FORMULATION AND EVALUATION OF AMOXICILLIN & POTASSIUM CLAVULANATE DISPERSIBLE TABLET

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

in

PHARMACEUTICS

Submitted by

261210016

Under the guidance of

Dr. U. UBAIDULLA, M. Pharm., Ph.D
Department of Pharmaceutics

C. L. BAID METHA COLLEGE OF PHARMACY
(An IS0 9001-2000 certified institute)
THORAIPAKKAM, CHENNAI-600097
APRIL-2014

Fax : 91-44-27438251 Internet : medoexpo@vsnl.com

medopharm
Private Limited

Date : 16/12/2013

CERTIFICATE

This is to certify that **Mr. S. Subbiah,** student of **C. L. Baid Metha College of Pharmacy** to the **Tamilnadu Dr. MGR Medical University**, Chennai, Tamilnadu, has worked on the project **"DESIGN, DEVELOPMENT AND EVALUATION OF AMOXICILLIN AND POTASSIUM CLAVULANATE DISPERSIBLE TABLETS 228.5MG"** at **Medopharm private Limited, Research and Development department**, Guduvanchery, under my direct supervision and guidance as a mandatory requirement towards fulfilment of **M. Pharm Degree**, during the period from Jun-2013 to Dec - 2013. He has worked diligently and sincerely to complete the Project which was assigned to him. After my review I am fully satisfied with his Project work.

I wish him success in all his future endeavours.

For Medopharm Pvt. Ltd.

Jayanta Kumar Bhuyan
AGM - R&D

Factory : 50, Kayarambedu Village, Guduvanchery - 603 202. Ph : 6745 6486 / 6745 6550
Corp. Office : "MEDO HOUSE" No.25, Puliyur 2nd Main Road, Trustpuram, Chennai-600 024.
Phone : 6614 9999 / Fax : 6614 9989 / 90 / 91

Phone : 24960151, 24960425
E-mail : principal@clbaidmethacollege.com
Website : www.clbaidmethacollege.org

C.L. Baid Metha College of Pharmacy

An ISO 9001 - 2000 certified institution

Jyothi Nagar, Old Mahabalipuram Road
Thorapakkam, Chennai - 600 097.

Affiliated to The Tamilnadu Dr. M.G.R. Medical University, Chennai.
Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education. New Delhi.

CERTIFICATE

This is to certify that Reg. No: 261210016 carried out the dissertation work on **"FORMULATION AND EVALUATION OF AMOXICILLIN & POTASSIUM CLAVULANATE DISPERSIBLE TABLET"** for the award of degree of **MASTER OF PHARMACY IN PHARMACEUTICS, THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32** and is bonafide research work done under my Supervision and Guidance in the Department of Pharmaceutics, C. L. Baid Metha College of Pharmacy, Chennai-97 during the academic year 2013-2014.

Place:
Date:

Dr. U. UBAIDULLA, M.Pharm., Ph.D.,
Department of Pharmaceutics.
C.L.Baid Metha College of Pharmacy
Thoraipakkam
Chennai-97.

Phone : 24960151, 24960425
E-mail : principal@clbaidmethacollege.com
Website : www.clbaidmethacollege.org

C.L. Baid Metha College of Pharmacy

An ISO 9001 - 2000 certified institution

Jyothi Nagar, Old Mahabalipuram Road
Thorapakkam, Chennai - 600 097.

Affiliated to The Tamilnadu Dr. M.G.R. Medical University, Chennai.
Approved by Pharmacy Council of India, New Delhi, and
All India Council for Technical Education. New Delhi.

CERTIFICATE

This is to certify that **Reg. No: 261210016** carried out the dissertation work on **"FORMULATION AND EVALUATION OF AMOXICILLIN & POTASSIUM CLAVULANATE DISPERSIBLE TABLET"** for the award of degree of **MASTER OF PHARMACY IN PHARMACEUTICS, THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32** under the guidance and supervision of **Dr.U.UBAIDULLA M. Pharm., Ph.D** in the Department of Pharmaceutics, C.L. Baid Metha College of Pharmacy, Chennai-600 097 during the academic year 2013-2014.

Place:
Date:

Prof.Dr.GRACE RATHNAM,M.Pharm.,Ph.D
Principal and Head of the Department,
Department of Pharmaceutics
C. L. Baid Mehta College of Pharmacy
Thoraipakkam
Chennai – 600 097.

DECLARATION

I do hereby declare that the thesis entitled **"FORMULATION AND EVALUATION OF AMOXICILLIN & POTASSIUM CLAVULANATE DISPERSIBLE TABLET"** by Reg. No: 261210016 submitted in partial fulfilments for degree of **MASTER OF PHARMACY IN PHARMACEUTICS** work done under the guidance and supervision of **Dr. U. UBAIDULLA, M. Pharm., Ph.D**, (Institutional guide) and **Mr. JAYANTHA KUMAR BHUYAN** (Industrial guide) during the academic year 2013-2014. The work embodied in this thesis is original, and is not submitted in part or full for any other degree or any other University.

Place:
Date:

Reg. No: 261210016
Department of Pharmaceutics
C.L.Baid Metha College of Pharmacy
Thoraipakkam
Chennai-600 097

ABBREVIATIONS

API	Active pharmaceutical Ingredient
SSG	Sodium starch glycolate
HPLC	High performance liquid chromatography
FTIR	Fourier transformer infrared spectroscopy
CCS	croscarmellose sodium
IR	Infrared spectroscopy
MCC	Micro crystalline cellulose
CP	Crospovidone
UV	Ultraviolet
ICH	International Conference on Harmonization
Int.Ph.	International Pharmacopoeia
RH	Relative Humidity
USP	United States Pharmacopoeia
IP	Indian Pharmacopoeia
CI	Compressibility Index
HR	Hausner's Ratio
WOW	Without water
RSD	Relative Standard Deviation

NOMENCLATURE

%	Percentage
µg/ml	Microgram/millilitre
Conc	Concentration
gm/cc	Gram/cubic centimetre
Hr	Hour
Kg/cm2	Kilogram/square centimetre
Min	Minute
Mm	Millimetre
Ng	Nanogram
ng/ml	Nanogram/millilitre
ng-hr/ml	Nanogram-hour/millilitre
Nm	Nanometer
SD	Standard Deviation
Sec	Seconds

CONTENTS

ACKNOWLEDGEMENT

The project like this needs the head and hands of many for its successful completion. Good number of well wishes has helped me to complete this project successfully with profound appreciation. I thank all the numerous acquaintance, which has extended support and contribution to my work.

First and foremost, I thank **GOD** for successful completion of this work.

It gives me an immense pleasure in expressing my deep sense of gratitude to my respected guide **Dr. U. UBAIDULLA M. Pharm., Ph.D.,** C.L. Baid Metha college of pharmacy for his remarkable guidance, constant encouragement and every scientific and personal concern throughout the course of investigation and successful completion of this work.

I would like to express my immense gratitude to my industrial guide **Mr. Jayanta Kumar Bhuyan, Manager**, Medopharm Pvt. Ltd, Guduvancheri, for his valuable guidance and support in each and every aspect of the project.

It is great pleasure and honour for me to owe gratitude to **Dr. Gracerathnam M.Pharm, Ph.D**., Principal, C. L. Baid Metha College of Pharmacy for all his support and for providing the facility to carry out this research work.

I would like to thank **Medopharm Pvt. Ltd**, Guduvancheri, for giving me an opportunity to perform my project work in their organization which helped me to mould my project work into a successful one.

I owe my special thanks to **Mr Pradeep Rout, Mr Chinmaya Saho, Mr Jitendra Patra and Mr Srinivas Patnaik, Mr. Karuna Mr. Anand M** for their valuable Advices and cooperation in bringing out this project work.

I am extended my whole hearted thanks to **Mr. Subhakanta kanungo**, **Mr. Bibhuti bhusan Dixit, Mr.Sivakumar** and Mr**. Manichellvan** Lab Technicians and others for their helping hand during my project work.

I feel proud to express my hearty gratitude and appreciation to all my Teaching and Non-teaching Staff members of **C.L.Baid Mehta College of Pharmacy** who encouraged completing this work.

I feel proud to express my hearty gratitude to all my classmates. Also I want to thank all of those, whom I may not be able to name individually, for helping me directly or indirectly.

Lastly I express my profound thanks to God and Devotees who has blessed me with peace of mind, courage and strength.

Last but not the least I wish to express my deepest sense to respect and love to my family members. My parents and my Sister for their constant support and encouragement throughout.

(Reg.No: 261210016)

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION

Oral route of administration is the most important method of administering drugs for systemic effects. Many pharmaceutical dosages are administered in the form of tablets, hard gelatin capsules, granules, powders, and liquids. Many patients, particularly pediatric and geriatric and bed ridden patients have difficulty in swallowing or chewing solid dosage forms. This problem is also applicable to active working or travelling people who do not have ready access to water. Recent advances in novel drug delivery systems (NDDS) aim to develop fast dissolving /disintegrating tablets to improve patience compliance. Dispersible tablets (DTs) Dissolve or disintegrate in saliva within a minute without the need of water or chewing.

Advantages of dispersible tablets include convenience of administration, patient compliance, rapid onset of action, increased bioavailability, accurate dosing as compared to liquids, good stability, ability to provide advantages of liquid medication in the form of solid preparation, ideal for paediatric anti geriatric patient and rapid dissolution/absorption of the drug. Some drugs are absorbed from the oral cavity (mouth, pharynx and esophagus) as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. Dispersible tablet also beneficial for schizophrenic, parkinsonism or developmentally disabled patients with persistent nausea, those with conditions of motion sickness, sudden episodes of allergic attack or coughing, and patients who do not have ready access to water

The various technologies used to prepare DTs include conventional methods like direct compression, wet granulation, and moulding, spray drying, freeze drying and sublimation. Direct compression represents a simple and cost effective tablet manufacturing technique. The basic approach used in the development of the dispersible tablets is the use of Superdisintegrants. Superdisintegrants facilitate the break upon disintegration of tablet content into smaller particles that can dissolve more rapidly than conventional dosage form. The commonly used superdisintegrants are Croscarmellosesodium, Crospovidone, Kollidon CLM and sodium Starch glycolate.

1.1 TABLETS [1]:

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in widespread use since the latter part of the19th centuries and their popularity continues. The term compressed tablet is believed to have been first used by 'John Wyeth and Brother of Philadelphian' during the same period moulded tablets were introduced to be used as hypodermic tablets for injections. Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer [e.g. simplicity & economy of preparation, stability and convenience in packing, shipping, and dispensing] and the patient [e.g. accuracy of dosage, compactness, and post ability, blandness of taste and ease of administration].

Although tablets are more frequently discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration.

1.2 ADVANTAGES OF TABLETS

- They are easy to administer.
- They are a unit dosage form, and they offer the greater 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 of all oral dosage forms.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They are in general the easiest and cheapest to package and ship of all oral dosage forms.

- They may provide the greatest ease of swallowing with the least tendency for "hang-up" above the stomach. Especially when coated, provided that tablet disintegration is not excessively rapid.

1.2 DISADVANTAGES OF TABLETS

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.

- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.

- Bitter tasting drugs, drugs with objectionable odour or drugs that are sensitive to oxygen or atmosphere moisture may require encapsulation or a special type of coating which may increase the cost of the finished tablets.

1.3 PROPERTIES OF AN IDEAL TABLET

- Tablet should be elegant having its own identity and free from defects such as Cracks, chips, contamination, discoloration etc.

- It should have chemical and physical stability to maintain its physical integrity over time.

- It should be capable to prevent any alteration in the chemical and physical Properties of medicinal agent(s).

- It should be capable of withstanding the rigors of mechanical shocks encountered in its production, packaging, shipping and dispensing.

- An ideal tablet should be able to release the medicament(s) in body in predictable and reproducible manner

1.5 IDEAL REQUIREMENTS OF TABLET DOSAGE FORM [2, 3, 4, 5]

The objectives of design and manufacture of the compressed tablet is to deliver orally the correct amount of drug in proper form, at or over the proper time and in desired location. Beside the physical and chemical properties of medical agents formulated as a tablet, it should possess following characteristics.

- Should be an elegant product having its own identity while free of defects such as chips, cracks, discoloration and contamination.
- Should have sufficient strength to withstand mechanical stress during its production, packing, shipping and dispensing.
- Should have the chemical and physical stability to maintain its physical attributes.
- The tablet must be able to release the medicinal agents in a predictable and reproducible manner.

1.6 TYPES OF TABLETS [3]

The route of administration or functions classifies tablets as:

1. **Tablet Ingested orally**
    - Standard compressed tablets
    - Multiple compressed tablets
        a) Compression-coated tablet
        b) Layered tablet
    - Modified Release tablet
    - Delayed Release tablet
    - Targetted Release Tablet
        a) Floating tablet
        b) Colon targeted tablet

- Chewable tablet
- Dispersible tablet

2. Tablet used in oral cavity

- Lozenges and Troches
- Sublingual tablet
- Buccal tablet
- Dental cones
- Mouth dissolving tablet

3. Tablets administered by other routes

- Vaginal tablet
- Implants

4. Tablets used to prepare solution

- Effervescent tablet
- Hypodermic tablet
- Soluble tablets

1.6 TABLETING TECHNIQUES

1. COMPRESSION COATED TABLETS

Compression-coated tablets have two parts, internal core and surrounding coat. The core is small porous tablet and prepared on one turret. For preparing final tablet, a bigger die cavity in another turret is used in which first the coat material is filled and the core tablet is mechanically transferred. Again the remaining space is filled with coat material and finally compression force is applied.

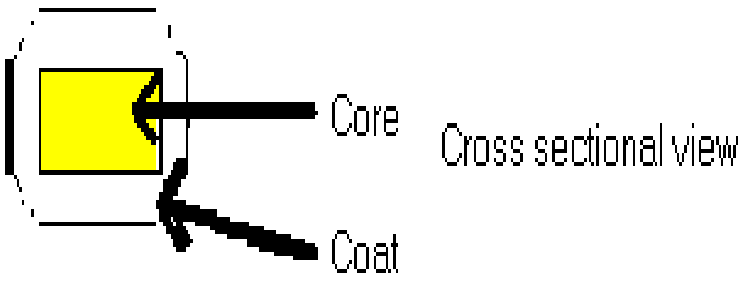


Figure 1: Cross-sectional view of Compression- Coated tablet

This tablet readily lend itself into a repeat action tablet as the outer layer provides the initial dose while the inner core release the drug later on. But when the core quickly releases the drug, entirely different blood level is achieved with the risk of over dose toxicity. To avoid immediate release of both of the layers, the core tablet may be coated with enteric polymer, so that it will not release the drug in stomach while, the first dose is added in outer coating.

2. LAYERED TABLET

When two or more active pharmaceutical ingredients are needed to be administered simultaneously and if they are incompatible, the best option for the formulation pharmacist would be to formulate layered tablet. It consists of several different granulations that are compressed to form a single tablet composed of two or more layers and usually each layer is of different color to produce a distinctive looking tablet. Each layer is fed from separate feed frame with individual weight control. Thus each layer undergoes light compression.

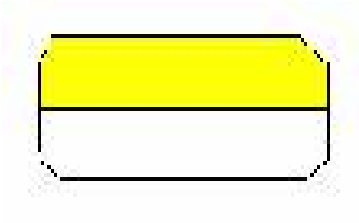


Figure 2: Cross-sectional view of Layered tablet

3. MODIFIED RELEASE TABLETS

Modified release tablets are coated or uncoated tablets containing auxiliary substances or prepared by procedures that are designed to modify the rate at which the active ingredients are released. Modified release tablets include enteric coated tablets, prolonged release tablets and delayed release tablets.

4. DELAYED RELEASE TABLETS

These are tablets that resist dissolution or disruption in the gastric field (stomach), but readily disintegrate in the intestinal fluid to release the drug, thus rendering them delayed release features.

5. CHEWABLE TABLETS

These are compressed tablets that are designed to be chewed rather than swallowed. It is a well-tolerated alternative to traditional pediatric drug formulations and offer significant advantages in children of two years of age and elder.

6. DISPERSIBLE TABLETS

Dispersible tablets are uncoated or film coated tablets that produce dispersion in an aqueous solution in less than one minute to form a smooth suspension without any coarse lumps. They can be prepared by using a simple formulation containing a single disintegrating agent without employing specific combination of Disintegrant, gum, and etc.

7. MOUTH DISSOLVING TABLETS

Mouth dissolving tablets are also known as orally disintegrating tablets or oro dispersible tablets. The Food and Drug Administration's (FDA) definition of an orally disintegrating tablet (ODT) is "A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue." The dissolution test is too rigorous for orally disintegrating tablets due to their fast DT, ideally less than 30 seconds. Mouth dissolving tablets dissolve rapidly in saliva without the need of water. In certain cases, major claim of Mouth dissolving tablets is faster C_{max} compared to traditional tablets.

CLASSIFICATION OF TABLETS

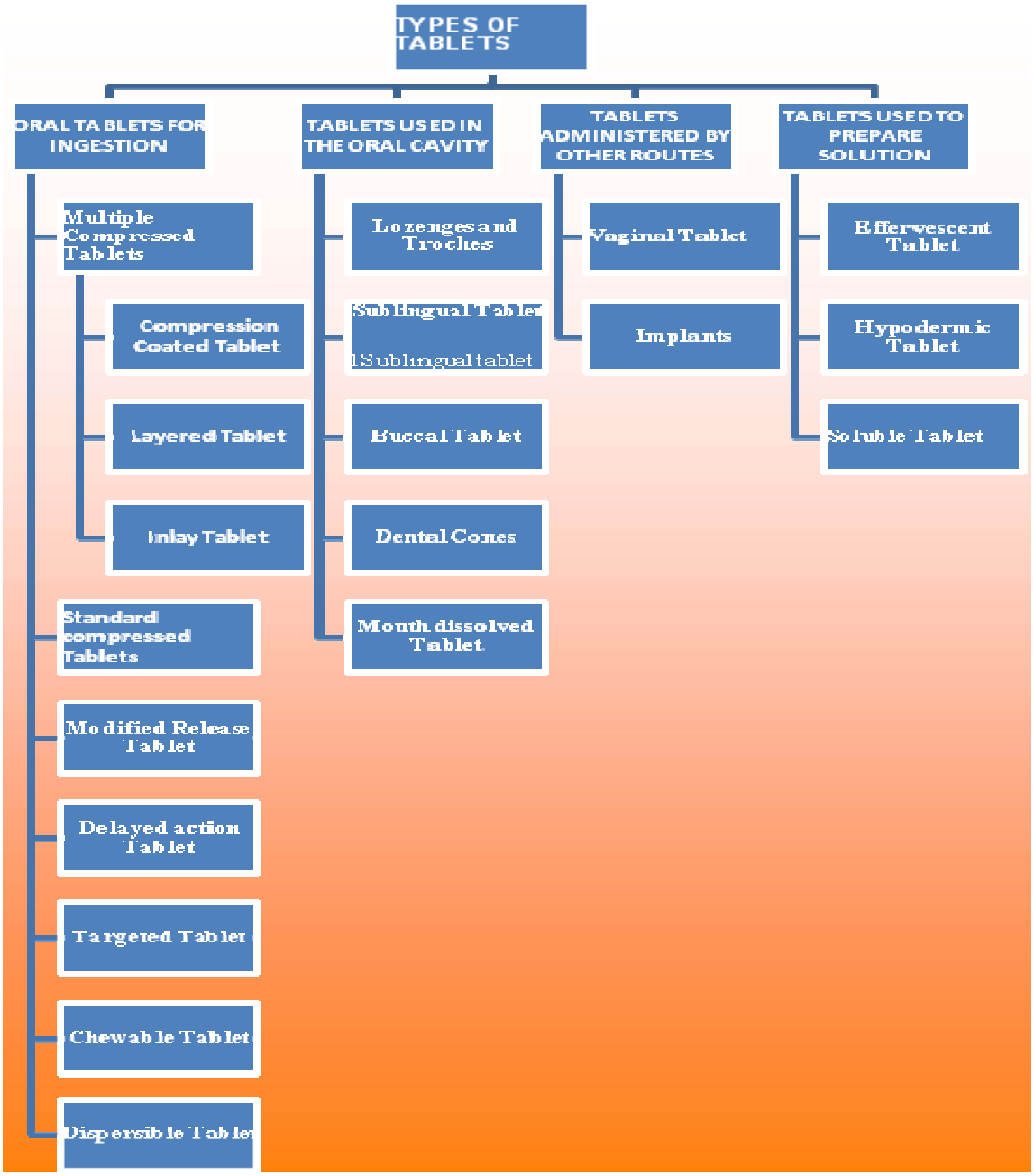


Fig 3: CLASSIFICATION OF TABLETS

1.8 EXCIPIENTS USED FOR PREPARING OF TABLET [3, 5]

Excipients balance the properties of the actives in the release of dosage forms. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

BULKING MATERIALS

Bulking materials are significant in the formulation of fast-melting tablets. The material contributes functions of a diluent, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol, polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Mannitol in particular has high aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.

EMULSIFYING AGENTS

Emulsifying agents are important excipients for formulating immediate release tablets they aid in rapid disintegration and drug release. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast-tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.

LUBRICANTS

Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.

FLAVORS AND SWEETENERS

Flavors and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients. Both natural and synthetic flavors can be used to improve the organoleptic characteristic of fast-melting tablets. Formulators can choose from a wide range of sweeteners including sugar, dextrose and fructose, as well as non-nutritive sweeteners such as aspartame, sodium saccharin, sugar alcohols and sucralose. The addition of sweeteners contributes a pleasant taste as well as bulk to the composition.

SUPER DISINTEGRANTS [6, 7]

A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment.

ADVANTAGES

1. Effective in lower concentrations
2. Less effect on compressibility and flow ability
3. More effective intra granularly

SOME SUPER DISINTEGRANTS ARE

1) Sodium Starch Glycol ate (Explotab, primo gel) used in concentration of 2-8 % & optimum is 4%.

MECHANISM OF ACTION: Rapid and extensive swelling with minimal gelling. Microcrystalline cellulose (Synonym: Avicel, celex) used in concentration of 2-15% of tablet weight. And Water wicking

2) Cross-linked Povidone (crospovidone) (Koll done) used in concentration of 2-5% of weight of tablet. Completely insoluble in water.

MECHANISM OF ACTION: Water wicking, swelling and possibly some deformation recovery. Rapidly disperses and swells in water, but does not gel even after prolonged exposure. Greatest rate of swelling compared to other disintegrants. Greater surface area to volume ratio than other disintegrants**.**

3) Low-substituted hydroxyl propyl cellulose, which is insoluble in water. Rapidly swells in water. Grades LH-11 and LH-21 exhibit the greatest degree of swelling. Certain grades can also provide some binding properties while retaining disintegration Capacity. Recommended concentration 1-5%

4) Cross linked carboxy methyl cellulose sodium (i.e. Ac-Di-sol) Croscarmellose sodium:

MECHANISM OF ACTION: Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentrations: 1-3% Direct Compression, 2-4% Wet Granulation

GAS PRODUCING DISINTEGRANTS

Gas producing disintegrants are used especially where extra rapid disintegration or readily soluble formulation is required. They have also been found of value when poor disintegration characteristics have resisted other methods of improvement. Care should be taken during tableting, particularly on moisture level. Composition is based upon the same principles as those used for effervescent tablets, the most common being mixtures of citric & tartaric acids plus carbonates or bicarbonates. In many instances lower concentration can be used with gas producing disintegrants than are required by other disintegrating agents. Certain peroxides that release oxygen have been tried, but they do not perform as well as those releasing carbon dioxide.

1.9. GENERAL STEPS FOR TABLET MAKING

- ❖ Granulation Milling
- ❖ Drying
- ❖ Blending
- ❖ Compression
- ❖ Coating

1. GRANULATION [8]

Granulation is one of the most important unit operations in the production of pharmaceutical oral dosage forms. Granulation is defined as an operation by which particles are agglomerated using binder solution or slugging to form granules. The main purpose of granulation is to improve powder properties by an increase in particle size owing to agglomeration of fine raw materials. The general purposes of granulation are to increase the apparent bulk density, enhance the flowability, modify the dissolution rate, lower the dust ability and enhance the stability

The characteristics of granulations are of interest in the formulation and development as well as in production of solid dosage forms because they affect the performance properties of the final product, such as disintegration and dissolution rate, tablet hardness, friability, and capping tendency. A poorly reproducible granulation process may give rise to difficulties and time-consuming troubleshooting in the production line. The characteristics of particulate matter in general can be divided into basic material characteristics: fundamental characteristics and derived bulk characteristics. The granulation characteristics evaluated by the development pharmacist are the derived bulk properties, that is, the properties related to subsequent processing, such as packing and flow properties, tablet compression, disintegration and dissolution properties. Some fundamental characteristics should also be involved in the development phase. Such characteristics include assessment and specification of granule structure and porosity, size distribution and friability, all of which may have a significant effect on the subsequent processing and the final product quality.

Three principle methods of developing powders for tablet making are:

1) Direct compression
2) Dry granulation
3) Wet granulation

2. DIRECT COMPRESSION [9]

Powders that can be mixed well do not require granulation and can be compressed into tablets through direct compression. In direct compression, a compressible vehicle is blended with the medicinal agent, lubricant and a disintegrate, and then the blend is compressed. The term direct compression is used to define the process by which tablets are compressed directly from powder blends of the active ingredients and suitable excipients (including fillers, disintegrant and lubricants), which will flow uniformly into a die cavity and form into a firm compact. No pretreatment of the powder blends by wet or dry granulation procedures is necessary. Mainly, Lactose monohydrate, anhydrous lactose, Dextrose, Compressible sugar, Micro crystalline cellulose, Starch, Unmilled Dicalcium phosphate etc. are used as suitable excipients for direct compression methods.

ADVANTAGES OF DIRECT COMPRESSION

- Economic
- It eliminates heat and moisture
- Prime particle dissociation
- Stability
- Particle size uniformity

DISADVANTAGES OF DIRECT COMPRESSION

- Although there are many significant advantages of direct compression over granulation, there exist important limitations:
- Uniform blending and prevention of unblending of low – dose drugs.
- Fillers often used are costlier than those used in granulation.
- Physical properties and functional specifications are more critical; properties of raw materials must be defined and carefully controlled.

- Dusting problems
- More sensitive to lubricant softening and over mixing than granulation.

3. DRY GRANULATION

Dry granulation is a technique in which materials used does not apparently assume any kind of liquid state. In dry granulation process, powder is densified between usually two counter-rotating rolls. This results in an (ideally) endless ribbon, which is subsequently fed into an external or integrated granulation (milling) unit, which mills the ribbons down to the desired granule size.

DRY GRANULATION CAN BE USED AS ADVANTAGE IN THE FOLLOWING SITUATIONS

- For moisture- sensitive and heat- sensitive materials.
- For improved disintegration, since the powder particles are not bonded together by a binder.
- For improved solubility, as with anhydrous soluble materials that tend to set them wet.
- For improved blending, since there is no migration of active ingredients as might occur during the drying of a wet granulation.

SOME OF THE DISADVANTAGES OF DRY GRANULATION ARE AS FOLLOWS

- It requires a specialized heavy-duty tablet press to form the slug.
- It does not permit uniform color distribution as can be achieved with wet granulation, where the die can be incorporated into the binder liquid.
- A pressure roll press such as the Chilsonator cannot be used with insoluble drugs since this may retard the dissolution rate.
- The process tends to create more dust than wet granulation, increasing the potential for cross-contamination.

TWO PROCESSES ARE USED FOR DRY GRANULATION:

a) Compression granulation
b) Roller compaction

a) DRY GRANULATION BY COMPRESSION GRANULATION

Compression granulation is a valuable technique in situation where the effective dose of a drug is too high for direct compression, and the drug is sensitive to heat, moisture or both. Example, many aspirin and vitamin formulations are prepared for tabletting by compression granulation involves the compaction of the components of a tablet formulation by means of a tablet press or specially designed machinery, followed by milling and screening prior to final compression into a tablet.

b) DRY GRANULATION BY ROLLER COMPACTION

The basic concept of compaction is to force fine powders between two counter rotating rolls. As the volume decreases through the region of maximum pressure, the material is formed into a solid compact or sheet. Some of the factors controlling the compaction process are roll surface, diameter, peripheral speed, separating force or pressure capabilities, feed screw design and basic compaction characteristics of material being processed. On a large scale, dry granulation can also be performed on a specially designed machine called roller compactor. Roller compactor utilizes two rollers that revolve towards each other. Roller compactor compacted ribbon like material or large pieces called briquettes, which can then be screened or milled into a granulation suitable for compression into tablets.

4. WET GRANULATION

Wet granulation is an important process in the formulation of solid dosage forms in the pharmaceutical industry. Wet granulation is used to improve flow, compressibility, bioavailability, and homogeneity of low dose blends, electrostatic properties of powders and stability of dosage forms. Granule formation and growth proceed because of effects of mobile-liquid bonding formed between the primary particles. During wet granulation the following material properties influence the granule formation and growth:

- Solubility of the particles in the binder liquid.
- Contact angle of the binder liquid to the solids.
- Mean particle size and size distribution of solids.
- Particle shape and surface morphology.

A crude way of determining the end point is to press a portion of the mass in the palm of the hand, if the ball crumbles under moderate pressure; the mixer is ready for next step of wet screening. Certain important parameters to be monitored during wet granulation are dry mixing time, binder addition time, kneading time, impeller speed (RPM), chopper speed (RPM) and the quantity of product.

Advantages of wet granulation:

- Enhances fluidity and compatibility, suitable for high-dose drugs with poor flow and /or compatibility.
- Reduces air entrapment and dustiness.
- Provides for the addition of a liquid phase (wet granulation) suited to dispersion of low-dose drugs in solution to ensure content uniformity.
- Enhances wettability of powders through hydrophilization (wet granulation).
- Permits handling of powders without loss of blend quality.

Disadvantages of wet granulation

- Each unit process brings its own set of complications.
- The large number of unit processes increases the chances of problems.
- Potential adverse effects of temperature, time and rate of drying on drug stability and distribution during drying.
- Overall, more costly than direct compression in terms of space, time and equipment required.

5. MILLING

Milling is a mechanical process of reducing the particle size of solids. During milling process, the solubility of poorly soluble drugs increases due to the decrease in Particle size and resultant increase in the surface area. The principle of operation depends upon direct pressure, impact from a sharp blow, attrition or cutting. The most commonly used mills in pharmaceutical manufacturing are the rotary cutter, hammer mills, roller and fluid-energy mill.

6. DRYING

A drying process is required in wet granulation to remove the solvent. Drying is used as a unit process in the preparation of granules, which can be dispensed in bulk or converted into tablets. Dried products are more stable than the moist ones, so drying is important in case of tablet manufacturing. Various equipments used for drying are:

- Static-bed dryer
- Moving-bed dryer
- Fluidized-bed dryer

7. BLENDING

Blending of powders is a process in which two or more dissimilar particulate solids are blended to give a random mix. A blending operation is required to mix the lubricants after drying of granulated particles. In most cases high degree of uniformity is essential for the final preparation. Blending mainly depends upon the properties of the powder, equipments used and the operating conditions. Most commonly used equipments for blending are Double-cone blender, V-blender, Ribbon blender, turbulent blend.

8. COMPRESSION [9]

Compression is the process of applying pressure to a material. In pharmaceutical tabletting an appropriate volume of granules in a die cavity is compressed between an upper and a lower punch to consolidate the material into a single solid matrix, which is subsequently ejected from the die cavity as an intact tablet. Tablet compression machine are designed with the following basic component.

Hopper for holding and feeding granules to be compressed

- Dies that define size and shape of tablets
- Punches for compressing the granules into tablets
- Cam track for guiding the movement of the punches
- A feeding mechanism for moving granulation from the hopper into the dies
- The granules filled in volumetric basis are then compressed into tablets under suitable compaction force.

The subsequent events that occur in the process of compression are:

- Transitional repacking
- Deformation at points of contact
- Fragmentation or deformation
- Bonding
- Deformation of the solid body,
- Decompression,
- Ejection.

The process of compression has been described in terms of the relative volume (ratio of volume of the compressed mass to the volume of the mass at zero void) and applied pressure. The quotient of the applied force and the area of true contact is the applied deformation pressure at the areas of true contact. It has been stated that smaller particles yield larger areas of true contact and thus bond more strongly. Density, porosity, hardness, tensile strength, specific surface, disintegration and dissolution are the properties of tablets that are influenced by compression.

1.10 MANUFACTURING PROBLEMS OF TABLETS [10]

The defects in tablet are as follows:

CAPPING

The partial or complete separation of the top or bottom crowns of a tablet from the Main body of the tablet is termed as capping.

LAMINATION

Lamination is the separation of a tablet into two more distinct layers.

CHIPPING

It is defined as the breakage of tablet edges.

CRACKING

Formation of small, fine cracks on the upper and lower central surface of tablets or Very rarely on the sidewall are termed as cracking.

STICKING

The partial or complete separation of the top or bottom crowns of a tablet from the main body of the tablet is termed as capping.

MOTTLING

An unequal distribution of color on a tablet with light or dark on the surface is termed as mottling.

DOUBLE IMPRESSION

It involves only those punches, which have a monogram or other engraving on them. Free rotation of either upper punch or lower punch during ejection of a tablet Causes double impression.

1.11 DISPERSIBLE TABLETS [11]

DEFINITION

Dispersible tablets are uncoated tablet that produce dispersion in an aqueous solution in less than 3 minute to form a smooth suspension without lumps. They can be prepared by following ways

1. Simple formulation containing a single disintegrating agent without specific combination of disintegrant, gum etc.

1.12 DESIRED CHARACTERISTICS OF DISPERSIBLE TABLET:

1] Bioavailability

2] Rapid drug therapy intervention is possible

3] Sufficient mechanical strength

4] Allow high drug loading

5] Rapid onset of therapeutic action

6] Good compatibility with development technology

7] Leaves no residue in mouth after oral administration

8] Stability

9] Conventional packaging and processing equipments allows the manufacturing of tablets at low cost

10] Be compatible with taste masking and other excipients

1.13 ADVANTAGES OF DISPERSIBLE TABLET

1. It can be administered to the patient who cannot swallow conventional dosage form such as bedridden patients, elderly and patient effected by renal failure and thus improves patient compliance.
2. It is suitable for bedridden, disabled, traveler and busy persons who does not contain water every time.
3. Good mouth feel property helps to mask the bitterness of medicines.
4. Rapid drug therapy intervention.
5. It provides rapid absorption of drugs and increased bioavailability
6. It allows high drug loading
7. No chewing needed.
8. The risk of suffocation during oral administration of conventional formulation due to physical obstructions is avoided and provides safety.

1.14 DISADVANTAGES OF DISPERSIBLE TABLETS

1. It requires proper packaging for safety and stabilization of stable drugs.
2. It is hygroscopic in nature, so must kept in dry place
3. It shows the fragile, effervescence granules property
4. If not formulated properly, it may leave unpleasant taste in mouth.
5. Since the tablet having insufficient mechanical strength, so careful handling is required

1.15 TRADITIONAL TASTE MASKING TECHNOLOGIES IN DISPERSIBLE TABLETS

1. Taste masking by Ion-exchange Resins.
2. Taste masking by coating with Hydrophilic Vehicles.
3. Taste masking using Flavors and Sweeteners.

1.16 FORMULATION ASPECTS IN DEVELOPING DIPSERSIBLE TABLETS:

Dispersible Tablets are formulated by several processes, which differ in their methodologies and vary in various properties such as:

1. Taste and mouth feel.
2. Mechanical strength of tablets
3. Drug dissolution in saliva.
4. Bio availability.
5. Stability.
6. Swallowability.

CHALLENGES IN FORMULATING ORAL DISINTEGRATING TABLETS:

1. MECHANICAL STRENGTH:

In order to swallow DTs to disintegrate in the oral cavity, they are either made of porous or soft molded matrices, which makes tablet friable and difficult to handle and hence requires peel-off blister packing which increases its cost

2. PALATABILITY

Since most drugs are unpalatable, orally disintegrating drug delivery system contains medicament in taste masked form .It dissolves in patient oral cavity, thus release the active ingredient which comes in contact with the taste buds.

3. AQUEOUS SOLUBILITY

Water soluble drugs pose various formulation challenges results in freezing point depression and formation of glassy solids that may collapse upon drying. Such collapse can be prevented by using various matrix forming excipients like mannitol.

4. AMOUNT OF DRUG

The application for technologies used for DTs is limited by the amount of drug into each unit dose. The drug dose must be lower than 400mg for insoluble drugs and 60mg for soluble drugs.

5. SIZE OF TABLET

The easiest size of tablet to swallow is 7-8mm while the easiest size to handle is 8mm.Therefore, tablet size that is easy to handle and easy to take is difficult to achieve.

6. HYGROSCOPICITY

Many orally disintegrating dosage forms are hygroscopic in nature. Hence they need protection from humidity.

MECHANISM OF DISPERSIBLE TABLETS

It involves the following mechanism –

- Incorporation of an appropriate disintegrating agent in the tablet formulation.
- For rapid disintegration and dissolution of the tablet, water must quickly enter into tablet matrix.
- Tablet is broken down into smaller particles.

1.17 EXCIPIENTS USED FOR PREPARATION OF DISPERSIBLE TABLET

1) SUPER DISINTEGRATES-

It increases the rate of disintegration and dissolution. For the success of orally disintegrating tablet, the tablet having quick dissolving property which is achieved by super disintegrants. Examples are- Crospovidone, MCC, Sodium starch glycolate, CMC, Carboxy methyl cellulose and modified corn starch.

2) **SWEETENERS AND SUGAR BASED EXCIPIENTS-**

Sugar based excipient act as bulking agents. They exhibit high aqueous solubility and sweetness and impart taste masking property. Examples are-Aspartame, Sugar derivative, Dextrose, Fructose, Mannitol, Sorbitol, Maltose etc.

3) **FLAVORS-**

It increases patient compliance and acceptability. Examples are-Vanilla, Citrus oil, Fruit essence, Eucalyptus oil, Clove oil, Peppermint oil etc.

4) **SURFACE ACTIVE AGENTS-**

It reduces interfacial tension and thus enhances solubilization of Dispersible tablets .Examples are-Sodium lauryl sulfate, Sodium doecyl sulfate, Polyoxyethylene sorbitan fatty acid esters, Polyoxyethylene steartes etc.

5) **BINDER-**

It maintains integrity of dosage form. Examples are-PVP, Polyvinyl alchol, Hydroxy propyl methylcellulose.

6) **COLOUR-**

It enhances appearance and organoleptic properties of dosage form. Examples are-Sunset yellow, Red iron oxide, Amaranth.

7) **LUBRICANTS-**

It helps reduces friction and wear by introducing a lubricating film. Examples are- Stearic acid, Magnesium stearate, Zinc stearte, Talc, Polyethylene glycol, Liquid paraffin, Colloidal silicon-di-oxide etc.

8) **FILLERS-**

It enhances bulk of dosage form. Examples are-Mannitol, Sorbitol, Xylitol, Calcium carbonate, Magnesium carbonate, Calcium sulfate, Magnesium trisilicate etc.

1.18 TECHNIQUES USED FOR PREPARATION OF DT's

A) CONVENTIONAL TECHNIQUES: Various conventional techniques are available for preparation of DT's are-

1. FREEZE DRYING:

It is a process in which water is sublimated from the product after freezing. In this heat sensitive drugs and biological are dried at low temperature that allows removal of water by sublimation.

2. SUBLIMATION:

In these, inert solid ingredient that volatilized readily was added to other tablet ingredient and mixture is compressed into tablets. The volatile material was then removed by the process of sublimation.

3. SPRAY-DRYING:

It produces very fine and highly porous powder. Tablets prepared from spray drying disintegrate within 20 sec when immersed in an aqueous medium.

4. MOLDING:

In these, water soluble ingredients are used to prepare molded tablets so that tablet dissolves rapidly. Molded tablets are very less compact then compressed tablets and exhibit porous structure for rapid dissolution.

5. MASS-EXTRUSION:

It involves softening the active blends using the solvent mixture of water soluble PEG. The granules of bitter tasting drugs are coat by dried cylinders and hence masking their bitter taste.

6. DISINTEGRATES ADDITION:

Because of its easy implementation and cost effectiveness, it is a popular technique for formulating Dispersible Tablet. The basic principle involved is addition of super-disintegrants in optimum concentration.

7. DIRECT COMPRESSION:

It is the easiest way of manufacturing tablets. It consists of a limiting number of processing steps, conventional equipments and commonly available excipients. Also it requires few unit operations as compared to wet granulation.

B. PATENTED TECHNOLOGIES: Various patented technologies available for preparation of ODT's are-

1. FLASHTAB TECHNOLOGY:

In these, tablets consists active ingredient in the form of micro crystals. It is conventional tableting technology. Pro grapharm laboratories have patented the flash tab technology.

2. WOW TAB TECHNOLOGY:

It involves adequate dissolution rate and hardness .It is patented by "Yamanouchi Pharmaceuticals Co". Wow means without water.

3. FLASH DOSE TECHNOLOGY:

It requires greater surface area for dissolution. Flash dose tablets consist of self binding shear form matrix termed as "floss". It has been patented by "Fuisz".

4. DURASOLV TECHNOLOGY:

It is a patented technology of "CIMA" labs. It consists of drug, fillers and lubricant. It requires low amount of active ingredient.

5. ZYDIS TECHNOLOGY:

It involves quick dissolution, increased bioavailability and self-preserving. It involves softening the active blends using the mixture of methanol and polyethylene glycol.

6. ORASOLV TECHNOLOGY:

It is patented technology of "CIMA" labs. It involves quick dissolution and taste masking of active ingredient.

2. LITERATURE REVIEW

AROHI VALERA. *et.al,* [11] The present work is aimed to develop a stable formulation of preferred combination of two antibiotics -Amoxicillin and Clavulanic acid to overcome packaging instability resulting in to swelling of blister pack due to their interaction causing gas generation. Amoxicillin and Clavulanic acid dispersible tablets were prepared by dry granulation method using different superdisintegrants i.e. Croscarmellose, Crospovidone and Sodium Starch Glycolate. 15°C temperature and 20%RH humidity were throughout maintained. Aspartame as a sweetener and pineapple flavor were used to increase palatability. The prepared tablets were evaluated for hardness, friability, Disintegration time and Wetting time and in vitro drug release. Analytical estimation was done by HPLC. Amoxicillin and Clavulanic acid dispersible tablets were found to be of good quality fulfilling all the requirements for tablets. The results indicated that concentration of Crospovidone, Croscarmellose sodium, Sodium starch glycolate significantly affected. Croscarmellose Sodium showed least friability, disintegration time as compared to batches prepared from Sodium starch glycolate and Crospovidone Amoxicillin and Clavulanic acid dispersible tablets were successfully formulated by dry granulation technique with improved patient compliance & immediate onset of action.

ANAB FATIMA SHEIKH, *et.al,* [12] The combination of amoxicillin and clavulanic acid is a widely used oral combination of antibiotic consisting of semisynthetic amino penicillin amoxicillin and a beta-lactamase inhibitor i.e. clavulanate potassium (potassium salt of clavulanic acid). A simple, rapid, and cost effective reverse phase high performance liquid chromatography method has been developed with greater precision and accuracy using Hibar-Purospher star reverse phase(RP-18e) column(4.6 x 250 mm, 5µm) for simultaneous determination of

amoxicillin trihydrate and clavulanate potassium in pharmaceutical formulations. The separation was achieved in isocratic mode using buffer-methanol in the ratio of 90:10 v/v with pH 3 (adjusted with O-phosphoric acid) as mobile phase at flow rate of 1.3 ml/min. The detection was made at 235 nm. The retention time of clavulanate potassium and amoxicillin trihydrate were 4.7 and 10.0 minutes respectively. The limit of detection was 0.015 µg/ml for amoxicillin and 0.12 µg/ml for clavulanate potassium.

GAUTHAM KUMAR, *et.al*,[13]: In present study , the fast dissolving tablets of Amoxicillin Trihydrate were prepared by direct compression technique using microcrystalline cellulose (MCC) as direct compressible diluents. Sodium Starch Glycolate(SSG) and croscarmellose sodium(CCS) used as synthetic disintegrants. The Swelling indices of the superdisintegrants were also compared. Among both the superdisintegrants croscarmellose sodium shows the highest swelling index. Theblends showed satisfactorily flow properties. Eight formulation were prepared using different concentrations of superdisintegrants and were investigated for their effect on the disintegration time and dissolution rate of the tablets. Tablets were also evaluated for weight variation, hardness, thickness friability and drug content. All the tablets exhibited acceptable pharmaco-technical properties. Tablets prepared with the blend of CCS(60mg) exhibited quicker disintegration. According to the present study, it was found that tablets of batch F8 (Blend containing CCS 60mg) showed better disintegrating property as well as % drug release (99.78% within 25 min) than the most widely used synthetic disintegrants like SSG in the formulation of FDTS.

SAURABH SHARMA. *et.al,* **(14)** Orodispersible tablets emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and peadetrics because of pshycological change s associated with the group of patients. Lornoxicam is a non-steroidal anti inflammatory drug with extremely potent anti-inflammatory and analgesic activity. Lornoxicam shows bitter taste and distinct pH-dependent solubility characterized by very poor solubility in acidic condition present in the stomach. Therefore in present study, Lornoxicam taste masked orodispersible tablet was prepared by direct compression method and optimized the effect of sodium starch glycolate as superdisintegrant and camphor as sublimizing agent on disintegration of tablet with the help of surface response plot, counter plot, Box-Cox plot for power

transformation selected factorial method design for analysis of variance were calculated by using 32 Full Factorial design –Expert 8.0.7.1 Trial versions. Orodispersible tablet batches were prepared and evaluated for pre-compression parameters, post compression parameters and then characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier transform infrared (FTIR) and in vitro release study of all batches from F1-F8 was carried out in Ph 1.2 at 37ºC + 0.5 °C and shows maximum drug release in 105 min.

NWOKOYE PEACE, *et.al*' [(15)] Oral suspensions of antibiotics are mainly available as dry powders for reconstitution. Many reconstituted antibiotic suspension is to be kept refrigerated in order to get the optimal benefit from the drug. However, many patients do not keep to the specified storage conditions for different reasons like no refrigerator and irregular power supply that may result in various degrees of degradation of the product. Pharmacists are therefore challenged on how to counsel patients when there is no refrigeration or erratic power supply for refrigeration. This study investigated stability of amoxicillin-clavulanate potassium suspension in simulated in-home conditions of erratic power supply and no refrigeration. Amoxicilin clavulanate suspensions were reconstituted and stored in three different in-home storage conditions with temperature ranging between 5-29°C over a period of 10 days. Samples from the suspension were assayed using a validated HPLC method. Percentage concentrations of amoxicillin-clavulanate potassium were over 90% up to fifth day, degradation was extensive by seventh day with amoxicillin concentration falling below 80% in two conditions while clavulanate had values less than 70% in all the three conditions. Reconstituted amoxicillin clavunate potassium stored at room temperature (27-29°C) is stable for five days; use of reconstituted suspension that was not properly refrigerated after the fifth day should be discouraged.

MATHEW EBIN P SOVICHAN, *et.al*' [(16)] The objective of this work was to develop a formulation of Amoxicillin trihydrate dispersible tablets of 320mg in a low production value, using cheap Amoxicillin trihydrate raw materials available in the market, with direct compression or wet granulation method. Amoxicillin trihydrate is a semisynthetic antibiotic, an analogue of Ampicillin with a broad spectrum of bactericidal activity against gram +ve and gram ve organism. Dispersible tablets are uncoated or film coated tablets intended to be dispersed in water before administration

giving a homogeneous dispersion. The WHO prefers dispersible dosage form for the elderly and paediatric patients due to its ease in the administration. Amoxicillin trihydrate dispersible tablet was manufactured with the different disintegrants such as maize starch, crospovidone, croscarmellose, sodium starch glycolate, croscarmellose. The powder blend was evaluated for angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. After compression the tablets were subjected to weight variation, %drug content, buoyancy studies and in-vitro release studies. The wet granulation was excluded from the formulation due to its high cost if production, direct compression was selected due to its low cost and ease of production. The optimized formulation F10 had showed 99.11% of drug release in 40 min and disintegration of tablet was 25 seconds. The result of FTIR analysis of pure drug alone and drug with excipients there was not showed any physical and chemical interaction. F10 had undergone DTA, which shows the thermal stability of the formulation. The stability studies of optimized formulation F10 at 30 C / 65%RH, 40 C / 75%RH did not show any change in tested parameters and release.

V.KALVIMOORTHI, *et.al,* [17] The antibiotics are available in many formulations in the market like solid dosage forms, liquid dosage forms, parental preparations etc. Amoxicillin clavulanate potassium acting as an antibiotic used in the treatment of patients with acquired pneumonia or acute bacterial sinusitis due to confirmed or suspected beta lactamase pathogens. It is an analog derived from the basic penicillin nucleus, 6-aminopencillanic acid. Totally nine formulations were made with different concentrations of coating polymers such as ethyl cellulose, hypromellose, opadry white and other ingredients were used in the same concentrations. Amoxicillin clavunate potassium tablets (cores) were prepared by direct compression method and coating of polymer to the tablets was done using pan coating. Tablets were evaluated for thickness, weight variation, hardness, friability, in – vitro dispersion time, disintegration time and dissolution study. Tablets shows uniform weight, hardness and friability data indicates good mechanical resistance of the tablets. Prepared tablets were evaluated for the disintegration test; all the tablets were disintegrated between 12 to 14th minute. The formulation F6 shows best disintegration time. The prepared formulations (F1 to F9) were subjected for dissolution studies. Among all the

formulations F6 shows better dissolution profile of 104.7% and 104.2 % drug release at 30th minute. This value is better when compared even with marketed formulation.

SELLAPPAN VELMURUGAN. *et.al,* [18] In this present work Orodispersible tablet of Stavudine was designed with a view to enhance the patient compliance. Oral dispersible tablet of Stavudine were prepared by direct compression method after incorporating Superdisintegrants sodium Starch glycol ate, Crospovidone, Croscarmellose, and kollidon CLM. Twenty formulation having Superdisintegrants at different concentration (5, 10, 15, 20%) level were Prepared. The prepared batches of tablets were evaluated for Tablet weight variation, content uniformity, hardness and friability. Effects of Superdisintegrants on wetting time, dispersion time, and in vitro release also have been studied. Tablet containing Kollidon CL M (20%) showed excellent in vitro dispersion time and drug release as compared to other formulations. After the color and flavor optimization study formulations F18 shows short dispersion time (18sec) with maximum drug release in10 min. FTIR & DSC results showed no evidence of interaction between the drug and Superdisintegrants.It is concluded that Oro dispersible Stavudine tablets could be prepared by direct compression method using kollidon CL M superdisintegrants.

REETA RANI THAKUR. *et.al,* [19] Oral route is the most convenient route for drug administration due to the highest component of compliance mainly the pediatrics and geriatrics. It is regarded as the most economical and safest method of drug delivery. Formulation of a orally disintegrating dosage form is beneficial for patients suffering from motion sickness, repeated emesis, mental disorder and dysphasia because they cannot swallow large quantity of water and it is easy to administer. The unique property of orally disintegrating dosage form is that they are readily disintegrating and dissolves in saliva and avoids the requirement of water which is the major benefit over conventional dosage form. Further, drug having the satisfactory absorption from the oral mucosa can be formulated in such type of dosage form.. This article includes requirement for orally disintegrating tablets, orally disintegrating films, chewing gums, oral wafers and buccal patches ,their advantages, disadvantages, challenges in formulation ,patented technologies, various technologies developed for formulated orally disintegrating dosage form ,super disintegrating agents in the formulation, evaluation method and various marketed products.

SHARMA ANUP TUKARAMJI, *et.al*[20], The primary aim of the present work was to formulate and evaluate taste masked dispersible tablets of chloroquine phosphate, an antimalarial drug using ion exchange resins like INDION 294 and TULSION 339 as a taste masking agents and superdisintegrating agents like crospovidone and sodium starch Glycolate in different concentrations. Characterization of drug was done by melting point determination, FTIR spectroscopy and UV Spectroscopy. Drug-resin complexes were prepared by Batch method using the resins in different ratios. Drug loading study was carried out at different PH. Indion 294 show highest release and taste masking ability by determining threshold bitterness concentration of the drug. The complexes were characterised by drug content, FTIR and DSC studies. Powder blends were prepared and evaluated for various physical properties. Dispersible tablets of drug-resin complex (DRC) were prepared by wet granulation method using crospovidone and sodium starch Glycolate in different concentration as superdisintegrants. Tablets were evaluated for thickness, hardness, friability, uniformity of weight, dispersion time, uniformity of dispersion, disintegration time, wetting time, wetting volume, content of active ingredient and dissolution studies. All the formulations show the evaluated parameters within the acceptable limit for dispersible tablets.

REKHA RAO, *et.al,* [21] Amoxicillin though originally introduced in the early 1970's for oral use in U.K., has found a gradually regular place as broad spectrum antibacterial to treat the infections of various diseases. Amoxicillin has been found to be more effective against gram positive than gram negative microorganisms and demonstrated greater efficacy to penicillin and penicillin V. Moreover, it has been found comparable to other antibiotics, e.g. Ampicillin, Azithromycin, Clarithromycin, Cefuroxime And Doxycycline in treatment of various infections/ diseases. In the past decade, amoxicillin has been reported to be useful in the management of many indications and is used to treat infections of the middle ear (otitis media) , tonsils (tonsillitis & tonsillo pharyngitis), throat, larynx (laryngitis) , pharynx (pharyngitis), bronchi (bronchitis), lungs (pneumonia), urinary tract (UTI), skin and to treat gonorrhoea. Recent studies suggested that it can be used as prophylaxis against bacterial endocarditis, in patients with prosthetic joint replacements and in dentistry.

The renewed interest of the molecule has prompted a review of the salient features of the drug.

R. BELMAR-LIBERATO, ***et.al,*** [22] In the recent past years, important efforts towards the prudent use of antimicrobials have been made in order to optimize antibacterial use, and maximize therapeutic effect while minimizing the development of resistance. Knowledge on the occurrence of resistance in bacteria could help in improving the clinical success of therapeutic decisions. Since the discovery of amoxicillin, this drug has been extensively used throughout the world in veterinary medicine, alone and also in combination with Clavulanic acid. This paper provides information regarding the current situation of resistance to Amoxicillin (And Amoxicillin-Clavulanic Acid) in animals in Europe. Most data comes from food-animal species, mainly from several national monitoring programmes of antimicrobial resistance, and information on companion animals is also available.

D.INDHUMATHI, *et.al,* [23] Mouth dissolving tablet offers a solution for pediatrics, geriatrics; psychiatric or mentally ill people and those have difficulty in swallowing tablets/capsules resulting in improved patient compliance. The aim is to formulate fifteen formulations of fast dissolving tablet of Fluoxetine using different superdisintegrants (Sodium Starch Glycolate, Croscarmellose, Crospovidone Pregelatinized starch) by wet granulation method and the tablets were evaluated for various physiochemical properties and found to be within the permissible limit. In vitro dissolution studies show the release is in the following order of disintegrants: Crospovidone >Pregelatinized starch > Croscarmellose > Sodium Starch Glycolate. From the study it has been found and concluded, crospovidone at a concentration of 5% w/w **(**F-XII) shows maximum in-vitro dissolution profile, this is also confirmed by In vivo pharmacokinetic studies, and hence it emerged as the overall best formulation hence suitable for preparing fast dissolving tablet of Fluoxetine.

KAMAL SAROHA. *et.al,* [24] The desire of improved palatability in orally administered products has prompted the development of numerous formulations with improved performance and acceptability. Orally Disintegrating tablets (ODTs) have received ever-increasing demand during the last few decades, and the field has become a rapidly growing area in the pharmaceutical industry. The unique property of mouth dissolving tablet is that they are rapidly disintegrating and/or dissolving and release the drug as soon as they come in contact with saliva, thus obviate the requirement of water during administration. This article reviews the earlier applications and methodologies of taste masking and also emphasize on the recent developments and approaches of bitterness reduction for orally used pharmaceuticals. Apart from the conventional methods of fabrication, this review also provides the detailed concept of some unique patents; technologies developed and marketed formulations of Mouth Dissolving Tablets (MDTs).

SUHAS KAKADE. *et.al,* [25] There is an increasing demand for more patient compliant dosage form and a novel method is the development orally disintegrating tablets which dissolve or disintegrates instantly on the patient tongue or buccal mucosa. It is suited for tablets undergoing high first pass metabolism and is used for improving bioavailability with reducing dosing frequency to minimize side effect and make it more cost effective. Sertraline is practically slightly soluble in water, its rapidly and extensively absorbed after oral administration, the absolute bioavailability is only approximately 44% due to extensive hepatic first pass metabolism. Hence the main objective of the study was to formulate orally disintegrating tablets of Sertraline to achieve a better dissolution rate and further improving the bioavailability of the drug. Orally disintegrating tablets prepared by direct compression and using super disintegrants like Crospovidone, Croscarmellose Sodium and Sodium Starch Glycolate Designate, designated as three different groups of formulation (A, B and C) respectively were prepared and evaluated for the pre compression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, drug content, disintegration time and in-vitro dissolution profile and found satisfactory. Among the three groups, group (C) containing Crospovidone emerged as the best formulation and showed maximum

dissolution rate with 98.49% drug release in 15 min. All three groups of formulations released the drug at faster rates than that of marketed conventional tablets of Sertraline.

M.V.KUMUDHAVALLI, *et.al*,[26] A rapid, sensitive and specific RP-HPLC method involving UV detection was developed and validated for determination and quantification of Amoxicillin and Potassium Clavulanate. Chromatography was carried out on a pre-packed Hypersil C18 (5µm, 250x4.6mm) column using filtered and degassed mixture of Phosphate buffer: Methanol (95:05) as mobile phase at a flow rate of 1.0ml/min and effluent was monitored at 220nm. The method was validated in terms of linearity, precision, accuracy, and specificity, limit of quantification and limit of detection. The assay was linear over the concentration range of Amoxicillin and Potassium Clavulanate was 25mcg-200mcg/ml and 5mcg to 40mcg/ml respectively. Accuracy of the method was determined through recovery studies by adding known quantities of standard drug to the pre analyzed test solution and was found to be 97.70%- 103.00% and 96.80%-102.01% within precision RSD of 0.432 and 0.988 for Amoxicillin and Potassium Clavulanate respectively. The system suitability parameters such as theoretical plates and tailing factor were found to be 3189.33, 1.225 and 7852.83, 1.08 respectively for Amoxicillin and Potassium Clavulanate. The method does require only 15 minutes as run time for analysis which prove the adoptability of the method for the routine quality control of the drug.

ILMA NUGRAHANI, *et.al*, [27] The aim of this research was to evaluate solid state interaction between Amoxicillin Trihydrate And Potassium Clavulanate. The interaction was observed by Differential Scanning Calorimeter (DSC), X-Ray Powder Diffractometer (XRPD), Fourier Transforms Infra Red (FTIR) and Scanning Electron Microscope (SEM). Mixtures of Amoxicillin Trihydrate And Potassium Clavulanate were prepared in molar ratios of 0:10, 1:9, 2:8, 3:7, 4:6; 5:5; 6:4; 7:3; 8:2; 9:1; 10:0 and analyzed by DSC to obtain the thermal profile and a phase diagram. From this phase diagram, the molar ratio point of interaction was determined. XRPD analysis was performed to check the type of physical interaction occurred and FTIR was conducted

to predict the chemical mechanism of interaction. Thermo profile obtained by DSC analysis of the binary systems showed that endothermic curves of molar fractions of 1:9—5:5 overlapped at 201°C. On the other hand, the diffractogram obtained from Powder X-Ray analysis was very similar with that of Amoxicillin Trihydrate alone. FTIR spectrum of binary system in the molar ratio of 5:5 showed the loss of hydrate spectra from Amoxicillin Trihydrate. We conclude that the interaction involved strong hydrogen bonding between hydrates of Amoxicillin With Potassium Clavulanate which produced a co-crystal system like a solid dispersion.

3. AIM AND OBJECTIVE OF THE STUDY

The aim of the research work is to formulate and evaluate of Amoxicillin and potassium clavulanate dispersible tablet.

The oral route is the most frequently used route for drug administration. Oral dosage forms are usually for systemic effects resulting from drug absorption through the various mucosa of the gastrointestinal tract. The parenteral route of administration is an important in mandatory condition; otherwise it is probable that at least 90% of all drugs used to produce systemic effects are administered by the oral route.

The drugs that are administered orally, solid dosage forms represent the preferred class of product. The reasons for this preference are as follows:

- Tablets and capsules represent unit dosage forms in which one unit dose of the drug has been accurately placed, whereas in liquid oral dosage forms measurements are typically in error when the drug is administered by the patient.

- Liquid oral dosage forms are much more expensive to ship and breakage or leakage during shipment is a more serious problem than with solid oral dosage forms.

- Liquids are less portable and require much more space.

- Drugs are in general less stable in liquid form than in a dry state and expiration dates tend to be shorter.

Compared with other routes, the advantages of the oral solid dosage forms are as follows:

- Simplest
- Most compliance
- Safety.

The disadvantages include relatively slow onset of action as compared to parenterals, difficult to swallow for kids, terminally ill and geriatric patients and destruction of certain drugs by the enzymes and the secretion of the GIT. e.g.: Insulin.

The most popular oral dosage forms are tablets, capsules, suspensions, solutions, emulsions. The other dosage forms that are administered orally are powders, granules, syrups and elixirs. Based on the above advantages, the selected antibiotic drug is developed as tablets for oral administration.

Fast Dissolving Drug Delivery System emerged from the desire to provide patient with conventional mean of taking their medication.

Difficulty in swallowing is a common problem of all age groups, especially elderly and paediatrics, because of physiological changes associated with these groups of patients other categories that experience problems using conventional oral dosage forms includes are the mentally ill, uncooperative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack or coughing. Sometimes it may be difficult to swallow conventional products due to unavailability of water.

These problems led to the development of novel type of solid oral dosage form called “dispersible Tablets”. This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva.

The growing importance of mouth dissolving tablet was underlined recently when European Pharmacopoeia adopted the term “Oro dispersible Tablet” as a tablet that to be placed in the mouth where it disperses rapidly before swallowing.

The main criteria for mouth disintegrating (dissolving) tablet is to disintegrate or dissolve rapidly in oral cavity with saliva in 15 to 60 seconds, without need of water and should have pleasant mouth feel . Mouth dissolving tablets are also known as fast dissolving tablet; melt in mouth tablet, rapiment, and porous tablet, dispersible tablet. The uses of amoxicillin and clavulanic acid dispersible tablet are used to treat certain infections caused by bacteria including infections of the ears, lungs, sinus, skin, and urinary tract.

OBJECTIVE OF THE STUDY

The aim of the study is to formulate and evaluate of Amoxicillin And Potassium Clavulanate dispersible tablets.

- The aim is to formulate formulations of fast dissolving tablet of amoxicillin and potassium clavulanate using different disintegrants (Sodium Starch Glycolate, Croscarmellose, Crospovidone, Maize starch) by direct compression technique.
- The evaluation of powder blend like Angle of Repose, Bulk Density, Tap density, Hausner ratio, Compressibility index is studied.
- Tablets are evaluated for various physiochemical properties.
- The Drug and Excipients Compatibility is studied using FTIR spectral studies.
- The effect of disintegrants on disintegration and dissolution of amoxicillin and potassium clavulanate dispersible tablet is also studied extensively.
- Accelerated stability studies are to be carried out for the final Amoxicillin And Potassium Clavulanate tablet as per ICH guidelines.

4. PLAN OF WORK

The present work is carried out formulate and evaluate of Amoxicillin & Potassium Clavulanate dispersible tablets by using different disintegrants.

4.1 PREFORMULATION STUDIES

The drug and excipients compatibility studies is done by using FTIR studies by taking FTIR for Amoxicillin, Potassium Clavulanate, and Amoxicillin And Potassium Clavulanate and optimized formulation.

4.2 FORMULATION DEVELOPMENT

Prototype formulations is developed using various disintegrants

4.3. POWDER BLEND CHARACTERIZATIONS

- Angle of repose
- Bulk density
- Tapped density
- Carr's Index
- Percentage compressibility
- Hausner ratio

4.4. COMPRESSION PARAMETERS

4.5. EVALUATION OF TABLETS

- Weight variation
- Hardness of the tablet
- Friability
- Thickness
- Disintegration test
- Drug content uniformity
- Fineness of dispersion test.

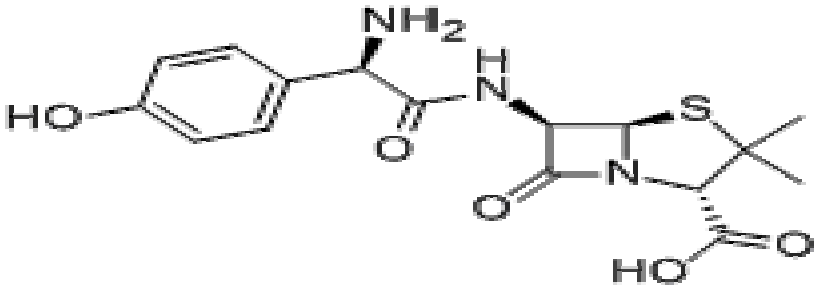
4.6. IN VITRO RELEASE STUDIES

4.7. STABILITY STUDIES

5. DRUG PROFILE

5.1 AMOXICILLIN [28, 29]

STRUCTURE



IUPAC NAME	(2S,5R,6R)-6-[(2R)-2-amino-2-(4-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo

DESCRIPTION

A broad-spectrum semi synthetic antibiotic similar to ampicillin except that its resistance to gastric acid permits higher serum levels with oral administration. Amoxicillin is commonly prescribed with clauvanic acid (a beta lactamase inhibitor) as it is susceptible to beta-lacatamase degradation

SOLUBILITY

Slightly soluble in water, very slightly soluble in ethanol (96.0%) practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides

Table No. 1

CHEMICAL DATA OF AMOXICILLIN

Formula	$C_{16}H_{19}N_3O_5S.3H_20$
Molecular mass	419.5g/mol

Table No .2

PHARMACOKINETIC DATA OF AMOXICILLIN

Bioavailability	95 Oral%
Protein binding	20%
Metabolism	Hepatic Metabolism
Half-life	61.3 minutes
Excretion	Most of the amoxicillin is excreted unchanged in the urine; its excretion can be delayed by concurrent administration of probenecid

INDICATION

For the treatment of infections of the ear, nose, and throat, the genitourinary tract, the skin and skin structure, and the lower respiratory tract due to susceptible (only b-lactamase-negative) strains of *Streptococcus* spp. (a- and b-hemolytic strains only), *S. pneumoniae*, *Staphylococcus* spp., *H. influenzae*, *E. coli*, *P. mirabilis*, or *E. faecalis*. Also for the treatment of acute, uncomplicated gonorrhea (ano-genital and urethral infections) due to *N. gonorrhoeae* (males and females).

PHARMACODYNAMICS

Amoxicillin is a moderate-spectrum antibiotic active against a wide range of Gram-positive, and a limited range of Gram-negative organisms. It is usually the drug of choice within the class because it is better absorbed, following oral administration, than other beta-lactam antibiotics. Amoxicillin is susceptible to degradation by β-lactamase-producing bacteria, and so may be given with clavulanic acid to increase its susceptability. The incidence of β-lactamase-producing resistant organisms, including *E. coli*, appears to be increasing. Amoxicillin is sometimes combined with clavulanic acid, a β-lactamase inhibitor, to increase the spectrum of action against Gram-negative organisms, and to overcome bacterial antibiotic resistance mediated through β-lactamase production.

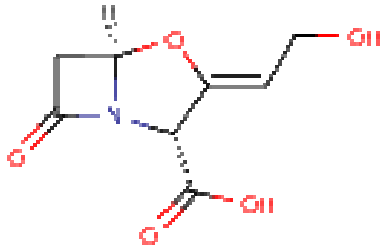
MECHANISM OF ACTION

Amoxicillin binds to penicillin-binding protein 1A (PBP-1A) located inside the bacterial cell well. Penicillins acylate the penicillin-sensitive transpeptidase C-terminal domain by opening the lactam ring. This inactivation of the enzyme prevents the

formation of a cross-link of two linear peptide glycan strands, inhibiting the third and last stage of bacterial cell wall synthesis. Cell lysis is then mediated by bacterial cell wall autolytic enzymes such as autolysins; it is possible that amoxicillin interferes with an autolysin inhibitor.

5.2 POTASSIUM CLAVULANATE [30]

STRUCTURE



IUPAC NAME	(2R,3Z,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylic acid

DESCRIPTION

A white or almost white, crystalline powder

SOLUBILITY

Slightly soluble in water, very slightly soluble in ethanol (96.0%) practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides

Table No.3

CHEMICAL DATA OF POTASSIUM CLAVULANATE

Formula	$C_8H_9NO_5$
Molecular mass	199.16

Table No. 4

PHARMACOKINETIC DATA POTASSIUM CLAVULANATE

Bioavailability	75%
Protein binding	Low (22 to 30%)
Metabolism	Hepatic Metabolism
Half-life	1 Hour
Excretion	Renal (30-40%)

INDICATION

For use with Amoxicillin, clavulanic acid is suitable for the treatment of infections with *Staph. aureus* and *Bacteroides fragilis*, or with beta-lactamase producing *H. influenza* and *E. coli*.

PHARMACODYNAMICS

Clavulanic acid, produced by the fermentation of *Streptomyces Clavuligerus*, is a beta-lactam structurally related to the penicillins. Clavulanic acid is used in conjunction with amoxicillin for the treatment of bronchitis and urinary tract, skin, and soft tissue infections caused by beta-lactamase producing organisms.

MECHANISM OF ACTION

Clavulanic acid competitively and irreversibly inhibits a wide variety of beta-lactamases, commonly found in microorganisms resistant to penicillins and cephalosporins. Binding and irreversibly inhibiting the beta-lactamase results in a resaturation of the antimicrobial activity of beta-lactam antibiotics against lactamase-secreting-resistant bacteria. By inactivating beta-lactamase (the bacterial resistance protein), the accompanying penicillin/cephalosporin drugs may be made more potent as well.

6. EXCIPIENT PROFILE [31, 32, 33]

6.1 AVICEL PH 101

1. NONPROPRIETARY NAMES

BP : Microcrystalline Cellulose

JP : Microcrystalline Cellulose

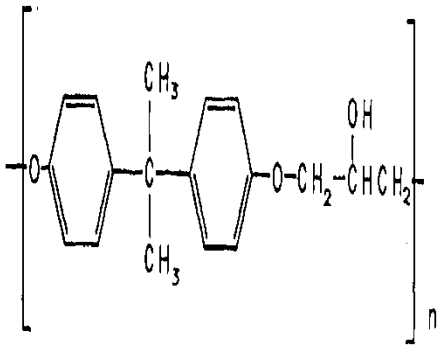
Ph Eur : Cellulose, Microcrystalline

USP-NF : Microcrystalline Cellulose

2. CHEMICAL NAME AND CAS REGISTRY NUMBER

Cellulose [9004-34-6]

3. STRUCTURE FORMULA



4. EMPIRICAL FORMULA AND MOLECULAR WEIGHT

$(C_6H_{10}O_5)_n$ _36 000

5. FUNCTIONAL CATEGORY

Adsorbent, suspending agent, tablet and capsule diluents, tablet disintegrant.

6. TYPICAL PROPERTIES

Description

Microcrystalline cellulose is a purified, partially de polymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Angle of Repose	**:**	498 for Ceolus KG; 34.48 For Emcocel 90M.
Compression Pressure		
Density (True)	:	1.512–1.668 g/cm^3

Melting point Chars at 260–270ºC.

Moisture content typically less than 5% w/w.

7. APPLICATION IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

8. STABILITY AND STORAGE CONDITIONS

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

9. INCOMPATIBILITIES

Microcrystalline cellulose is incompatible with strong oxidizing agents.

6.2 MAIZE STARCH

1. NONPROPRIETARY NAMES

BP : Maize starch

Potato starch

Rice Starch

Tapioca Starch

Wheat Starch

JP : Corn Starch

Potato Starch

Rice Starch

Wheat Starch

Ph Eur : Maize Starch

Pea Starch

Potato Starch

Rice Starch

Wheat Starch

USP-NF: Corn Starch

Potato Starch

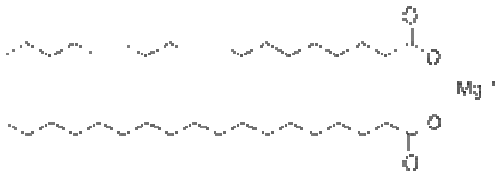
Tapioca Starch

Wheat Starch

2. CHEMICAL NAME AND CAS REGISTRY NUMBER

Starch [9005-25-8]

3. STRUCTURE FORMULA



4. EMPRICAL FORMULA AND MOLECULAR WEIGHT

$(C_6H_{10}O_5)$ n where n = 300–1000.

5. FUNCTIONAL CATEGORY

Tablet and capsule diluent; tablet and capsule disintegrant; tablet binder; thickening agent.

6. TYPICAL PROPERTIES

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.

Density (True): 1.478g/cm^3

Moisture Content

All starches are hygroscopic and absorb atmospheric moisture to reach the equilibrium humidity. The approximate equilibrium moisture is characteristic for each starch.

At 50% relative humidity:

12% for corn starch;

14% for pea starch,

18% for potato starch;

14% for rice starch;

13% for wheat starch.

Excessively dried starches with humidity lower than the equilibrium humidity are commercially available. These products should be stored in thermetically sealed containers to maintain their low moisture content.

7. APPLICATION IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

Starch is a versatile excipient used primarily in oral solid-dosage formulations where it is utilized as a binder, diluents, 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 quantities of 3–10% w/w can act as an anti adherent and lubricant in tabletting and capsule filling.

In tablet formulations, freshly prepared starch paste is used at a concentration of 3–20% w/w (usually 5–10%, depending on the starch type) as a binder for wet granulation. The required binder ratio should be determined by optimization studies, using parameters such as tablet friability and hardness, disintegration time, and drug dissolution rate.

Starch is one of the most commonly used tablet disintegrants at concentrations of 3–25% w/w; a typical concentration is 15%.When using starch, a prior granulation step is required in most case to avoid problems with insufficient flow and segregation. A starch–lactose compound has been introduced enabling the use of granular starch in direct compression, improving the tableting process and the disintegration time of the tablets. However, starch that is not pre gelatinized does not compress well and tends to increase tablet friability and capping if used in high concentrations Starch, particularly the fine powders of rice and wheat starch, is also used in topical preparations for its absorbency of liquids. Starch paste is used in ointment formulations, usually in the presence of higher ratios of glycerin. Starch has been investigated as an excipient in novel drug delivery systems for nasal, and other site-specific delivery systems. The retro gradation of starch can be used to modify the surface properties of drug particles. Starches are useful carriers for amorphous drug preparations, such as pellets with immediate or delayed drug release obtained, for example, by melt extrusion, and they can improve the bioavailability of poorly soluble drugs.

Starch, particularly rice starch, has also been used in the treatment of children's diarrheal diseases. Specific starch varieties with high amylase content (resistant starches) are used as insoluble fiber in clinical nutrition, and also for colon-targeting applications. Due to their very high gelatinization temperature, these starches are used in extrusion/spheronization processes.

Starches with high amyl pectin content (waxy starches) are used as the starting material for the synthesis of hydroxyl ethyl starch, a plasma volume expander. Native starches conforming to pharmacopeia specifications are used as the raw materials for

the production of starch-based excipients and active pharmaceutical ingredients, frequently covered with their own pharmacopeial monographs.

8. STABILITY AND STORAGE CONDITIONS

Dry starch is stable if protected from high humidity. Starch is considered to be chemically and microbiologically inert under normal storage conditions. Starch solutions or pastes are physically unstable and are readily metabolized by microorganisms; they should therefore be freshly prepared when used for wet granulation. Starch should be stored in an airtight container in a cool, dry place.

9. INCOMPATIBILITIES

Starch is incompatible with strongly oxidizing substances. Coloured inclusion compounds are formed with iodine.

6.3. SODIUM STARCH GLYCOLATE

1. NONPROPRIETARY NAMES

BP : Sodium Starch Glycolate

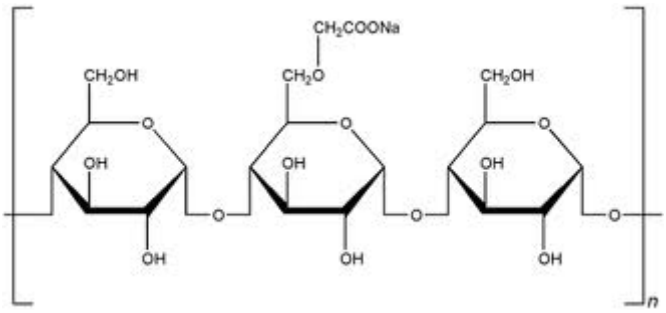
PhEur : Sodium Starch Glycolate

USP-NF : Sodium Starch Glycolate

2. CHEMICAL NAME AND CAS REGISTRY NUMBER

Sodium carboxy methyl starch [9063-38-1]

3. STRUCTURE FORMULA



4. EMPIRICAL FORMULA AND MOLECULAR WEIGHT

The USP32–NF27 describes two types of sodium starch glycolate, Type A and Type B, and states that sodium starch glycolate is the sodium salt of a carboxy methyl ether of starch or of a crosslinked carboxy methyl ether of starch.

The Ph Eur 6.0 describes three types of material: Type A and TypeB are described as the sodium salt of a cross linked partly O carboxy methylated potato starch. Type C is described as the sodium salt of a partly O-carboxy methylated starch, cross linked by physical dehydration. Types A, B, and C are differentiated by their pH, sodium, and sodium chloride content.

The Ph Eur and USP–NF monographs have been harmonized for Type A and Type B variants.

Sodium starch glycol ate may be characterized by the degree of substitution and cross linking. The molecular weight is typically 5 _10^5–1_10^6.

5. FUNCTIONAL CATEGORY

Tablet and capsule disintegrant

6. TYPICAL PROPERTIES

Description

Sodium starch glycol ate is a white or almost white free-flowing very hygroscopic powder. The Ph Eur 6.0 states that when examined under a microscope it is seen to consist of: granules, irregularly shaped, ovoid or pear-shaped, 30–100 mm in size, or rounded, 10–35 mm in size; compound granules consisting of 2–4 component so occur occasionally; the granules have an eccentric hilum and clearly visible concentric striations. Between crossed nicol prisms, the granules show a distinct black cross intersecting at the hilum; small crystals are visible at the surface of the granules. The granules show considerable swelling in contact with water.

Density (bulk)

0.756 g/cm^3 for Glycolys;

0.81 g/cm^3 for Primojel;

0.67 g/cm^3 for Tablo.

Density (tapped)

0.945 g/cm3 for Glycolys;

0.98 g/cm^3 for Primojel;

0.83 g/cm^3 for Tablo.

Density (true)

1.56 g/cm^3 for Primojel;

1.49 g/cm^3 for Tablo.

Melting point does not melt, but chars at approximately 200ºC.

Particle size distribution 100% of particles less than 106 mm in size. Average particle size (d50) is 38mm and 42 mm for Primo jel by microscopy and sieving, respectively. Solubility Practically insoluble in methylene chloride. It gives a translucent suspension in water.

Specific surface area

0.24m^2/g for Glycolys;

0.185m^2/g for Primojel;

0.335m^2/g for Tablo.

7. APPLICATION IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time.

Sodium starch glycolate has also been investigated for use as a suspending vehicle.

8. STABILITY AND STORAGE CONDITIONS

Tablets prepared with sodium starch glycol ate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

The physical properties of sodium starch glycolate remain unchanged for up to 3 years if it is stored at moderate temperatures and humidity.

9. INCOMPATIBILITIES

Sodium starch glycolate is incompatible with ascorbic acid

6.4. CROS POVIDONE

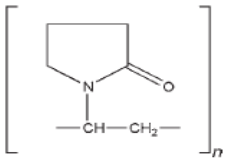
1. NONPROPRIETARY NAMES

- BP : CrosPovidone
- JP : CrosPovidone
- Ph Eur : CrosPovidone
- USP : Povidone

2. CHEMICAL NAME

1-Ethenyl-2-pyrrolidinone homo polymer

3. STRUCTURE FORMULA



4. EMPIRICAL FORMULA AND MOLECULAR WEIGHT

$(C_6H_9NO)_n$ 2500–3 000 000

5. FUNCTIONAL CATEGORY

Disintegrant, dissolution enhancer, suspending agent, tablet binder.

6. TYPICAL PROPERTIES

Description

Povidone occurs as a fine, white to creamy-white colored, odourless or almost odourless, hygroscopic powder.

Acidity/alkalinity pH = 3.0–7.

Density (bulk) : 0.29–0.39 g/cm^3

Density (tapped): 0.39–0.54 g/cm^3

Density (true) : 1.180 g/cm^3

Melting point : 150°C

Moisture content: Povidone is very hygroscopic, significant amounts of moisture being absorbed at low relative humidities.

Solubility : Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution

Flow ability : Free flowing

7. APPLICATIONS IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

- CrosPovidone is used in a variety of pharmaceutical formulations; it is primarily used in solid dosage forms.

- CrosPovidone is used as a solubilizer in oral and parenteral formulations, and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms.

8. STABILITY AND STORAGE CONDITIONS

CrosPovidone may be stored under ordinary conditions without undergoing decomposition or degradation. The powder is hygroscopic; it should be stored in an airtight container in a cool, dry place.

9. INCOMPATIBILITIES

Crospovidone is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals.

6.5. CROSCARMELLOSE SODIUM

1. NONPROPRIETARY NAMES

BP : Croscarmellose Sodium

JP : Croscarmellose Sodium

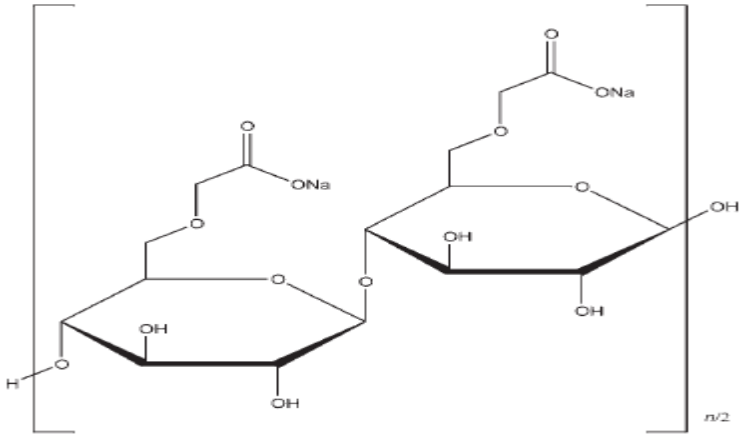
Ph Eur : Croscarmellose Sodium

USP-NF : Croscarmellose Sodium

2. CHEMICAL NAME

Cellulose, carboxy methyl ether, sodium salt

3. STRUCTURE FORMULA



4. EMPIRICAL FORMULA AND MOLECULAR WEIGHT

Croscarmellose sodium is a cross linked polymer of carboxy methyl cellulose sodium.

5. FUNCTIONAL CATEGORY

Tablet and capsule disintegrant.

6. TYPICAL PROPERTIES

Description

Croscarmellose sodium occurs as an odorless, white or grayish white powder.

Density (tapped): 0.819 g/cm^3 for Ac-Di-Sol

Density (true): 1.543 g/cm^3 for Ac-Di-Sol

to 4–8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

Specific surface area: 0.81–0.83m^2/g

7. APPLICATIONS IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules. In tablet formulations, croscarmellose sodium may be used both direct-compression and wet-granulation processes.

8. STABILITY AND STORAGE CONDITION

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

9. INCOMPATIBILITIES

Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as Aluminum, Mercury, And Zinc.

6.6 AEROSIL

1. NONPROPRIETARY NAMES

BP : Colloidal Anhydrous Silica

JP : Light Anhydrous Silicic Acid

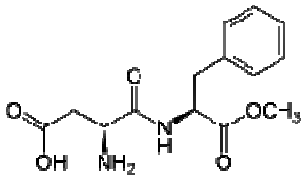
PhEur : Silica, Colloidal Anhydrous

USP-NF : Colloidal Silicon Dioxide

2. CHEMICAL NAME

Silica [7631-86-9]

2. STRUCTURE FORMULA



4. EMPIRICAL FORMULA AND MOLECULAR WEIGHT

SiO_2 60.08

5. FUNCTIONAL CATEGORY

Adsorbent**;** anti caking agent; emulsion stabilizer; glidant**;** suspending agent; tablet disintegrant; thermal stabilizer;

Viscosity-increasing agent.

6. TYPICAL PROPERTIES

Description

Colloidal silicon dioxide is sub microscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-colored, odorless, tasteless, amorphous powder.

Density (Bulk) : 0.029-0.042

Melting point : 1600ºC

Particle size distribution

Primary particle size is 7–16 nm. Aerosil forms loose agglomerates of 10–200 mm.

Refractive index: 1.46

Solubility

Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water. For Aerosil, solubility in water is 150 mg/L at 258C (pH 7).

Specific gravity: 2.2

7. APPLICATIONS IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling. Colloidal silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations. With other ingredients of similar refractive index, transparent gels may be formed. The degree of viscosity increase depends on the polarity of the liquid (polar liquids generally require a greater concentration of colloidal silicon dioxide than nonpolar liquids). Viscosity is largely independent of temperature. However, changes to the pH of a system may affect the viscosity. In aerosols, other than those for inhalation, colloidal silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles. Colloidal N silicon dioxide is also used as a tablet disintegrant and as an dispersing agent for liquids in powders. Colloidal silicon dioxide is frequently added to suppository formulations containing lipophilic excipients to increase viscosity, prevent sedimentation during molding, and decrease the release rate. Colloidal silicon dioxide is also used as an adsorbent during the preparation of wax microspheres; as a thickening agent for topical preparations; and has been used to aid the freeze-drying of nano capsules and Nanosphere suspensions.

8. STABILITY AND STORAGE CONDITION

Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a Ph 0–7.5, colloidal silicon

dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity increasing properties of colloidal silicon dioxide are reduced; and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates.(14) Colloidal silicon dioxide powder should be stored in a well-closed container.

9. INCOMPATIBILITIES

Incompatible with diethyl stilbestrol preparations.

6.7 ASPARTAME

1. NONPROPRIETARY NAMES

BP : Aspartame

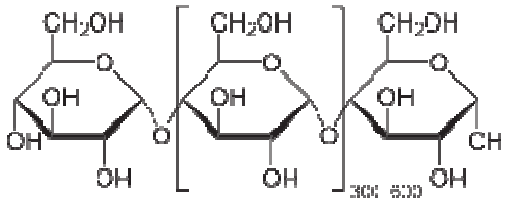
PhEur : Aspartame

USP-NF : Aspartame

2. CHEMICAL NAME

N-L-a-Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]

3. STRUCTURE FORMULA



4. EMPIRICAL FORMULA AND MOLECULAR WEIGHT

$C_{14}\ H_{18}N_2O_5$ 294.30

5. FUNCTIONAL CATEGORY

Sweetening agent

6. TYPICAL PROPERTIES

Description

Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

ACIDITY/ALKALINITY

pH = 4.5–6.0 (0.8% w/v aqueous solution)

BRITTLE FRACTURE INDEX 1.05

BONDING INDEX

0.8_102 (worst case)

2.3_102 (best case)

FLOWABILITY

44% (Carr compressibility index)

DENSITY (BULK)

0.5–0.7 g/cm^3 for granular grade;

0.2–0.4 g/cm^3 for powder grade;

0.17 g/cm^3 (Spectrum Quality Products).

DENSITY (TAPPED)

0.29 g/cm^3 (Spectrum Quality Products)

DENSITY (TRUE) 1.347 g/cm^3

Effective angle of internal friction 43.08

Melting point 246–247ºC

SOLUBILITY

Slightly soluble in ethanol (95%); sparingly soluble in water. At 208C the solubility is 1% w/v at the iso electric point (pH 5.2). Solubility increases at higher temperature and at more acidic pH, e.g., at pH 2 and 208C solubility is 10% w/v.

SPECIFIC ROTATION

22 =_2.38 in 1N HCl

7. APPLICATIONS IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power

is 180–200 times that of sucrose. Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal). However, in practice, the small quantity of aspartame consumed provides a minimal nutritive effect.

8. INCOMPATIBILITIES

Differential scanning calorimetry experiments with some directly compressible tablet excipients suggests that aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate. Reactions between aspartame and sugar alcohols are also known

6.8 STRAWBERRY FLAVOUR

1. NONPROPERIATARY NAMES

BP : Strawberry flavor

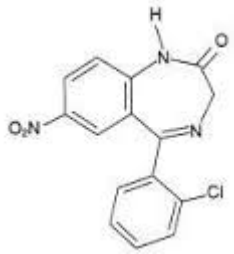
PhEur : Strawberry flavor

USP-NF : Strawberry flavour

2. CHEMICAL NAME

(E)-2-pentenal butyric acid

3. STRUCTURAL FORMULA



4. FUNCTIONAL CATEGORY

Flavouring agent.

5. APPLICATION IN PHARMACEUTICAL FIELD

It is used in various pharmaceutical products.

Oral

Cough drops /Lozenges

Cough syrups

Mouth sprays

Mouth wash

Toothpaste

External

Lip balms

Ointments

Salves

Sprays

6.9 MAGNESIUM STERATE

MAGNESIUM STEARATE

1. NONPROPRIETARY NAMES:

BP	:	Magnesium Stearate
JP	:	Magnesium Stearate
PhEur	:	Magnesium Stearate
USP-NF	:	Magnesium Stearate

2. CHEMICAL NAME

Octadecanoic acid

3. STRUCTURE FORMULA

$[CH_3(CH_2)_{16}COO]_2Mg$

4. EMPIRICAL FORMULA AND MOLECULAR WEIGHT

$C_{36}H_{70}MgO_4$ 591.24

5. FUNCTIONAL CATEGORY

Tablet and capsule

6. DESCRIPTION

Magnesium sterate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

TYPICAL PROPERTIES

Crystalline forms High-purity magnesium stearate has been isolated as a trihydrate, a dihydrate, and an anhydrate.

Density (bulk)	:	0.159 g/cm^3
Density (tapped)	:	0.286 g/cm^3

Density (true) : 1.092 g/cm^3

Flash point : 250°C

Flow ability : Poorly flowing, cohesive powder.

Melting range : 117–150°C

Solubility : Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Specific surface area : 1.6–14.8m^2/g

7. APPLICATIONS IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

- Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations.
- It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.
- It is also used in barrier creams.

8. STABILITY AND STORAGE CONDITIONS

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

9. INCOMPATIBILITIES

Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.

6.10 YELLOW OXIDE OF IRON

1. NONPROPRIETARY NAMES: Iron oxide yellow monohydrate: E172; hydrated ferric oxide; iron (III) oxide monohydrate, yellow; pigment yellow 42; yellow ferric oxide. Iron (III) oxide hydrated: Bayferrox920Z; CI 77492; ferric hydroxide; ferric hydroxide oxide; ferric hydrate; ferric oxide hydrated; Ferroxide 510P; iron hydrate; iron hydroxide; iron hydroxide oxide; Mapico Yellow EC; Sicovit Y10; yellow ochre; yellow iron oxide

2. CHEMICAL NAME: Iron oxide yellow [51274-00-1] (monohydrate); [20344-49-4] (hydrate) Iron oxide yellow [51274-00-1] (monohydrate) [20344-49-4] (hydrate)

3 STRUCTURE FORMULA Iron oxides are defined as inorganic compounds consisting of anyone of or combinations of synthetically prepared iron oxides, including the hydrated forms

4. EMPIRICAL FORMULA AND MOLECULAR WEIGHT

a) Fe_3O_4 231.54

b) Fe_2O_3 159.70

c) $Fe_2O_3\_H_2O$ 177.70 (monohydrate); $FeHO_2$ 88.85 (hydrate)

5. FUNCTIONAL CATEGORY

Colorant

6. TYPICAL PROPERTIES

4.1 g/cm^3 for iron oxide yellow ($Fe_2O_3\_H_2O$).

Solubility Soluble in mineral acids; insoluble in water.

7. APPLICATIONS IN PHARMACEUTICAL FORMULATION OR TECHNOLOGY

Iron oxides are widely used in cosmetics, foods, and pharmaceutical applications as colorants and UV absorbers. As inorganic colorants they are becoming of increasing importance as a result of the limitations affecting some synthetic organic dyestuffs. However, iron oxides also have restrictions in some countries on the

quantities that may be consumed, and technically their use is restricted because of their limited color range and their abrasiveness.

8. STABILITY AND STORAGE CONDITIONS

Iron oxides should be stored in well-closed containers in a cool, dry place.

9. INCOMPATIBILITIES

Iron oxides have been reported to make hard gelatin capsules brittle at higher temperatures when the residual moisture is 11–12%. This factor affects the use of iron oxides for coloring hard gelatin capsules, and will limit the amount that can be incorporated into the gelatin material.

7. MATERIALS AND METHODS

7.1 LIST OF INSTRUMENTS AND MANUFACTURER

Table No. 5. LIST OF INSTRUMENTS AND MANUFACTURER

S.NO	EQUIPMENTS	MANUFACTURER
1	Tablet compression machine-27 station(single Rotary)	CIP Machinery
2	Die Punch	CIP Machinery
3	Planetary Mixer	Kenwood
4	Hot air oven	Lab India
5	Dissolution apparatus(usp)	Electro lab
6	Electromagnetic sieve shaker(ESM-8)	Electro lab
7	Tablet Hardness tester(8M)	Dr.Schleuniger, pharmaton USA
8	PH meter	Lab India
9	Reverse phase High Pressure Liquid chromatography (HPLC)	Shimadzu
10	Electronic Weighing Balance	Essec Teraoka Lid(Japan)
11	Digital high precision balance(single pan)	Mettler-Toledo(Switzerland)
12	Disintegration tester	Electro Lab
13	Roche Friabilator USP	Electro Lab
14	Mechanical stirrer	Remi Motors, Bombay
15	Tabbed density tester	Electro Lab
16	Bulk density apparatus	Electro Lab
17	Stability chambers	Thermo lab,Mumbai
18	Sieves (A.S.T.M)	Rajdhani
19	Digital Vernier Calipers CD-6 inch CSX	Mitutoyo Corp, Japan
20	Humidity Chamber HTC 3003	Thermo lab

7.2 DRUG EXCIPIENTS AND THE MANUFACTURER

Table No. 6. DRUG EXCIPIENTS AND THE MANUFACTURER

S.No	Materials Name	COMPANY NAME
1.	Amoxicillin trihydrate (powder) BP	DSM Anti Infectives India Ltd. India
2.	Colloidal silicon dioxide (Aerosil) USP/BP	Degussa, Germany
3.	Maize starch USP/BP	Maize Products, Ahemedabad, India
4.	Potassium Clavulanate + Avicel blend (1: 1) BP	Fermic, S.a.de c.v, Mexico D.F / LEK Pharmaceuticals, Germany
5.	Microcrystalline cellulose (Avicel pH 101) USP/BP	FMC Biopolymer, Ireland.
6.	Powdarome Strawberry Premium flavor IH	Firmenich.
7	Yellow oxide of irons	Roha Dyes & Chemicals.
8	Magnesium stearate USP/BP	Nitika Chemicals, Nagpur
9	Sodium starch Glycolate	Signet pharma agencies, Mumbai.
10	Crospovidone	ISP Technologies, USA
11	Croscarmellose Sodium	Signet Pharma Agencies Mumbai.
12	Aspartame	Firmenich

8. EXPERIMENTAL WORK

CALIBRATION CURVE OF AMOXICILLIN TRIHYDRATE

100 mg of amoxicillin trihydrate was accurately weighed and dissolved in 25 ml of methanol in 100 ml volumetric flask and volume was made up to the mark using methanol, to make (1000 µg/ml) standard stock solution. Then 2 ml stock solution was taken in another 100 ml volumetric flask and further diluted in 100 ml of methanol to make (20 µg/ml) standard stock solution, then final concentration were prepared with water. The absorbance of standard solution was determined using UV/VIS spectrophotometer at 220nm [(26)]

CALIBRATION CURVE OF DILUTED POTASSIUM CLAVULANATE: Accurately weighed 100mg Diluted Potassium Clavulanate was transferred into 100ml volumetric flask and dissolved in small quantity of methanol and the volume was made up with water to give a stock solution of concentration of 1mg?ml. further dilutions were made in the range of 2-10mcg/ml with water and absorbance was measured at 220 nm[(26)]

PREFORMULATION STUDIES

IR SPECTROSCOPIC ANALYSIS[(27)]

The IR absorption spectra of the pure drug and with different excipients were taken in the range of 4000-400 cm-1 using KBR disc method. Triturate 1-2 mg of the substance to be examined with 300-400 mg, specified quantity; of finely powered and dried Potassium bromide .These quantities are usually sufficient to give a disc of 10-15mm diameter and spectrum of suitable intensity by a hydraulic press. The Infrared spectrum of Amoxicillin and Potassium Clavulanate was recorded by using FT-IR spectroscopy and observed for characteristic peaks of drug

METHOD OF PREPARATION

FORMULATION COMPOSITIONS

In the present research work, a dispersible tablet of Amoxicillin and Potassium Clavulanate was formulated using direct compression method . Wet granulation method was not used because this formulation is highly sensitive to moisture and temperature conditions[11]. Therefore Direct compression method was used for the manufacture of Amoxicillin and Potassium Clavulanate dispersible tablets.

Sixteen formulations were prepared by direct compression method using different disintegrants in various ratios of from F1 to F4 using maize starch as disintegrant in the ratios of 5, 10, 12.5 and 15, and F5 to F8 using CCS as disintegrant in the ratios of 5, 10, 12.5 and 15, and F9 to F12 using Crospovidone as disintegrant in the ratios of 5, 10, 12.5 and 15, and F13 to F16 using sodium starch glycolate as disintegrant in the ratios of 5, 10, 12.5 and 15. All the formulation and composition was shown in Table No: 7.

The Commonly used sweetening agents are Aspartame, Sugar derivative, Dextrose, Fructose, Mannitol, Sorbitol, Maltose etc. In this present study Aspartame is used as sweetening agent.

The Commonly used Flavouring agents are Vanila, Citrus oil, Fruit essence, Eucalyptus oil, clove oil, Peppermint oil, strawberry flavor. In this present study Strawberry flavor is used as a flavouring agent.

Table No.7

Composition of formulations (F1 – F16)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Amoxicillin	234.3	234.3	234.3	234.3	234.3	234.3	234.3	234.3	234.3	234.3	234.3	234.3	234.3	234.3	234.
Potassium Clavulanate	75.70	75.70	75.70	75.70	75.70	75.70	75.70	75.70	75.70	75.70	75.70	75.70	75.70	75.70	75.7
MCC AVICEL PH 101	149	144	141.5	139	149	144	141.5	139	149	144	141.5	139	149	144	141.
Maize starch	5	10	12.5	15	-	-	-	-	-	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	5	10	12.5	15	-	-	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	-	-	5	10	12.5	15	-	-	-
SSG	-	-	-	-	-	-	-	-	-	-	-	-	5	10	12.
Aerosil	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Aspartame	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Strawberry	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Yellow oxide of Iron	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Total Weight	500	500	500	500	500	500	500	500	500	500	500	500	500	500	500

F1 –F4: Maize starch, F5-F8: Croscarmellose sodium, F9 – F12 : Crospovidone F13-F16: Sodium starch glycolate (SSG)

EVALUATION OF BLEND

The evaluation of blend was done by the following parameters

a) ANGLE OF REPOSE [34,35 ,36,)]

The frictional force in a loose powder can be measured by the angle of repose. Angle of Repose is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the measure of the flow ability of powder/granules.

A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured48.

Angle of repose was calculated from the average radius using the following

Formula.

$\theta = \text{Tan}^{-1} (h/r)$ Where,

θ = Angle of repose

h = Height of the pile

r = Average radius of the powder cone

Table No 8

Limitation of Angle of repose

Angle of repose	Type of flow
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very Poor

Higher the angle of repose the rougher and more irregular is the surface of the particles.

b) BULK DENSITY [34, 35, 36]

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Usually, bulk density is of great importance when none considers the size of a high-dose drug product or homogeneity of a low-dose formulation. Apparent bulk density (g/ml) of all types of drug were determined by pouring preserved (40-mesh) gently 25 gm of sample through a glass funnel into a 100 ml graduated cylinder. Bulk density was calculated.

$$\text{Bulk density (g/ml)} = \frac{\text{Weight of sample (gm)}}{\text{Volume occupied by the sample (ml)}}$$

The Bulk Characterization is done in Electrolab-Tap Density Tester by method USP-I.

c) TAPPED DENSITY [34, 35, 36]

Tapped densities of all types of granules were determined by pouring gently 25 gm of sample through a glass funnel into a 100 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained.

In USP TAP DENSITY TESTER, tap density is measured in 500 taps, 750 taps & 1250 taps with drop/time-249 .Volume occupied by the sample after tapping were recorded and tapped density was calculated.

$$\text{Tap density (g/ml)} = \frac{\text{Weight of sample (gm)}}{\text{Volume occupied by the sample (ml)}}$$

Experimentally, the true density of a powder is determined by suspending drug particles in solvents of various densities and in which the compound is insoluble. Wetting and penetration may be enhanced by addition of some quantities of surfactant to the solvent mixture. After centrifuging the suspending molecule the exact tap density is determined

d) PERCENTAGE COMPRESSIBILITY [34, 35, 36,)]

Compressibility is the ability of powder to decrease in volume under pressure .Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. A useful empirical guide is given by the Carr's compressibility or compressibility index. Compressibility measures gives idea about flow property of the granules as per Carr's index which is as follow

Table No. 9

Limitation of Percentage compressibility index

Compressibility	Flow description
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair
23 – 35	Poor
35 – 38	Very poor
> 40	Extremely poor

e) HAUSNER RATIO [, 34, 35, 36)]

It provides an indication of the degree of densification which could result from vibration of the feed hopper.

Bulk density
Hausner ratio = Tapped density
Lower Hausner ratio − better flowability
Higher Hausner ratio − poor flow ability

Table No.10

Limitation of Hausner's Ratio

Hausner's ratio	Type of flow
<1.25	**Good flow**
1.25 – 1.5	**Moderate**
>1.5	**Poor flow**

MANUFACTURING PROCESS OF DISPERSIBLE TABLET

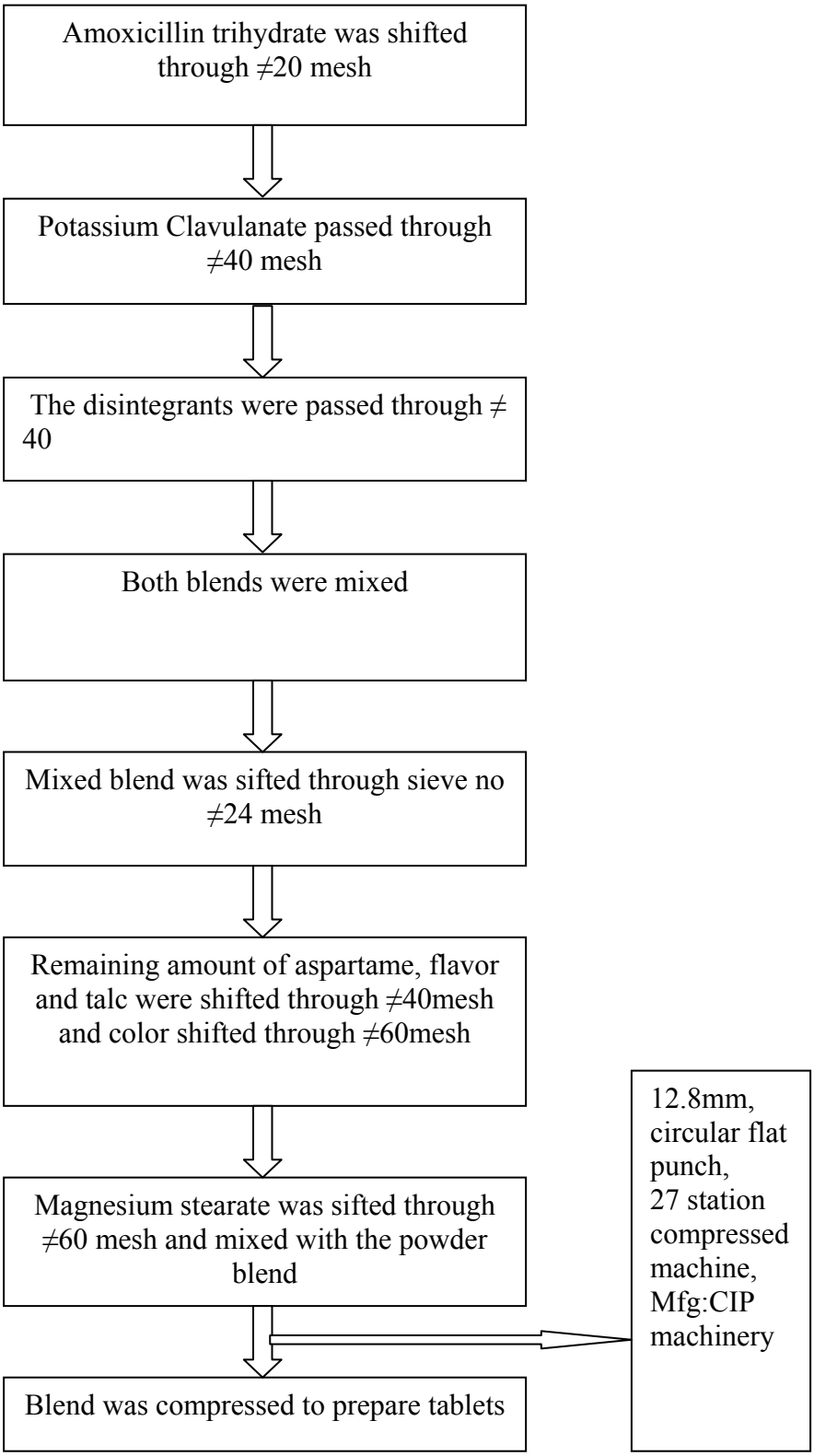


Figure No. 4 Flowchart for manufacturing of Dispersible Tablets

MANUFACTURING PROCEDURE

- Amoxicillin trihydrate was shifted (Electrolab) through≠ 20 mesh
- Potassium Clavulanate, disintegrant all were passed through ≠40 mesh. Both blends (Kenwood planetary mixer) were mixed.
- Mixed blend was sifted through sieve no ≠24 mesh.
- Remaining amount of aspartame, flavor and talc were shifted through ≠40mesh and colour shifted through ≠60 mesh.
- Magnesium stearate was sifted through ≠ 60mesh and mixed with the powder blend
- Blend was compressed to prepare tablets.

EVALUATION OF TABLETS [37]

IPQC TESTS:

After Compression all the tablets should be checked for the physical appearance and removal of any obvious defective tablets.

All the tablets should be inspected only on the tablet inspection belt attached with metal detector.

Record the weight of good tablets and rejection for each batch.

a) SHAPE OF TABLETS

Randomly picked tablets from each formulation were examined for the shape of the tablets.

b) WEIGHT VARIATION

The test ensures that all the tablets in each batch are of same potency, within reasonable limits. Each tablet in the batch should be uniform in weight and weight variation if any, should be generally within ± 10% for tablets weighing 130 mg or less, ± 7.5% for tablets weighing more than 130 mg and up to 324 mg and ± 5% for tablets weighing 325 mg or more. According to the official test, 20 tablets were weighed individually and collectively. Average weight per tablet was calculated from the collective weight. Then the weights of the individual tablets were compared with the average weight to determine weight variation.

c) HARDNESS TEST

Tablets require a certain amount of strength, or resistance to friability, to withstand the mechanical shocks of handling in manufacture, packaging, and shipping. The strength of the tablet was determined by Dr Schleuniger pharmaton apparatus. The force of fracture was recorded.

d) FRIABILITY

Friability test was performed to assess the effect of friction and shock which may often cause tablets to chip, cap or break. It generally reflects poor cohesion of tablet ingredients. Weighed tablets sample was placed in the chamber and the friabilator was operated for 100 revolutions at 25 RPM and the tablets were weighed again. Compressed tablets should not lose more than 1% of their weight.

e) TABLET THICKNESS

Variation in the tablet thickness may cause problems in counting and packaging in addition to weight variation beyond the permissible limits. Tablet thickness should be controlled within a ± 3% of a standard value. Tablet thickness was measured by Vernier calipers.

DISINTEGRATION TEST

The disintegration time was determined by using USP Tablet disintegration test apparatus using 900 ml of distilled water without disk. Time taken by tablets (Sec) for complete disintegration of the tablets until no mass remaining in apparatus was measured.

UNIFORMITY OF DISPERSION TEST [38]

The fineness of dispersion test was done by place 2 tablets in 100 ml of water and stir until completely dispersed. A smooth dispersion is produced, which passes through a sieve no. #25.

WETTING TIME

The wetting time and capillarity of oral dispersible tablets were measured by a conventional method. Tablet was placed in a petri dish containing 10 ml water at room temperature and the times for complete wetting of tablets were recorded.

DRUG CONTENT UNIFORMITY

The drug content was done by chromatographic method.

CHROMATOGRAPHIC CONDITIONS

Column	:	C18, 250mmX4.0m, 5µm.
Detector	:	UV detector at 220 nm
Manufacturer Name	:	schimadzu
Flow rate	:	2.0 ml/min
Temperature	:	Ambient
Buffer preparation	:	Dissolve 7.8 g of Sodium di-hydrogen orthophosphate in 1000 ml of water with a ortho-phosporic acid to a Ph OF 4.4

MOBILE PHASE

A mixture of Buffer &Methanol (950:50), filter and degas. Standard solution: weigh accurately 50 mg of Amoxicillin Trihydrate WS. And 46.0mg Diluted Potassium Clavulanate WS. In 100 ml volumetric flask. Add 60 ml water, sonicate to dissolve, and make up volume with water.

SAMPLE PREPARATION

Weigh and powdered 20 tablets, transfer powder containing 250mg Amoxicillin in 500 ml volumetric flask. Add 400ml of water and sonicate to dissolve. Make up the volume up to the mark with water. Filter the sample solution through 0.45 µm membrane filter paper.

PROCEDURE

Separately inject 20µl of the standard solution in replicate and calculate RSD of standard area (RSD NMT 2.0%), tailing factor NMT 2.0 and the column efficiency is NLT 1500 theoretical plates, Inject Test solution into the chromatogram and record the

chromatograph and measure the response for the major peaks and calculate the result by comparison

CALCULATION

Amoxicillin (Release in %)

$$= \frac{\text{Spl area}}{\text{Avg. std area}} \times \frac{\text{Std wt}}{100} \times \frac{5}{25} \times \frac{900}{1} \times \frac{\text{Std purity}}{100} \times \frac{100}{\text{Label claim}}$$

POTASSIUM CLAVULANATE (RELEASE IN %)

$$= \frac{\text{Spl area}}{\text{Avg. std area}} \times \frac{\text{Std wt}}{100} \times \frac{5}{25} \times \frac{900}{1} \times \frac{\text{Std purity}}{100} \times \frac{100}{\text{Label claim}}$$

IN VITRO DRUG RELEASE STUDIES:

The in vitro dissolution of amoxicillin and potassium clavulanate dispersible tablets prepared by direct compression method using Dissolution test apparatus TDT-06T (Electro lab, Mumbai, India) at the USP type II apparatus at 75rpm. The dissolution studies were conducted in 900 ml of water as a dissolution media at 37°C + 0.5 ºC. Optimized batches Amoxicillin and Potassium Clavulanate dispersible tablet from F1-F16 were suspended in 900 ml of water was withdrawn at 0, 5, 10, 15, 30, 60, 180, 300,600,900 sec with a pipette and filter through 0.45µm what man filter and then analyzed Amoxicillin and Potassium Clavulanate dispersible tablet content was determined in triplicate by (UV/Vis Spectrophotometer, Shimadzu - 1800) spectrophotometrically at_max 220 nm. Fresh medium (5 ml) which was pre warmed at 37°C and was replaced immediately into the dissolution medium after each sampling maintain its constant volume throughout the test.

AMOXICILLIN (RELEASE IN %)

$$\frac{\text{Spl area}}{\text{Avg. std area}} \times \frac{\text{Std wt}}{100} \times \frac{5}{25} \times \frac{900}{1} \times \frac{\text{Std purity}}{100} \times \frac{100}{\text{Label claim}}$$

POTASSIUM CLAVULANATE (RELEASE IN %)

$$\frac{\text{Spl area}}{\text{Avg. std area}} \times \frac{\text{Std wt}}{100} \times \frac{5}{25} \times \frac{900}{1} \times \frac{\text{Std purity}}{100} \times \frac{100}{\text{Label claim}}$$

STABILITY [39, 40, 41]

The term "stability," with respect to a drug dosage form, refers to the chemical and physical integrity of the dosage unit and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination. The shelf life of the dosage form is the time lapse from initial preparation to the specified expiration date. The monograph specifications of identity, strength, quality, and purity apply throughout the shelf life of the product.

The stability parameters of a drug dosage form can be influenced by environmental conditions of storage (temperature, light, air, and humidity), as well as the package components. Pharmacopeia articles should include required storage conditions on their labelling. These are the conditions under which the expiration date shall apply. The storage requirements specified in the labelling for the article must be observed throughout the distribution of the article (i.e., beyond the time it leaves the manufacturer up to and including its handling by the dispenser or seller of the article to the consumer). Although labeling for the consumer should indicate proper storage conditions, it is recognized that control beyond the dispenser or seller is difficult. The beyond-use date shall be placed on the container label.

STABILITY PROTOCOLS

Stability of manufactured dosage forms must be demonstrated by the manufacturer, using methods adequate for the purpose. Monograph assays may be used for stability testing if they are stability-indicating (i.e., if they accurately differentiate between the intact drug molecules and their degradation products). Stability considerations should include not only the specific compendial requirements, but also

changes in physical appearance of the product that would warn users that the products continued integrity is questionable.

Stability studies on active substances and packaged dosage forms are conducted by means of "real-time," long-term tests at specific temperatures and relative humidities representing storage conditions experienced in the distribution chain of the climatic zone(s) of the country or region of the world concerned. Labeling of the packaged active substance or dosage form should reflect the effects of temperature, relative humidity, air, and light on its stability. Label temperature storage warnings will both reflect the results of the real-time storage tests and allow for expected seasonal excursions of temperature.

Table No 11: The stability Protocol was given in the following table

Study	Storage condition	Minimum time period covered by data at submission
Long term	25±2ºC and 60±5% RH Or 30±2ºC and 65±5% RH	12 months
Intermediate	30±2ºC and 65±5% RH	6 months
Accelerated	40±2ºC and 75±5% RH	6 months

PROCEDURE

The stability studies were conducted by storing the tablet in a stability chamber at 25±2ºC/60±5% RH and 40±2ºC/75±5% RH. The tablets are wrapped in ALU-ALU pack and its stored for one month. After one month, tablets were analyzed for its physical properties and dissolution profile.

9. RESULTS AND DISCUSSION

1. PRE-FORMULATION STUDIES

CALIBRATION CURVE

FOR AMOXICILLIN TRIHYDRATE:

Calibration curve of Amoxicillin Trihydrate was prepared in water at determined wavelength 220nm. The calibration curve was linear between 20 to 100 μg/ml concentration ranges. The r^2 and slope were found to be 0.993 and 0.005 shown in figure no. 5 and table no. 12.

FOR POTASSIUM CLAVULANATE:

Calibration curve of Potassium Clavulanate was developed in water at above determined wavelength 220nm. The calibration curve was linear between 2 to 10 μg/ml concentration ranges. The r^2 and slope were found to be 0.989 and 0.055 shown in figure 6 and table no 13.

2. DRUG EXCIPIENT COMPATIBILITY

Drug and excipients interaction was checked out by comparing the FTIR spectra of pure drug Amoxicillin Trihydrate, diluted Potassium Clavulanate FTIR spectra of the physical mixture of drug and excipients shown in Table No 14 - 17 and in Figure No 7 -10

IR spectra result indicates that no significant difference in characteristic peak at wave numbers of the drug in presence of the excipients. From the results it can be concluded that drug and excipients are compatible.

2. EVALUATION OF POWDER BLEND

The results of the evaluation of the powder blend was shown in Table No:18. Angle of repose ranged from 25.11 to 29.11 and the compressibility index from 12-17. The LBD and TBD of the prepared granules ranged from 0.52 to 0.85 and 0.65 to 0.96 respectively. Hausner's ratio was found to be 1.2 or less than 1.2. The results of angle of Repose indicated good flow property of the granules and the value of the compressibility index further showed support for the flow property.

3. DISINTEGRATION TEST

The results of the disintegration test were shown in Table No: 19. Disintegration is the most important characteristic test of dispersible tablet, formulation F8 with Croscarmellose Sodium (CCS) 15% shows an excellent disintegration time of 55 seconds when compared with other formulations.

4. EVALUATION OF TABLETS

The results of the evaluation of tablets were shown in Table No: 19. The thickness and average weight were found in the range of 3±0.1mm and 502 ±5 mg for all the formulation. In each formulation, weight variation was observed within the I.P limit ±5%. The hardness of different formulations was ranged from 5-7 kg /cm^2. All the formulations exhibited less than 1% friability. The results were found to be within the content of uniformity limits (95 to 100.5%). It shows that the drug was uniformly distributed throughout the tablets. The wetting time for all the formulation was found to be between 73 to 123 seconds. All the formulations were passed the dispersibility test.

5. INVITRO DISSOLUTION STUDIES

The results of the in vitro dissolution studies were shown in table no 22-37 and in Figure no 11-26**.** In vitro dissolution test reveals the release increase from 89% to a maximum of almost 98% for Amoxicillin and from 89% to a maximum of almost 97% for Potassium Clavulanate. The release is in the following order of disintegrants Croscaramellose sodium > Crospovidone > Sodium Starch Glycolate > Maize starch. The

maximum in vitro dissolution was found to be with formulation F8. The formulation with Sodium starch Glycolate 15% shows least in vitro dissolution of 89% and the formulation F8 Containing Croscarmellose Sodium were found to be contain maximum in vitro dissolution of 98%. It clearly shows that disintegrant (Croscarmellose Sodium 15%) is the best when compared to other disintegrants. The reason may be high porous structure and water wicking mechanism into porous network of tablet hence increases in concentration of Croscarmellose Sodium accounts for rapid release [13, 16].

STABILITY STUDIES

The results of the stability studies were shown in Table No 38. The stability of optimized formulation F8 was monitored up to 4 weeks at 40°C ± 2°C and 25 °C±2°C temperature. Periodically (Initial and 4 weeks) samples were removed and evaluated by different parameters like Average Weight, Disintegration time (sec), Drug content (%), Hardness (kg/cm^2), Friability (%) and Thickness. There were no major changes observed during stability of Amoxicillin and Potassium Clavulanate dispersible tablet ((F8).

Table No: 12
Calibration Curve of Amoxicillin

S.no	Concentration	Absorbance
1	0	0
2	20	0.146
3	40	0.248
4	60	0.387
5	80	0.466
6	100	0.576

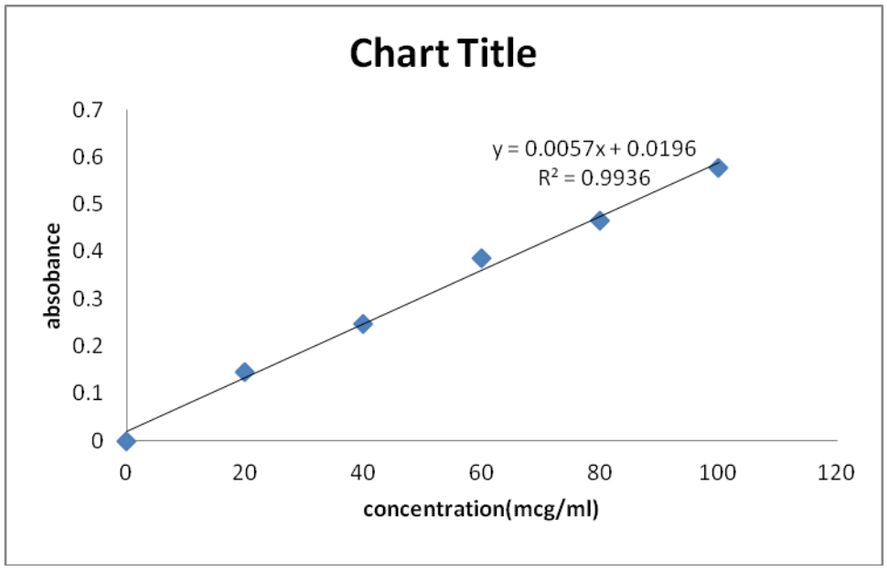


Figure No 5
Calibration Curve of Amoxicillin

Table No13
Calibration Curve of Diluted Potassium Clavulanate

S.No	Concentration	Absorbance
1	0	0
2	2	0.15
3	4	0.24
4	6	0.39
5	8	0.453
6	10	0.566

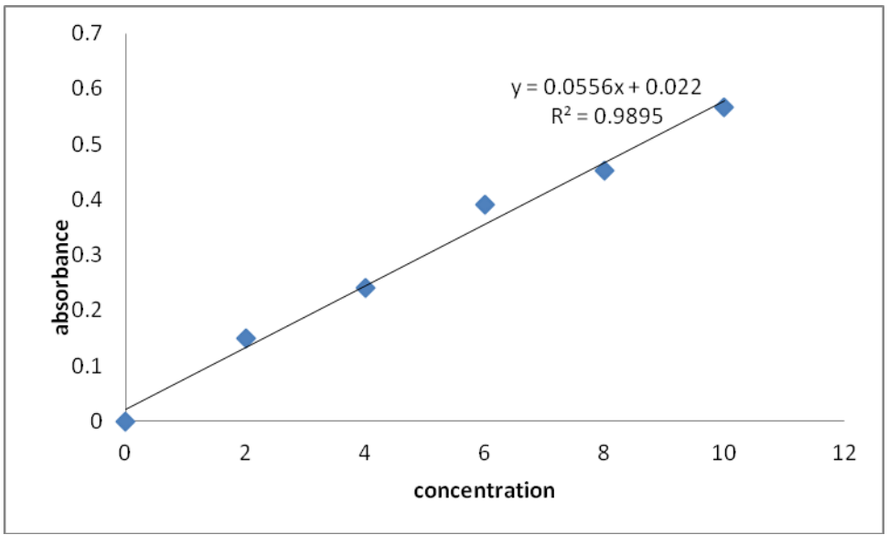


Figure No 6
Calibration Curve of Diluted Potassium Clavulanate

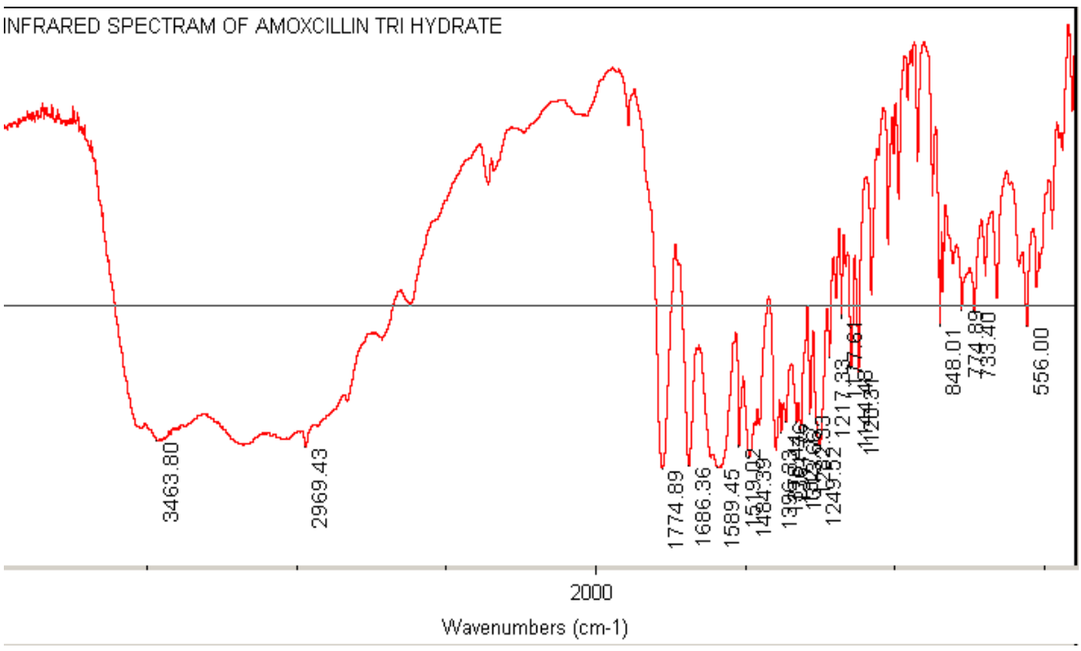


Figure 7
FTIR Spectrum of Amoxicillin Trihydrate

Table No 14
Ftir Interpretation of Amoxicillin Trihydrate

Wave number in cm^{-1}	Assignment	Mode of vibration
1774	C00H	STRETCHING
1589	NH	BENDING
1396	CN	STRETCHING
3463	NH	STRETCHING

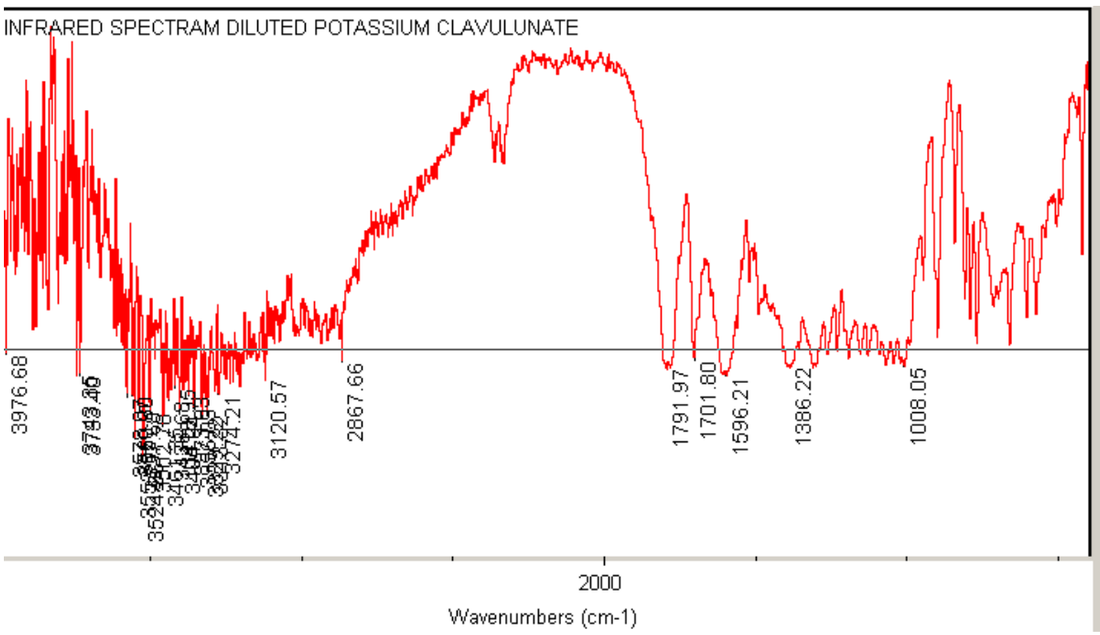


Figure No 8
FTIR Spectrum of Diluted Potassium Clavulanate

Table No 15
FTIR interpretation of Diluted Potassium Clavulanate

Wave number in cm^{-1}	Assignment	Mode of vibration
3976	0H	STRETCHING
1791	C=O	STRETCHING
1596	C=C	STRETCHING
1386	C=O	STRETCHING

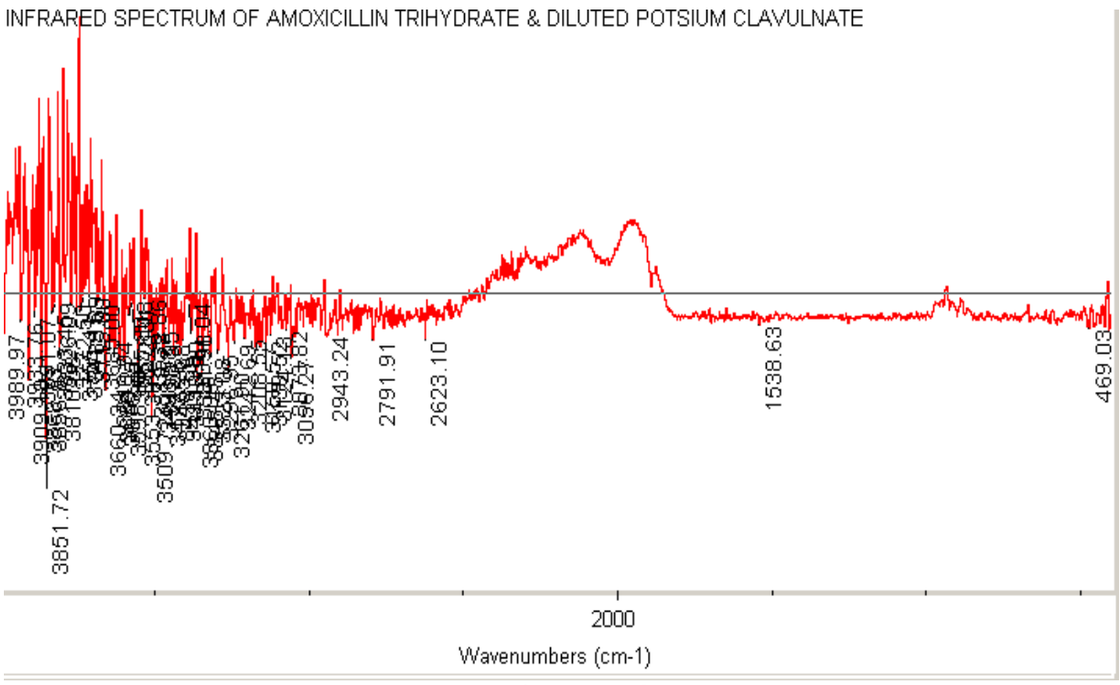


Figure No 9
FTIR Spectrum of Amoxicillin Trihydrate and Diluted Potassium Clavulanate

Table No 16
FTIR Interpretation of Amoxicillin Trihydrate and Diluted Potassium Clavulanate

Wave number in cm^{-1}	Assignment	Mode of vibration
3970	0H	STRETCHING
3463	NH	STRETCHING
1791	C=O	STRETCHING
1766	C=C	STRETCHING
1619	NH	BENDING
1603	NH	BENDING
1401	CN	STRETCHING
1387	C-C	STRETCHING

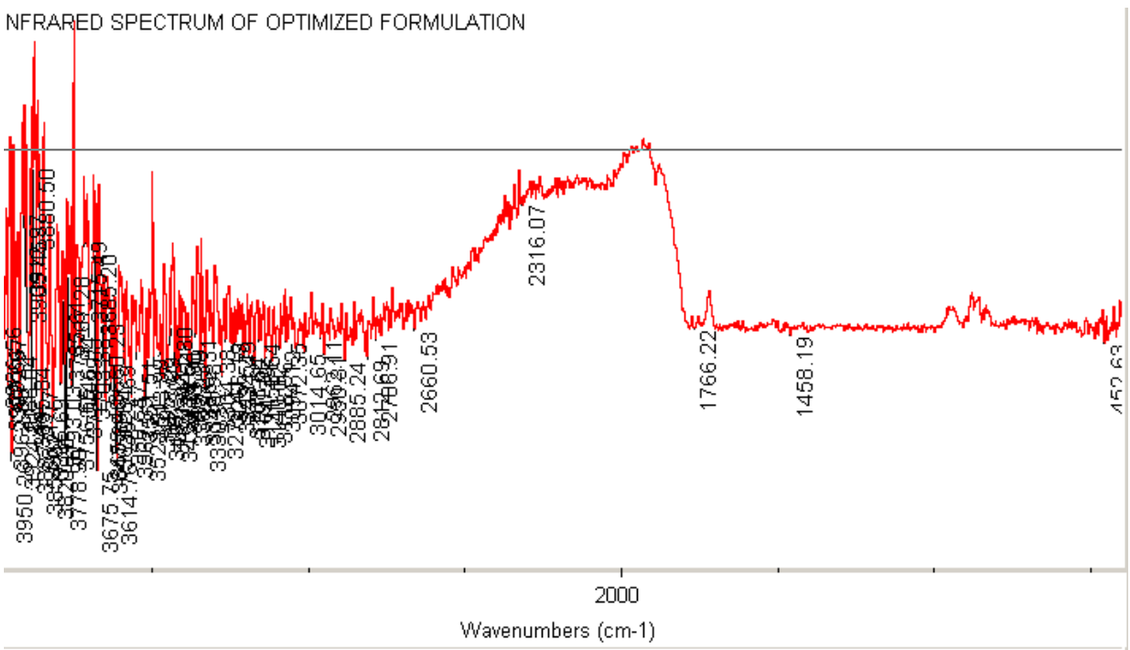


Figure No 10
FTIR Spectrum of Optimized Formulation

Table No 17
Ftir Interpretation of Optimized Formulation

Wave number in cm^{-1}	Assignment	Mode of vibration
3970	0H	STRETCHING
3463	NH	STRETCHING
1791	C=O	STRETCHING
1766	C=C	STRETCHING
1619	NH	BENDING
1603	NH	BENDING
1401	CN	STRETCHING
1387	C-C	STRETCHING

Table No. 18
Evaluation of Powder blend

Sl No.	Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
1	**Angle of Repose**	26.53 ±0.22	25.11 ±0.25	25.24 ±0.24	27.81 ±0.12	28.33 ±0.20	29.11 ±0.27	25.90 ±0.32	26.90 ±0.25	25.51 ±0.27	25.48 ±0.25	25.72 ±0.24	26.31 ±0.25	26.21 ±0.28	26.75 ±0.29	25.25 ±0.23	25.50 ±0.27
2	**Bulk density (gm/ml)**	0.725 ±0.32	0.750 ±0.36	0.825 ±0.33	0.850 ±0.32	0.605 ±0.13	0.610 ±0.35	0.725 ±0.36	0.813 ±0.33	0.605 ±0.38	0.855 ±0.33	0.635 ±0.38	0.525 ±0.36	0.540 ±0.32	0.525 ±0.34	0.530 ±0.36	0.600 ±0.37
3	**Tapped density (gm/ml)**	0.954 ±0.13	0.925 ±0.30	0.960 ±0.23	0.861 ±0.34	0.825 ±0.32	0.850 ±0.43	0.850 ±0.37	0.925 ±0.35	0.800 ±0.38	0.954 ±0.32	0.835 ±0.36	0.714 ±0.36	0.680 ±0.38	0.650 ±0.32	0.700 ±0.30	0.725 ±0.35
4	**%Carr's index**	15.20 ±0.23	16.30 ±0.32	15.40 ±0.33	16.20 ±0.35	16.50 ±0.36	17.00 ±0.38	14.30 ±0.35	15.33 ±0.32	15.71 ±0.38	13.25 ±0.37	12.75 ±0.53	12.52 ±0.36	15.21 ±0.23	16.75 ±0.30	15.21 ±0.37	15.75 ±0.34
5	**Hausner's Ratio**	1.115 ±0.12	1.033 ±0.15	1.166 ±0.16	1.012 ±0.13	1.163 ±0.18	1.193 ±0.17	1.172 ±0.12	1.137 ±0.16	1.122 ±0.15	1.102 ±0.18	1.114 ±0.15	1.160 ±0.18	1.159 ±0.10	1.138 ±0.12	1.120 ±0.18	1.008 ±0.16

Table No. 19
Evaluation of Physiochemical Properties of Tablet

Sl No.	Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
1	Average Weight (Mg)	503± 2	502± 3	503± 2	502± 2.5	502± 2.8	501± 3.5	500± 5	500± 4.5	501± 3.5	503± 1.5	502± 3.5	502± 2.5	502± 3.2	504± 3.5	503± 2.5	504± 2.5
2	Thickness (mm)	3± 0.11	3.2± 0.12	3.1± 0.13	3.0± 0.15	3.2± 0.17	3.5± 0.12	3.6± 0.18	3.7± 0.16	3.1± 0.15	3.8± 0.17	3.5± 0.15	3.9± 0.18	3.6± 0.16	3.2± 0.12	3.8± 0.11	3.3± 0.12
3	Hardness (Kg/Cm^2)	7± 0.23	6± 0.12	6.4± 0.20	5.0± 0.22	5± 0.12	5± 0.25	5± 0.20	5± 0.28	7.0± 0.12	6.4± 0.23	6.5± 0.25	7.0± 0.28	5.4± 0.25	6.5± 0.28	6.6± 0.27	5.4± 0.29
4	Friability (%)	0.8± 0.06	0.7± 0.04	0.6± 0.05	0.8± 0.08	0.52± 0.07	0.47± 0.06	0.48± 0.04	0.36± 0.02	0.62± 0.06	0.7± 0.08	0.9± 0.06	0.62± 0.06	0.65± 0.08	0.82± 0.06	0.75± 0.02	0.64± 0.05
5	Wetting time (sec)	117± 1	123± 2	106± 3	100± 1	99± 4	93± 2	105± 5	92±3	89±4	85±2	79±6	73±4	105± 6	95±5	90±6	84±5
6	Disintegration Time (Secs)	85± 0.32	80± 0.23	75± 0.35	80± 0.32	70± 0.53	76± 0.32	82± 0.34	55± 0.36	73± 0.38	79± 0.36	87± 0.38	98± 0.39	91± 0.38	73± 0.23	89± 0.30	82± 0.33
7	Uniformity of dispersion	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
8	Assay of Amoxicillin (%)	96.24	96.50	97.25	96.54	98.98	98.53	98.79	99.00	98.21	98.35	98.50	98.72	96.23	96.52	96.70	97.52
9	Assay of Clavulanic acid (%)	96.10	96.20	96.00	96.34	98.78	98.32	98.60	98.87	98.00	98.15	98.30	98.52	96.00	96.42	96.50	97.00

Table No: 20

DISSOLUTION PROFILE OF FORMULATIONS (F1-F16)

DISSOLUTION PROFILE - AMOXICILLIN

Sl. No.	TIME (SECONDS)	(% of Drug release)															
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	5	35	37	39	41	48	45	46	47	45	45	46	47	43	43	44	46
3	10	40	42	44	46	50	52	53	55	48	52	52	54	47	51	52	51
4	15	52	55	57	59	64	64	65	67	62	62	63	65	59	62	62	65
5	30	60	62	62	63	70	71	73	75	68	70	70	73	65	65	64	65
6	60	70	73	75	77	85	87	83	86	78	78	80	82	75	75	77	80
7	180	80	80	79	80	92	92	89	95	86	88	86	91	80	80	79	81
8	300	82	82	81	85	93	94	90	95	89	90	87	93	85	85	83	85
9	600	85	86	84	87	95	95	93	97	90	90	90	93	87	87	86	88
10	900	87	88	89	90	97	97	97	98	95	95	96	96	89	89	90	92

F1-F4=Maize Starch, F5-F8=CCS, F9-F12=Crospovidone, F13-F16= Sodium Starch Glycolate.

Table No: 21

Dissolution profile of formulation F1-F16

DISSOLUTION PROFILE – Potassium Clavulanate

Sl. No.	Time (Seconds)	(% of Drug release)															
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
1	0	0	0	0	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
2	5	28	32	35	39	40	42	44	44	39	42	44	44	37	42	44	43
3	10	35	37	42	44	48	46	50	50	47	50	52	50	47	50	50	48
4	15	49	48	54	55	62	63	60	64	60	61	58	63	55	61	55	63
5	30	57	56	60	60	67	69	67	70	65	65	66	70	60	63	63	64
6	60	68	64	70	72	80	83	80	82	75	75	78	80	72	73	72	75
7	180	75	75	74	77	90	85	82	90	80	80	80	85	75	75	75	78
8	300	80	80	78	79	92	90	88	93	89	88	87	90	85	84	80	80
9	600	85	81	82	85	95	94	92	95	90	89	88	91	86	86	84	85
10	900	86	87	85	89	97	96	95	97	92	91	95	93	87	87	88	90

F1-F4=Maize Starch, F5-F8=CCS, F9-F12=Crospovidone, F13-F16= Sodium Starch Glycolate.

Table No. 22
***Invitro* Dissolution Profile of Formulation F1 Starch 5%**

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	35	28
10	40	35
15	52	49
30	60	57
60	70	68
180	80	75
300	82	80
600	85	85
900	87	86

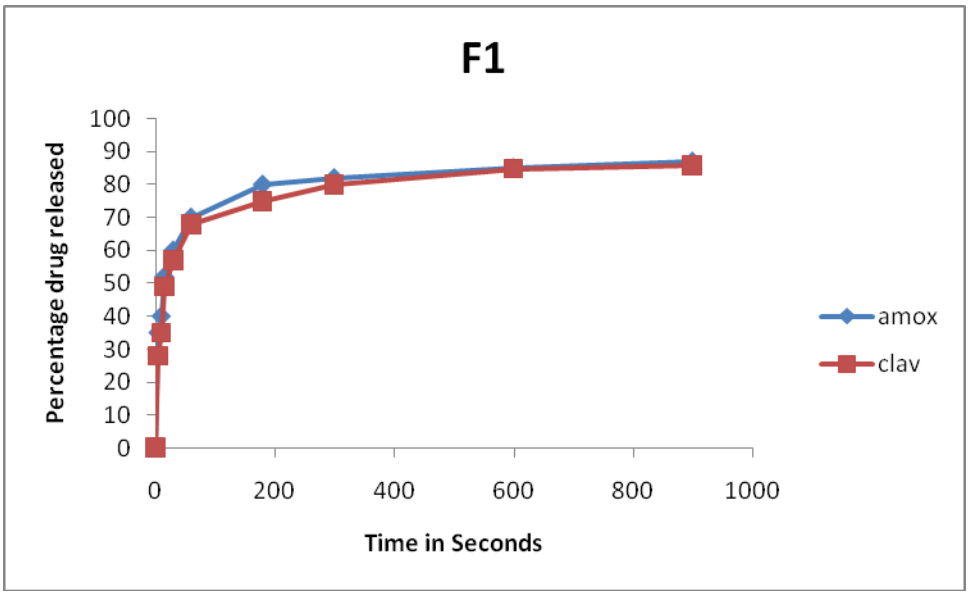


Figure No 11
Invitro Dissolution Profile of Formulation f1 starch 5%

Table No 23

***Invitro* Dissolution Profile of Formulation F2 Starch 10%**

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	37	32
10	42	37
15	55	48
30	62	56
60	73	64
180	80	75
300	82	80
600	86	81
900	88	87

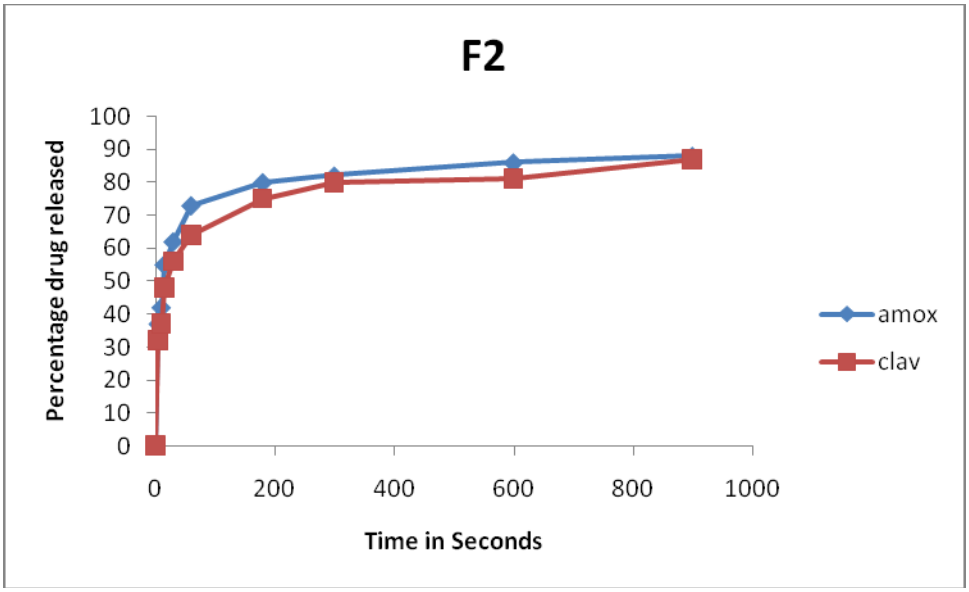


Figure No 12

***Invitro* Dissolution Profile of Formulation F2 Starch 10%**

Table No 24
Invitro Dissolution Profile of Formulation F3 Starch 12.5%

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	39	35
10	44	42
15	57	54
30	62	60
60	75	70
180	79	74
300	81	78
600	84	82
900	89	85

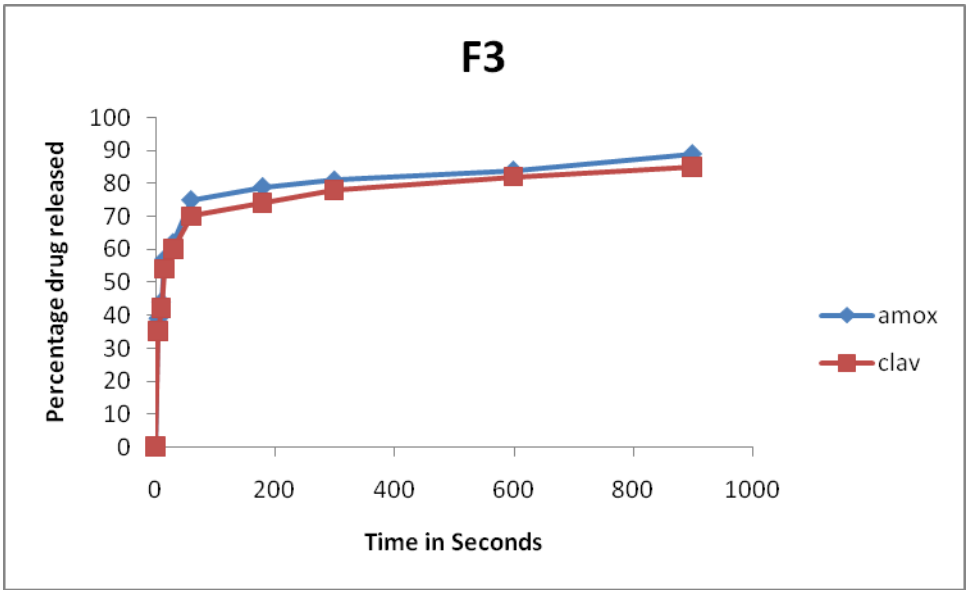


Figure No 13
***Invitro* Dissolution Profile of Formulation f3 starch 12.5%**

Table No 25

***Invitro* Dissolution Profile of Formulation F4 starch 15%**

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	41	39
10	46	44
15	59	55
30	63	60
60	77	72
180	80	77
300	85	79
600	87	85
900	90	89

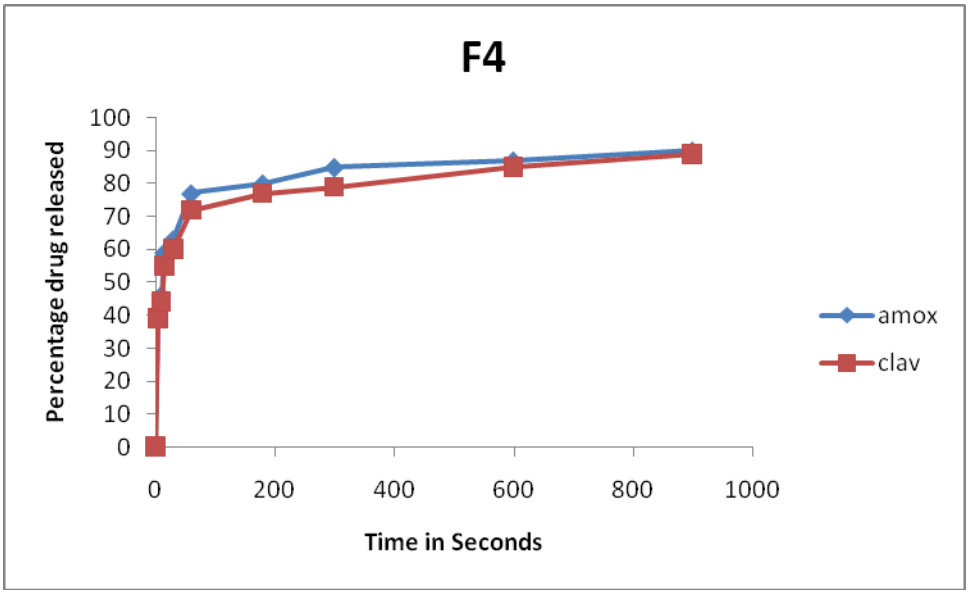


Figure No 14

***Invitro* Dissolution Profile of Formulation F4 Starch 12.5%**

Table No 26
***Invitro* Dissolution Profile of Formulation F5 CCS 5%**

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	48	40
10	50	48
15	64	62
30	70	67
60	85	80
180	92	90
300	93	92
600	95	95
900	97	97

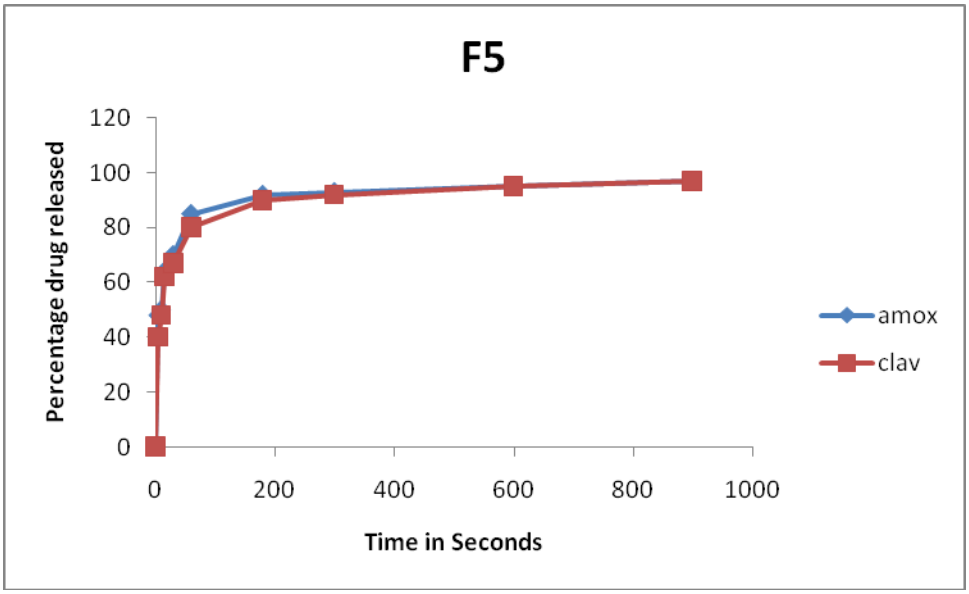


Figure No 15
***Invitro* Dissolution Profile of Formulation F5 CCS 5%**

Table No 27
***Invitro* Dissolution Profile of Formulation F6 CCS 10%**

Time in Secs	Amoxicillin	Clavulanic acid
0	0	0
5	45	42
10	52	46
15	64	63
30	71	69
60	87	83
180	92	85
300	94	90
600	95	94
900	97	96

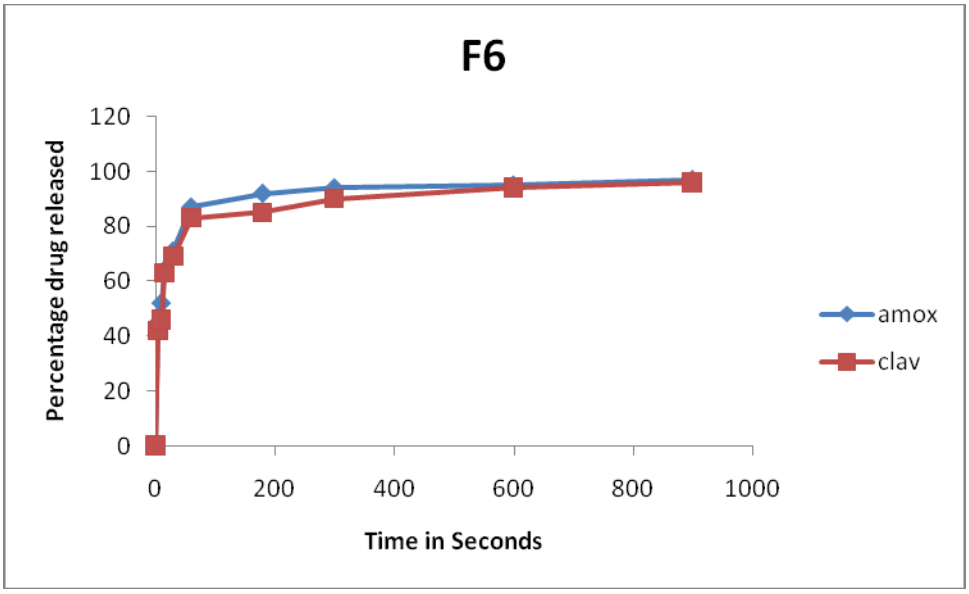


Figure No. 16
***Invitro* Dissolution Profile of formulation F6 CCS 10%**

Table No 28
***Invitro* Dissolution Profile of Formulation F7 CCS 12.5**

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	46	44
10	53	50
15	65	60
30	73	67
60	83	80
180	89	82
300	90	88
600	93	92
900	97	95

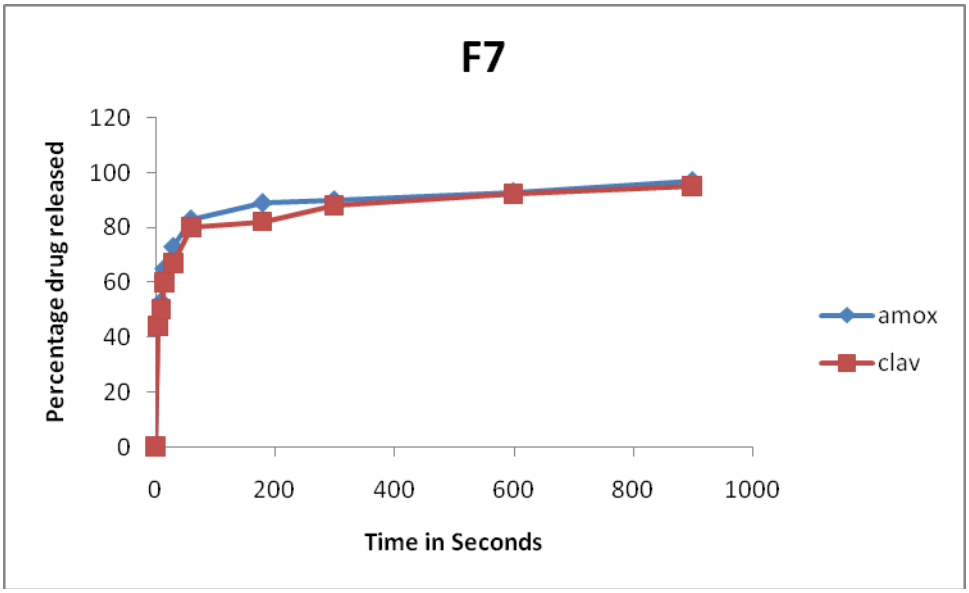


Figure No 17
***Invitro* Dissolution Profile of Formulation F7 CCS 12.5%**

Table No 29
***Invitro* Dissolution Profile of Formulation F8 CCS 15%**

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	47	44
10	55	50
15	67	64
30	75	70
60	86	82
180	95	90
300	95	93
600	97	95
900	98	97

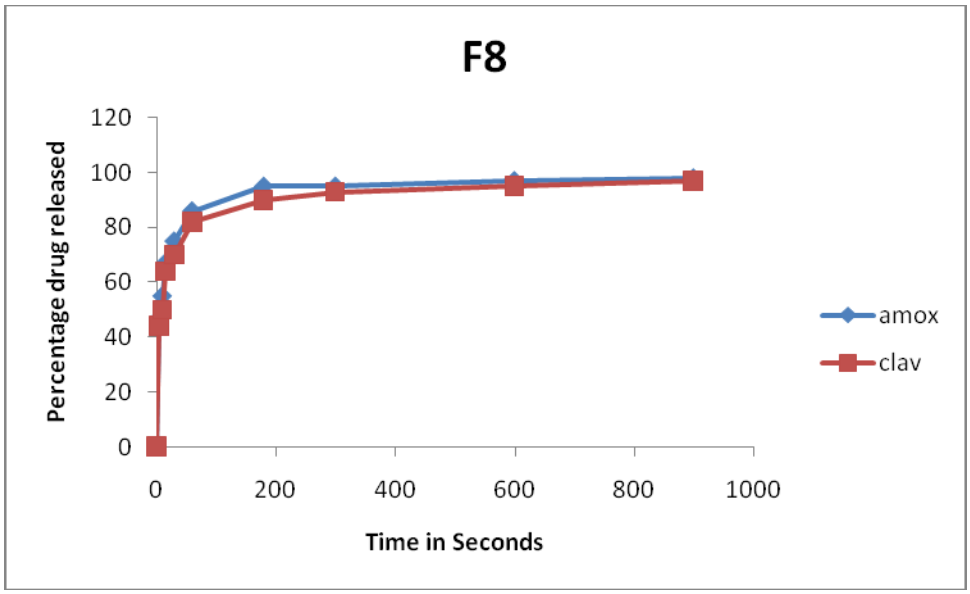


Figure No 18
***Invitro* Dissolution Profile of Formulation F8 CCS 15%**

Table No 30
***Invitro* Dissolution Profile of Formulation F9 CP5%**

Time in Secs	Amoxicillin	Clavulanic acid
0	0	0
5	45	39
10	48	47
15	62	60
30	68	65
60	78	75
180	86	80
300	89	89
600	90	90
900	95	92

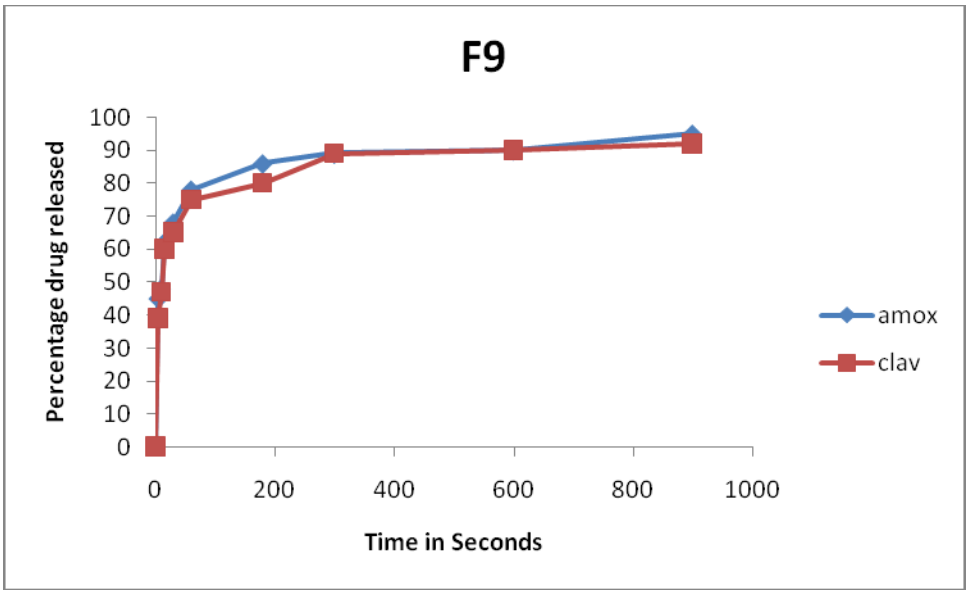


Figure No 19
***Invitro* Dissolution Profile of Formulation F9 Cp 5%**

Table No 31
***Invitro* Dissolution Profile of Formulation F10 Cp10%**

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	45	42
10	52	50
15	62	61
30	70	65
60	78	75
180	88	80
300	90	88
600	90	89
900	95	91

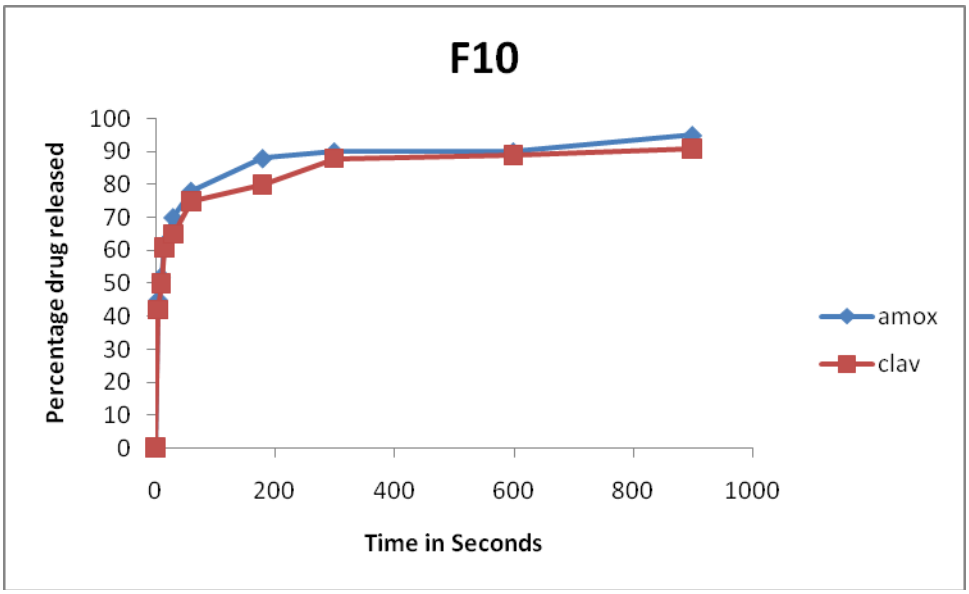


Figure No 20
***Invitro* Dissolution Profile of Formulation F9 Cp 10%**

Table no 32
***Invitro* Dissolution Profile of Formulation F11 cp12.5%**

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	46	44
10	52	52
15	63	58
30	70	66
60	80	78
180	86	80
300	87	87
600	90	88
900	96	95

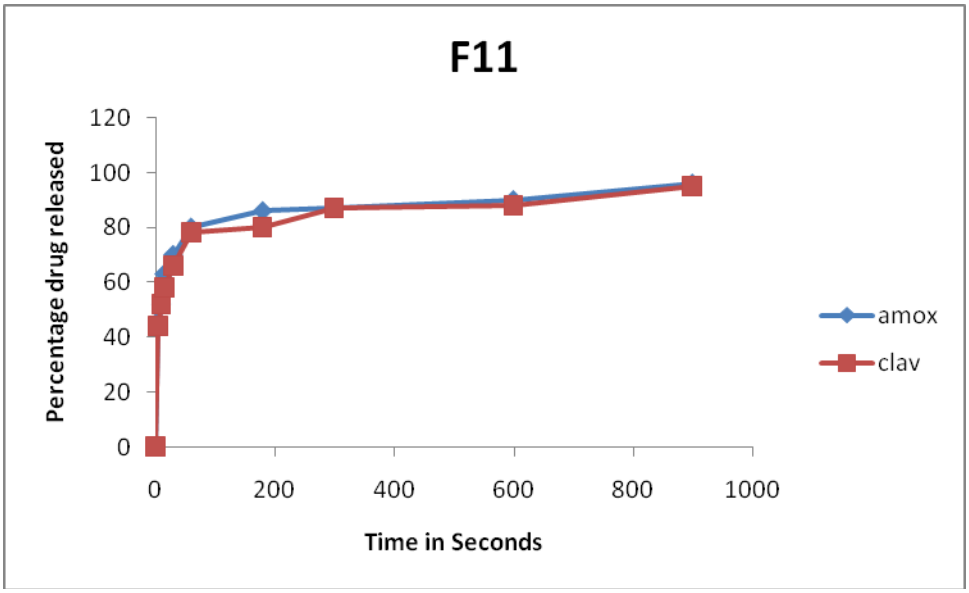


Figure No 21
***Invitro* Dissolution Profile Profile of Formulation F11 Cp 12.5%**

Table No 33
***Invitro* Dissolution Profile of Formulation F12 Cp15%**

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	47	44
10	54	50
15	65	63
30	73	70
60	82	80
180	91	85
300	93	90
600	93	91
900	96	93

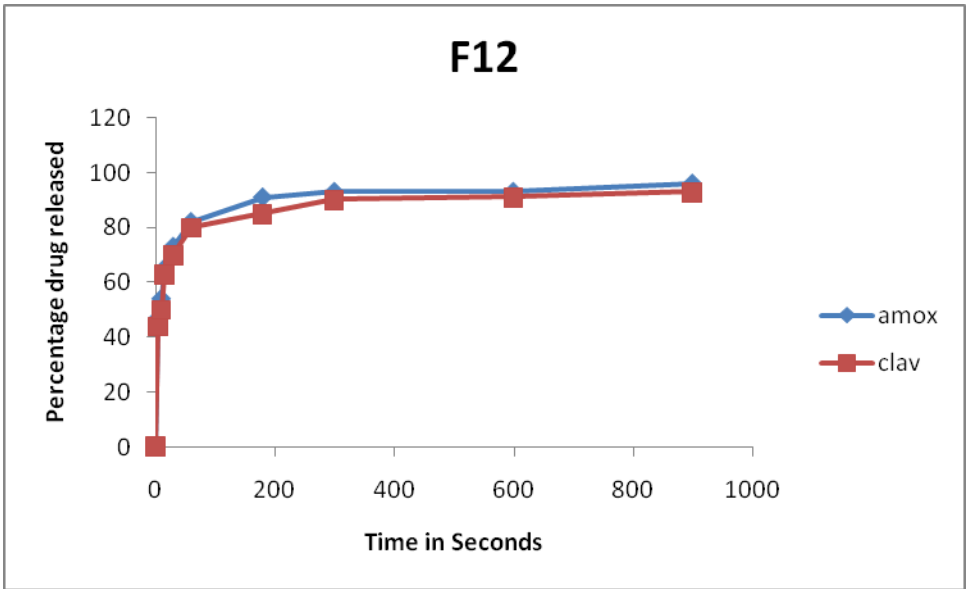


Figure No 22
***Invitro* Dissolution Profile of Formulation f12 cp 15%**

Table No. 34
***Invitro* Dissolution Profile of Formulation F13 SSG 5%**

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	43	37
10	47	47
15	59	55
30	65	60
60	75	72
180	80	75
300	85	85
600	87	86
900	89	87

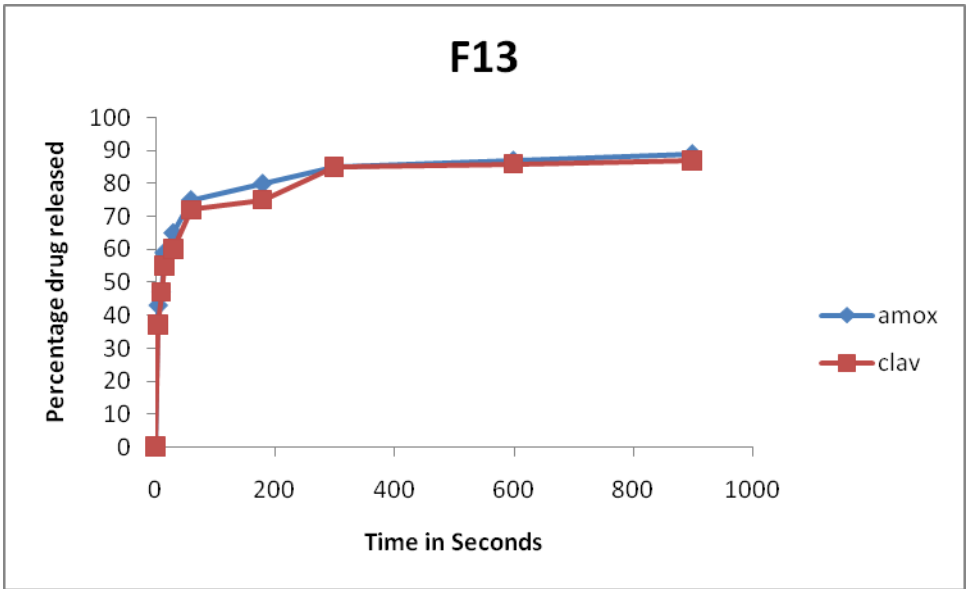


Figure No 23
***Invitro* Dissolution Profile of Formulation F13 SSG 5%**

Table No 35

***Invitro* Dissolution Profile of Formulation F14 SSG 10%**

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	43	42
10	51	50
15	62	61
30	65	63
60	75	73
180	80	75
300	85	84
600	87	86
900	89	87

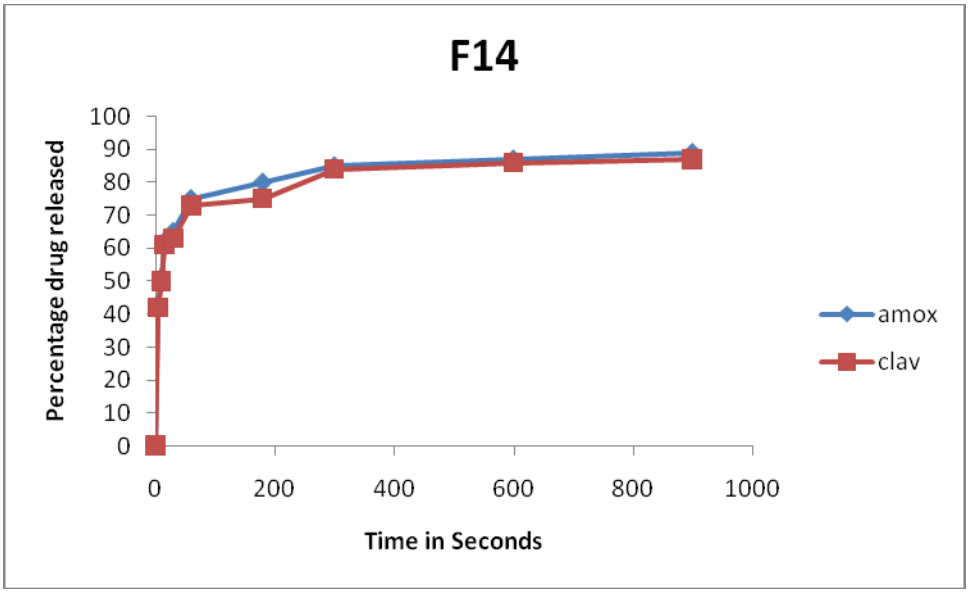


Figure no 24

***Invitro* Dissolution Profile of Formulation F14 SSG 10%**

Table No 36
***Invitro* Dissolution Profile of Formulation F15 SSG12.5%**

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	44	44
10	52	50
15	62	55
30	64	63
60	77	72
180	79	75
300	83	80
600	86	84
900	90	88

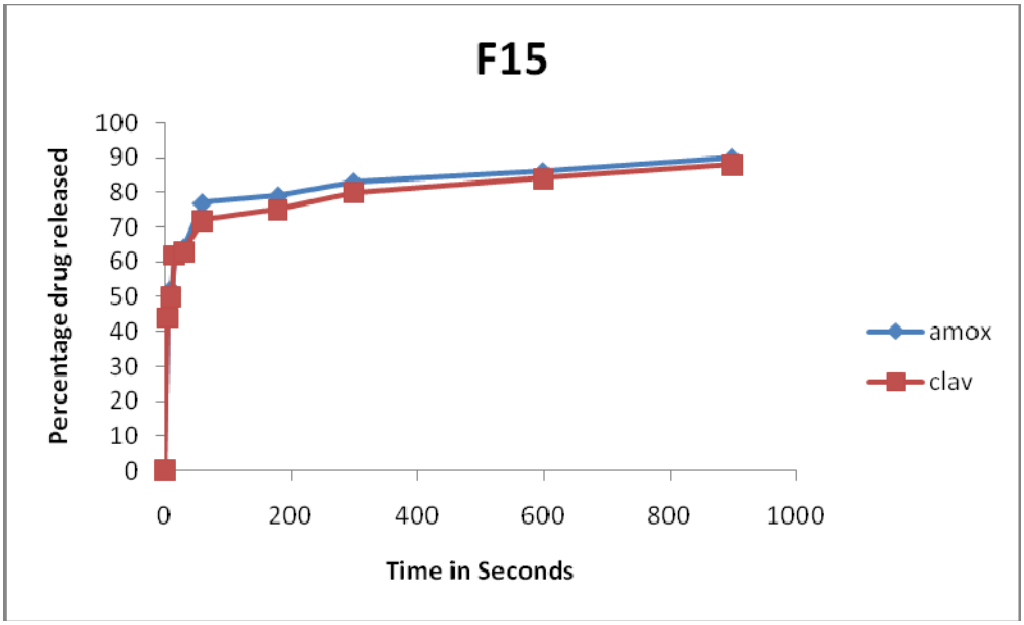


Figure No 25
***Invitro* Dissolution Profile of Formulation F15 SSG 12.5%**

Table No 37
***Invitro* Dissolution Profile of Formulation F16 SSG 15%**

Time in secs	Amoxicillin	Clavulanic acid
0	0	0
5	46	43
10	51	48
15	65	63
30	65	64
60	80	75
180	81	78
300	85	80
600	88	85
900	92	90

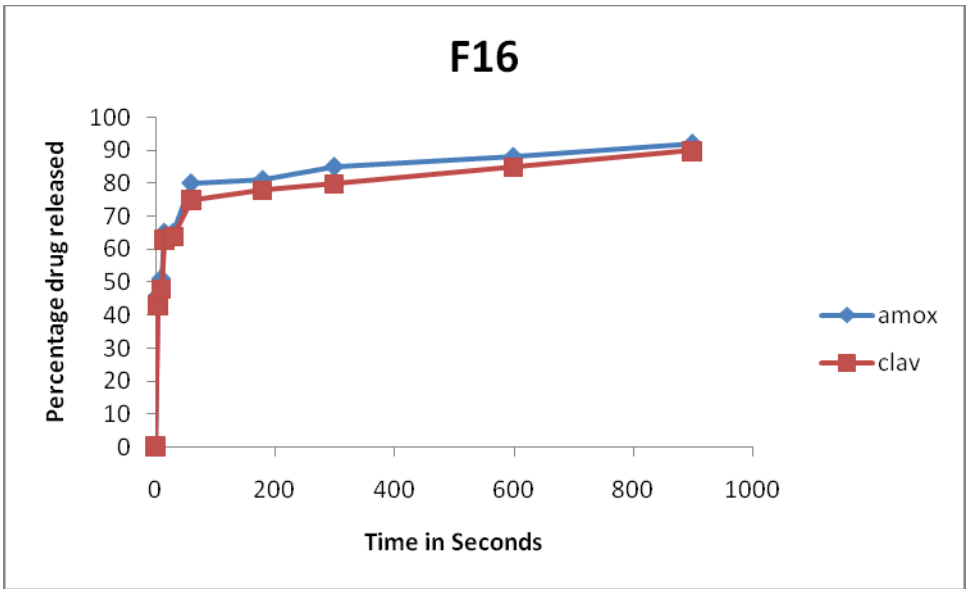


Figure No 26:
***Invitro* Dissolution Profile of Formulation F16 SSG 15%**

Table No. 38
STABILITY REPORT

CONDITION	Relative Humidity	PERIOD (weeks)	Colour	Average wt (mg)	Hardness(Kg/cm$^{2)}$	Friability (%)	Disintegration time	Thickness (mm)	Assay amox (%)	Assay Clav (%)
25 ^{0}C ± 2 ^{0}C	60% RH ± 5% RH	0	White	500±5	5±0.5(Kg/cm$^{2)}$	0.36±0.05	55±5 sec	3±0.1	99.00%	98.87%
		4	White	499±4	4.5±0.3(Kg/cm$^{2)}$	0.30±0.5	55±2 sec	3±0.2	97.78%	97.00%
40□ C ± 2□C	75% RH ± 5% RH	0	White	500±5	5±0.5(Kg/cm$^{2)}$	0.36±0.05	55±6 sec	3±0.1	99.00%	98.87%
		4	white	498±4	4.5±0.4(Kg/cm$^{2)}$	0.32±0.05	55±4 sec	3±0.3	96.20%	96.31%

10. CONCLUSION

The amoxicillin and potassium clavulanate dispersible tablets have been developed with direct compression method. The sixteen various compositions of formulations were prepared using Maize Starch, Sodium Starch Glycolate, Crospovidone, Croscarmellose sodium as a disintegrants. The powder blend were subject to various physical characteristics tests such as bulk density, tapped density, Hausner's ratio, compressibility index and core tablets were evaluated for weight variation, hardness, thickness, disintegration time and the results were found within specification. *In-vitro* dissolution profile of sixteen formulations was carried out by using four disintegrants like Maize Starch, Sodium starch Glycolate, Crospovidone and Croscarmellose sodium. The *In-vitro* dissolution profile of F8 using croscarmellose sodium (15%) was found maximum release when compared to other formulations. The optimized batch tablets were packed in ALU-ALU pack and performed stability studies at 40°C/75% RH. All the results were found to be satisfactory. Sweetening agent i.e Aspartame and flavouring agent i.e strawberry flavour were used to increase palatability of the dispersible tablet. Hence the designed and developed formula of combination of Amoxicillin and Potassium Clavulanate dispersible tablets could be used as alternate dosage form.

11. SUMMARY

The present work is aimed to develop a stable formulation of preferred combination of two antibiotics -Amoxicillin and Potassium Clavulanate by using various disintegrants. Amoxicillin and Potassium Clavulanate dispersible tablets were prepared by direct compression method using different disintegrants i.e. Croscarmellose, Crospovidone Maize starch and Sodium Starch Glycolate. Aspartame as a sweetener and strawberry flavor were used to increase palatability. The Powder blends were subject to various physical characteristics test such as bulk density, tapped density, Hausner's ratio and Compressibility Index. The prepared tablets were evaluated for hardness, friability, Disintegration time and Wetting time and in vitro drug release. Amoxicillin and Potassium Clavulanate dispersible tablets were found to be of good quality fulfilling all the requirements for dispersible tablets. The results indicated that concentration of Crospovidone, Croscarmellose sodium, Sodium starch glycolate and maize starch significantly affected the release property of the drug. Croscarmellose sodium showed high disintegration time as compared to batches prepared from Maize starch, Sodium starch Glycolate and Crospovidone. The *In-vitro* dissolution profile of F8 using Croscarmellose Sodium (15%) was found better than all other formulations. The optimized batch tablets were packed in ALU-ALU pack and performed stability studies at 40°C/75%RH. There is no change in the physiochemical properties of the tablet during the stability period. Hence the designed and developed formula of combination of Amoxicillin and Potassium Clavulanate dispersible tablets was found suitable alternate dosage form.

12. REFERENCES

1. Remington: the science and practice of pharmacy, 20th Edition, Volume I, Pg No. 858-885.
2. Aulton m, Pharmaceutics: the science of dosage form design, Pg. no. 304-321.
3. Leon Lachman, Herbert A. Liberman and Joseph L. Kanig, The Theory and practice of Industrial Pharmacy, 3rd Edition, Pg. no. 293-345.
4. Ansel H,Allen L. and Jr. Popovich N, Ansel's Pharmaceutical dosage forms and drug delivery systems, 8th edition, Pg.no.227-259.
5. Lachman L, Liberman L, and Schwartz J, Pharmaceutical Dosage forms: tablets, 2nd Edition, volume I, Pg.no.88-121.
6. Aulton M,; Pharmaceutics : The science of dosage form design; international student edition; 304-321,347-368
7. Aulton, M.E., and wells, T.I,"Pharmaceutics: The Science of Dosage form design", London, England: Churchill Livingstone, 1988,133.
8. Parikh D, Drugs and pharmaceutical sciences: Handbook of pharmaceutical granulation technology, volume 81, Pg.no. 99, 151, 227.
9. Section 3- Compression/compaction by Dr. Keith Marshall. Pg no:350-360
10. P.K. Shiromani "Tabletting Tips" in Pharma & Bio ingredient Published in January 2006.
11. Arohi Valera, Prathik Upadhyay, Jayant Deshpande,Shreeraj Shah, Jaymin Patel Development of stable formulation and Evaluation of combination of Amoxicillin and Clavulanic acid JPSBR Volume 3 Issue 4 sep 2013 (127-135)
12. Anab Fathima, Syed Baqir Naqvi, Dr. Sheikh Abdul Khaliq(Rehan), Javed Iqbal,Dilnawaz Shaikh, Shaheen Perveen simultaneous and Rapid determination of Amoxicillin and Clavulanic acid in Pharmaceutical Formulations by Reversed phase High Performance Liquid Chromatography (RP-HPLC) Method, African Journal of Pharmaceutical sciences and pharmacy, vol-4, issue-1 2013.
13. Kamal Saroha, Gautam Kumar, Yash Paul International Journal of Pharma & Bio Sciences: Vol-4, Issue 1, Mar 2013 Pg: 254.

14. Saurabh Sharma,Optimized the Effect of Disintegrant Sublimizing Agent Formulation of Lornoxicam Taste Masked Orodispersible tablet International Journal Of Pharmaceutical & Research Science , Vol. 2, Issue 1: January: 2013, 480-50.
15. Nwokoye Peace, Oyetunde Olubukola and Akinleye Moshood, Stability of reconstituted Amoxicillin Clavulanate Potassium under simulated in-home storage Conditions. Journal of Applied Pharmaceutical Science 02 (01); 2012: 28-3.
16. Jayaprakash S, Mathew Ebin P Sovichan, Lalith cherian, Rani S,R Praveen Raj Study on the effects of various disintegrants on Amoxicillin Trihydrate dispersible tablets. IRJP 2012,3(5).
17. V.Kalvimoorthi, M.ThamizhMozhi, M. Rajasekaran and J.Karthi formulation and in-vitro evaluation of Amoxicillin Clavulanate potassium tablet. International Journal of Analytical, Pharmaceutical and Biomedical Sciences. July-Sept-2012,96-100
18. Sellappan velmurugan and Satish babu yadari.Formulation and evaluation of oro dispersible tablets of Stavudine. International Journal of Chemical and Pharmaceutical Sciences. 2012, June., Vol.3 (2) 83-92
19. Reeta Rani Thaku r, Sonia Narwal. orally disintegrating preparations: recent advancement in formulation and technology. journal of Drug Delivery & Therapeutics; 201 2, 2(3): 87-96.
20. Sharma Anup Tukaramji, Moon Rajkumar Sukdeo Formulation and Evaluation of Taste masked Dispersible Tablets of Chloroquine Phosphate International Research Journal Of Pharmacy 2012 3(9) 286-292.
21. Simar preet kaur, Rekha rao, Sanju nanda.amoxicillin: a broad spectrum antibiotic.Int ernational Journal of Pharmacy and Pharmaceutical Sciences Vol3, Issue 3, 2011.
22. R. Belmar-Liberato, A. Gonzalez-Canga, P. Tamame-MartinM. Escribano-Salazar. Amoxicillin and Amoxicillin-Clavulanic acid resistance in veterinary medicine – the situation in Europe: Veterinarni Medicina, 56, 2011 (10): 473–48.
23. D. Indhumathi .Formulation and Evaluation of oro dissolving tablet of Fluoxetine using disintegrants. International Journal of Pharma and Bio Sciences.JAN –MAR 11.833-847.

24. Kamal Saroha, Pooja Mathur, Surender Verma, Navneet Syan and Ajay Kumar. Mouth dissolving tablets: An overview on future compaction in oral formulation technologies. Der Pharmacia Sinica, 2010, 1 (1): 179-187.
25. Suhas M.Kakade, Vinod S.Mannur, Ravindra V.Kardi, Ketan B.Ramani, AyazA. Dhada Formulation and Evaluation of orally disintegrating tablets of Sertraline International Journal of Pharma Research & Development Vol 1 Issue 2012 Feb 2010.
26. B.Jayakar, M.V.Kumudhavalli, R.Margret Chandira,M.Kumar, C.Saravanan Method Development and Validation of RP-HPLC method for simultaneous determination of Amoxicillin and Potassium Clavulanate International Journal of PharmaTech Research Vol-2 No-1 Mar 2010 906-909.
27. Ilma Nugrahani, Sukmadjasyarie, Sundani nurono. solid state interaction between Amoxicillin trihydrate and Potassium Clavulanate. Malaysian Journal of Pharmaceutical Sciences,Vol. 5, No. 1, 45–57 (2007
28. Drug Bank, Amoxicillin drug profile, 2014.
29. British Pharmacopeia, Amoxicillin Drug Profile, 2014
30. Drug Bank, Potassium Clavulanate drug profile, 2014
31. S.K. Nacheagari and A.K. Bansal "Excipients for solid dosage forms" 8) Libermann H A, Lachmann L, Schwartz J B eds Tablet: volume 1, New York NY, Marcel Dekker Inc, 1990, Page No 131-245.
32. R.C. Rowe, P.J Sheskey, M.E.Quinn Handbook of pharmaceutical excipient, 6th edi London: Pharmaceutical press.
33. Raymond C Rowe, Paul J sheske and Sian Cowen, et al "Handbook of Pharmaceutical Excipients", Pharmaceutical press 5th edition 767-769.
34. Lordi NG, LachmanL. Liberman HA, Theory and Practice of Industrial Pharmacy,3rd edition 1987.
35. Remington J., Remington: The science and Practice of Pharmacy; Nineteenth Edition: Volume 11: 1615-1641.
36. Swarbrick J and Boylan J ; Encyclopedia of Pharmaceutical Technology; volume 7: 121-160.
37. Indian Pharmacopeia, Indian Pharmacopeia Commission 7th edition 2014.

38. USP-NF25, Amoxicillin tablets for oral suspension. 2007, page no:1406.

39. Kulkarni G.T, Indian Journal of Pharmaceutical Science Gowthamrajan K, Suresh B, Stability testing of Pharmaceutical Product, 2004; 38(4): 194-202

40. International Conference Harmonization (ICH) harmonized tripartite guideline for Stability testing of new drugs substances and products Q1A (R2)aug-2003. Q1 (R2). 2004; 38(4): 194-202

41. C.T.Rhodes, T.Cartesan. Drug Stability principle and procedure, 3rd edition New York. 2001 p. 21-46