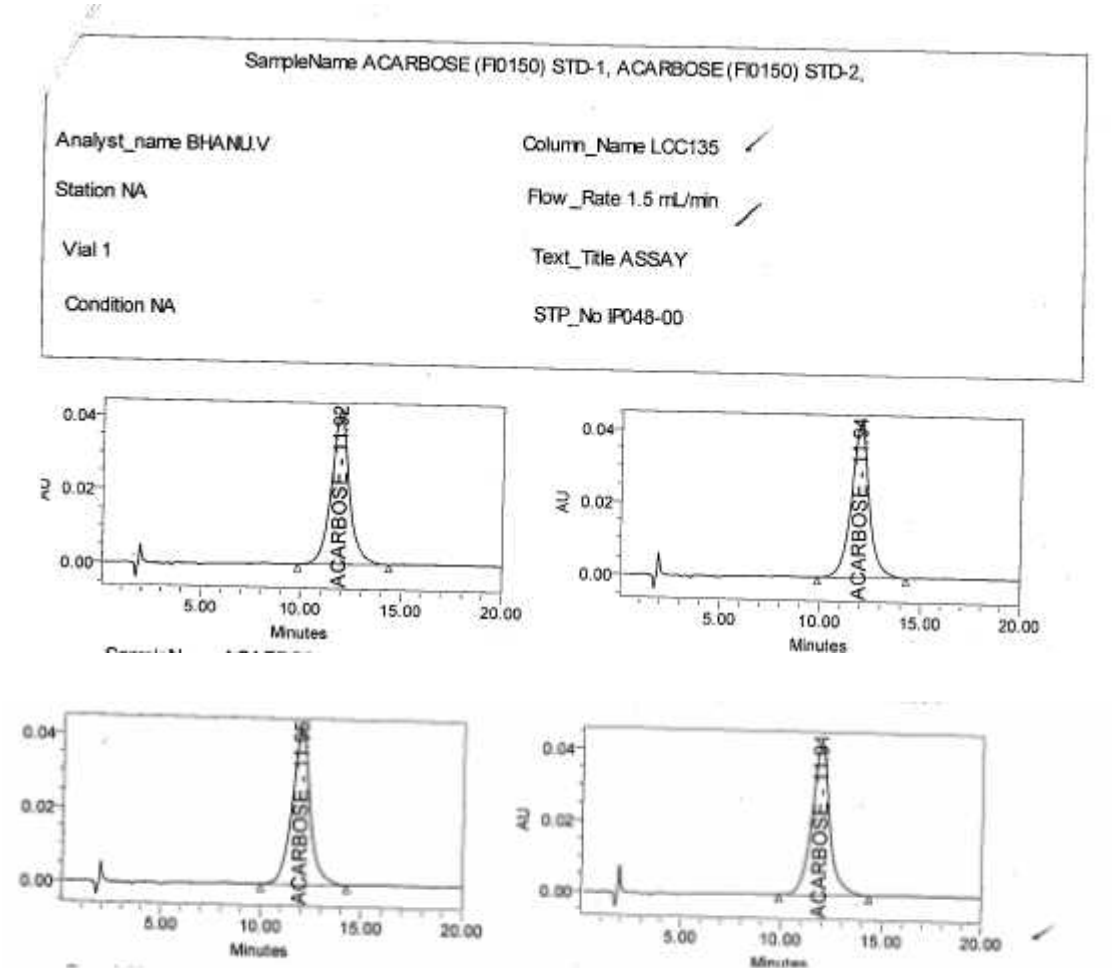
	Vial	Retention Time	Name	Area	% Area
1	1	8.854	ACARBOSE	2799903	100.00
Mean				2799903	
% RSD					

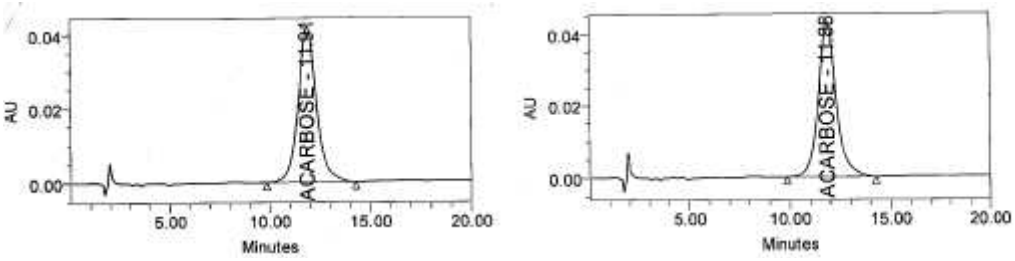
PROCESS VALIDATION: ASSAY OF ACARBOSE CORE TABLETS

Batch A:

STANDARD GRAPH:

Figure No:20





Name : ACARBOSE

	Vial	Retention Time	Name	Area	% Area	USP Tailing	USP Plate Count
1	1	11.920	ACARBOSE	2581957	100.00	1.1	954
2	1	11.940	ACARBOSE	2615842	100.00	1.1	970
3	1	11.952	ACARBOSE	2632135	100.00	1.1	949
4	1	11.918	ACARBOSE	2653834	100.00	1.1	1001
5	1	11.911	ACARBOSE	2640404	100.00	1.1	915
6	1	11.888	ACARBOSE	2643526	100.00	1.1	984
Mean		11.922		2627950		1.1	962
% RSD				1.0			

SAMPLE:

Figure No:21

SampleName ACARB-50 (FID150) SPL-1, ACARB-50 (FID150) SPL-2

Analyst_name BHANU.V

Column_Name LCC135

Station NA

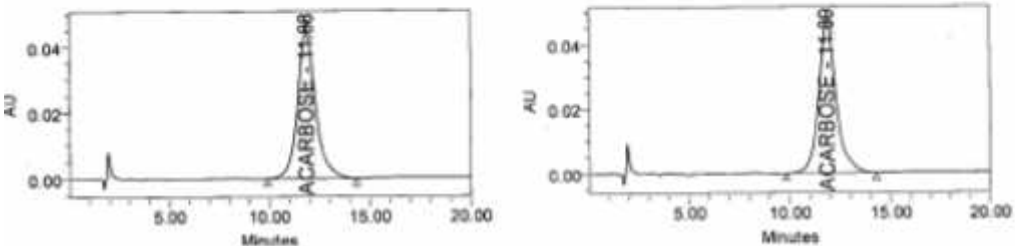
Flow_Rate 1.5 mL/min

Vial 2

Text_Title ASSAY

Condition NA

STP_No IP048-00



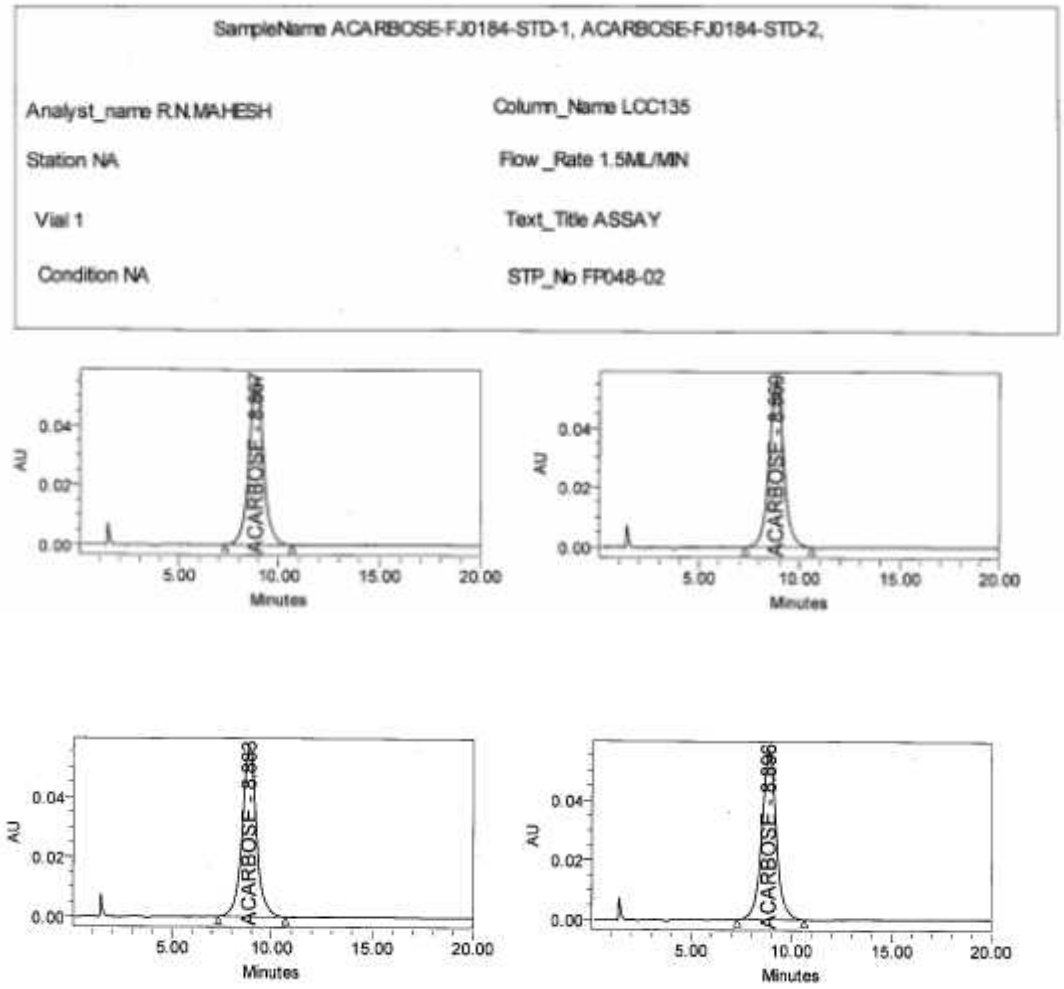
Name : ACARBOSE

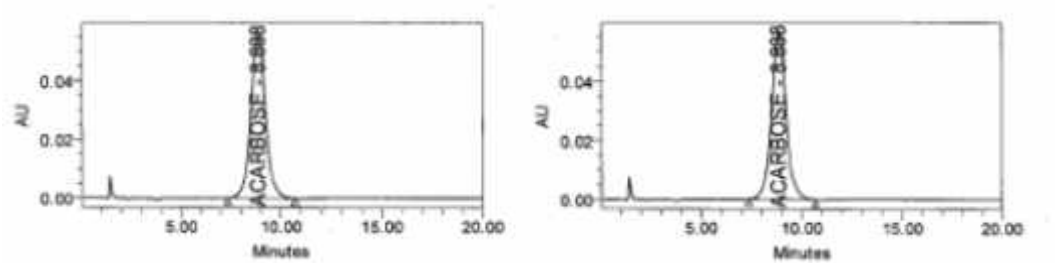
	Vial	Retention Time	Name	Area	% Area
1	2	11.886	ACARBOSE	2766929	100.00
2	2	11.892	ACARBOSE	2786221	100.00
Mean				2776575	
% RSD				0.5	

Batch B:

STANDARD GRAPH:

Figure No:22





Name : ACARBOSE

	Vial	Retention Time	Name	Area	% Area	USP Tailing	USP Plate Count
1	1	8.867	ACARBOSE	2779301	100.00	1.0	820
2	1	8.869	ACARBOSE	2782130	100.00	1.0	826
3	1	8.883	ACARBOSE	2791706	100.00	1.0	830
4	1	8.896	ACARBOSE	2788952	100.00	1.0	834
5	1	8.888	ACARBOSE	2784341	100.00	1.0	833
6	1	8.888	ACARBOSE	2784114	100.00	1.0	829
Mean		8.882		2785090		1.0	829
% RSD				0.2			

SAMPLE:

Figure No:23

SampleName ACARB-50MG-FJ0184-SPL-1, ACARB-50MG-FJ0184-SPL-2

Analyst_name R.N.MAHESH

Column_Name LCC135

Station NA

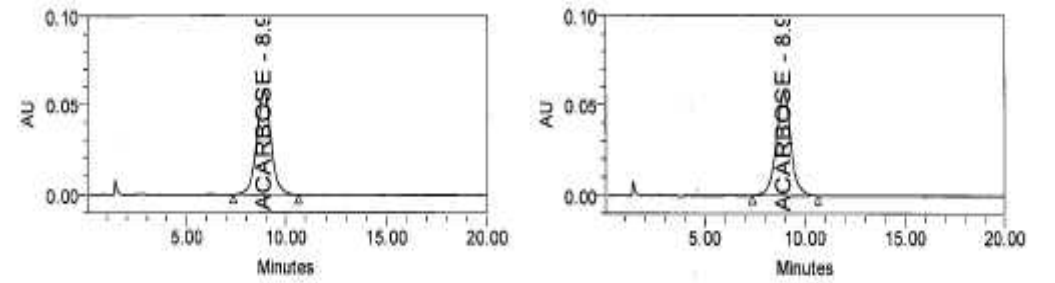
Flow_Rate 1.5ML/MIN

Vial 2

Text_Title ASSAY

Condition NA

STP_No FP048-02



Name : ACARBOSE

	Vial	Retention Time	Name	Area	% Area
1	2	8.918	ACARBOSE	2829456	100.00
2	2	8.946	ACARBOSE	2830389	100.00
Mean				2829923	
% RSD				0.0	

Batch C:

STANDARD GRAPH:

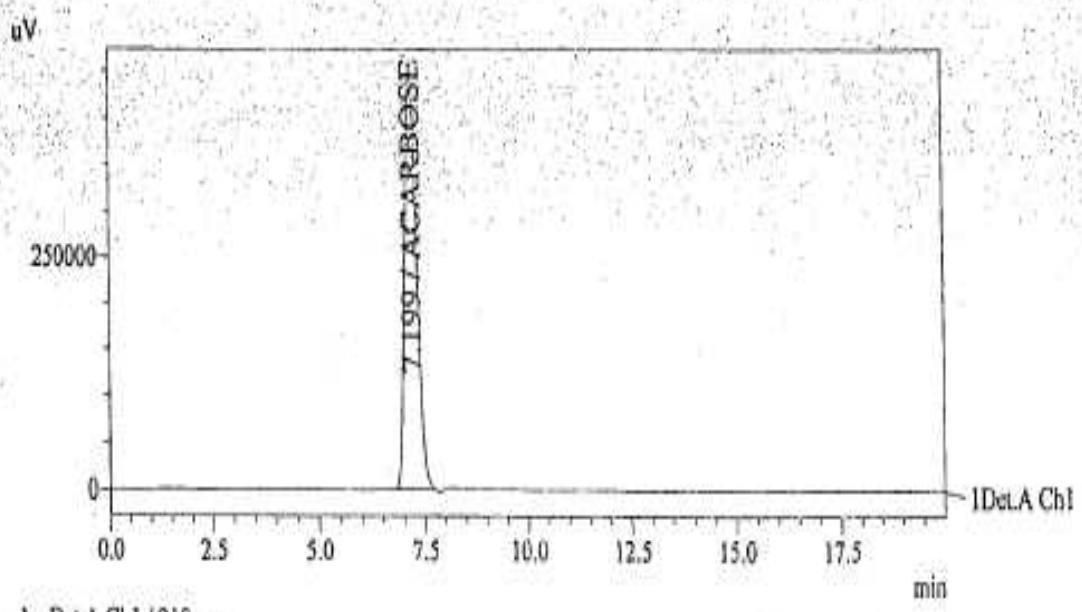
Figure No:24

Instrument ID :QCE055

Sample Name :STANDARD (FE0187)
Acquired by :orchid
Data Name :05507-02709.lcd
Vial No. :1
Injection Volume :20
Flow :1.5 ML/MIN
Time aquired :12:20:21 AM/20/06/07
Time processed :10:22:38 AM/20/06/07

Wavelength :210

STP No. :FP048-02
Station :NA
Condition :NA
Analyst :N.BABU
Column No. :LCC084



1 Det.A Ch1 / 210nm

C:\QCE055\Data\QCE055_JUN_07\05507-02709.lcd

Detector A Ch1 210nm

Peak#	Sample Name	Ret. Time	Area	Area %
1	ACARBOSE	7.199	8969501	100.00
Total			8969501	100.00

SAMPLE:

Figure No:25

SampleName ACARBOSE SPEED-2 (FE0271)

Analyst_name R.N.MAHESH

Column_Name LCC091

Station NA

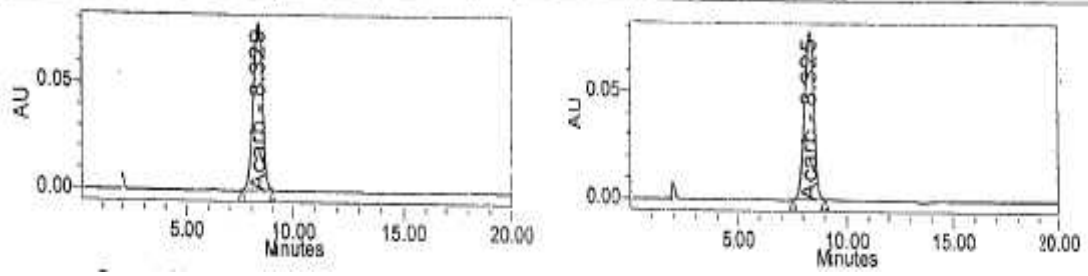
Flow_Rate 1.5ML/MIN

Vial 11

Text_Title ASSAY

Condition NA

STP_No FP048-02



Name: Acarb

	Vial	Retention Time	Name	Area	% Area
1	11	8.329	Acarb	2291046	100.00
2	11	8.325	Acarb	2290433	100.00
Mean				2290739	
% RSD				0.0	

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