



SCREENING OF NATURAL AND SYNTHETIC SUPERDISINTEGRANT IN FORMULATION AND EVALUATION OF GINGEROL ORODISPERSIBLE TABLETS

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ABSTRACT

Orodispersible tablets (ODTs) have received rapid-increasing demand during the last decade and the field has become a ever growing area in the pharmaceutical industry. Orodispersible tablets (ODTs) are those solid dosage forms when put on tongue, disintegrate or dissolve instantaneously, releasing the drug, within a few seconds without the need of water, offering immediate release and enhanced bioavailability, to achieve better patient compliance. Gingerol has been traditionally used to treat gastrointestinal symptoms, nausea and emesis. Moreover, nausea and emesis are common side effects of chemotherapy. The activation of vagal afferent mediated by serotonin (5-HT) is crucial in the mechanism of emesis. Gingerol inhibited emetic signal transmission in vagal afferent neurons by suppressing the

5-HT receptor, and similarly 6-shogaol had the strongest inhibitory efficacy. Furthermore, ginger extract alleviated chemotherapy-induced nausea and emesis by suppressing the activation of 5-HT receptors in enteric neurons. The tablets were prepared by using extracted natural superdisintegrants such as *Musa paradisiaca* starch, modified *Musa paradisiaca* starch (starch glutamate) and synthetic superdisintegrant sodium starch glycolate in different ratios by using direct compression method. Micro crystalline cellulose as direct compressible material and aspartame as sweetener were also included. The IR spectral studies showed no interaction between drug and superdisintegrants. Satisfactory results were obtained when prepared tablets subjected to post compression evaluation tests such as uniformity of weight,

thickness, drug content, Invitro dispersion time, wetting time, water absorption ratio and Invitro disintegration studies. Tablets were also subjected to *in vitro* drug release studies by using USP dissolution apparatus. Of all the formulations, the tablets formulated with 6% Modified *Musa paradisiaca* starch (GIODT3) showed the least wetting time of 17.66 seconds, which had a direct impact on high water absorption ratio $96.63 \pm 0.41\%$. It was observed that the increased concentration of superdisintegrants decreased the disintegration time and optimized the drug release. Modified *Musa paradisiaca* starch(starch glutamate) in the concentration of 6 % acts as an eminent superdisintegrant and disintegrates the tablet within 17.66 seconds fulfilling the criteria of ODT. Further the higher dissolution rate of the GIODT3 formulation 99.89% at the end of 16 min indicated that modified *Musa paradisiaca* starch(starch glutamate) is a better choice among the renowned synthetic super disintegrant like sodium starch glycolate. From the results it is concluded, that in comparison with modified *Musa paradisiaca* starch (starch glutamate), *Musa paradisiaca* starch and sodium starch glycolate, the modified natural super disintegrant i.e., starch glutamate act as a good superdisintegrating agent and showed it acts as a promising additive in formulation of Orodispersible tablets of anti-emetic drug, Gingerol.

KEYWORDS: Orodispersable tablets (ODTs), Gingerol, Natural and synthetic Superdisintegrants, Enhanced bioavailability, Patient's compliance, Evaluation.

1. INTRODUCTION

Drug delivery system is an efficient tool for enhancing market, extending product life cycles and creating opportunities. Drug delivery system (DDS) makes a significant contribution to global pharmaceutical sales through market segmentation, and is moving rapidly. Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, non invasive method and ease of administration leading to high level of patient compliance. The most popular dosage forms are being conventional tablets and hard gelatin capsules. One important drawback of such dosage forms is Dysphagia " or difficulty in swallowing for many patients; almost 50% of the population is affected by such problem. Hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. Recently, Oro dispersible drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance. In some cases such as motion

sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. To overcome such problems, fast disintegrating tablets or orodispersible tablets have emerged as an alternative dosage form. Recent advances in novel drug delivery systems (NDDS) aim for enhancing the safety of a drug molecule while maintaining its therapeutic efficacy so as to achieve better patient compliance. Pharmaceutical technologists have put in their best efforts to develop an Orally dispersible drug delivery system.

Drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reason that the oral route achieved such popularity may be attributed to its ease of administration as well as the traditional belief that by oral administration the drug is well absorbed as the food stuffs ingested daily. In fact, the development of pharmaceutical products for oral delivery, irrespective of physical form involves varying extents of optimization of dosage form within the inherent constraints of GI physiology. Therefore, a fundamental understanding of various disciplines, including GI physiology, pharmacokinetics, pharmacodynamics and formulation design are essential to achieve a systemic approach to the successful development of an oral dosage form. The more sophisticated a delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system.

1.1. DEFINITION

The Center for Drug Evaluation and Research (CDER), US FDA defined orally dissolving/disintegrating tablets (ODDTs) as “A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue”. Recently European Pharmacopoeia also adopted the term “Oro Dispersible Tablet” defined as uncovered tablet for buccal cavity, where it disperses before ingestion. Oro dispersible tablets (ODT) are also known as fast dissolving, mouth dissolving, rapid-dissolve, quick disintegrating, quick dissolving, and porous tablets. Fast disintegrating tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. When faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the 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 tablets dosage form.^[1,2]

The basic approach in development of ODT is the use of super disintegrants like cross linked carboxymethyl cellulose (cross carmellose), sodium starch glycolate (primogel, explotab), cross linked polyvinylpyrrolidone (cross povidone) etc, which provide instantaneous disintegration of tablet after putting on tongue, there by release the drug in saliva^[3,4] The bioavailability of some drugs may be increased due to absorption of drug in oral cavity and also due to pre gastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first pass metabolism is reduced as compared to standard tablet. The target populations for these new orally-dissolving/disintegrating dosage forms have generally been pediatric, geriatric, and bedridden or developmentally disabled patients.^[5] Patients with persistent nausea, who are traveling, or who have little or no access to water are also good candidates for ODDTs.

1.2. BIOPHARMACEUTICAL CONSIDERATION

When new drug delivery system put on, it is must that to consider Biopharmaceutical factor like metabolism and excretion.

Pharmacokinetics

Study has done on absorption, distribution, metabolism m and excretion in this consideration. Drug attains therapeutic level after absorption and therefore elicits pharmacological effect, so both rate and extend of absorption is important. There is delay in disintegration and therefore dissolution in conventional dosage form while ODTs is rapidly disintegrates in oral cavity and dissolution is rapid. Due to disintegration of ODTs in mouth absorption in started from mouth, pharynx and esophagus. Some factors like age, GI pH, and blood flow through GI are taken into consideration, because elders may be considered as separate unique Medicare population. There are many factors on which drug distribution depends like tissue permeability, perfusion rate, binding of drug to tissue, disease state, drug interaction etc. In geriatric patients, decrease in body mass and total body water result in decreased volume of distribution of water-soluble drugs and increased volume of distribution (Vd) of lipid soluble drugs. Duration and intensity of action depends upon rate of drug removal from the body or site of action i.e. biotransformation. Decrease in liver volume, regional blood flow to liver reduces the biotransformation of drug through oxidation, reduction and hydrolysis. Excretion by renal clearance is slowed, thus half-life of renal excreted drugs increase.

Pharmacodynamics

Drug receptor interaction impaired in elderly as well as in young adult due to undue development of organ.

- Decreased ability of the body to respond baro reflexive stimuli, cardiac output, and orthostatic hypotension may see in taking antihypertensive like prazosin.
- Decreased sensitivity of the CVS to β -adrenergic agonist and antagonist. Immunity is less and taken into consideration while administered antibiotics.
- Altered response to drug therapy-elderly show diminished bronchodilator effect of theophylline shows increased sensitivity to barbiturates. Concomitant illnesses are often present in elderly, which is also taken into consideration, while multiple drug therapy prescribed.
- Research workers have clinically evaluated drug combination for various classes' cardiovascular agents, diuretics, anti-hypertensive in geriatrics. The combination choice depends on disease state of the patient.

1.3. REQUIREMENTS OF ORO DISPERSABLE TABLETS:

The tablets should

- Not require water to swallow and should dissolve or disintegrate in the mouth within a few seconds.
- Allow high drug loading.
- Be compatible with taste masking and other excipients.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
- Exhibit low sensitivity to environmental conditions such as humidity and temperature.
- Be adaptable and amenable to existing processing and packaging machinery.
- Allow the manufacture of tablets using conventional processing and packaging equipments at low cost.

1.4. ADVANTAGES OF ORO DISPERSABLE TABLETS^[6]

ODTs offer dual advantages of solid dosage forms and liquid dosage forms along with special features which include:

- **Accurate dosing:** Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.
- **Enhanced bioavailability:** Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and esophagus.
- **Rapid action:** Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in oral cavity.
- **Patient compliance:** No need of water to swallow the dosage form. Hence, it is convenient for patients who are traveling and do not have immediate access to water.
- **Ease of administration:** Convenient to administer specially for geriatric, pediatric, mentally disabled and bed ridden patients who have difficulty in swallowing.
- **Obstruction free:** No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.
- **Enhanced palatability:** Good mouth feel, especially for pediatric patients as taste masking technique is used to avoid the bitter taste of drug.
- **Simple packaging:** No specific packaging required. It can be packaged in push through blisters.
- **Business Avenue:** Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.
- **Cost effective:** Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.

1.5. DESIRED CHARACTERICS OF ORO DISPERSABLE TABLETS^[7-11]

1.5.1 Taste of Active Ingredients

Taste is an important parameter in administering drugs orally. Undesirable taste is one of the important formulation problems that are encountered with many drugs. Administration of bitter drugs orally with acceptable level of palatability is a key issue for healthcare providers. Proven methods for bitterness reduction and inhibition have resulted in improved palatability of oral pharmaceuticals. Taste masking of the drug may be achieved with preventing the exposure of drug to the tongue through processing or adding competing taste-masking agents.

Exposure of solubilized drug to the oral cavity can be prevented by encapsulation in polymer system or complexation. Taste-masking technologies are increasingly focused on aggressively bitter-tasting drugs like the macrolide antibiotics, non-steroidal anti-

inflammatory drugs, and penicillins. As a consequence, more efficient techniques such as coating, microencapsulation, and granulation have been used in combination with the sweeteners.

1.5.2 Drug Properties

For the ideal ODT technology, the drug properties should not significantly affect the tablet property. Many drug properties could potentially affect the performance of ODTs. For example, the solubility, crystal morphology, particle size, hygroscopicity, compressibility, and bulk density of a drug can significantly affect the final tablet's characteristics, such as tablet strength and disintegration. ODT technology should be versatile enough to accommodate unique properties of each drug.

The drugs belonging to Biopharmaceutical Classification System Class II, i.e., the drugs with poor solubility and high permeability are best suitable moieties for ODTs. Tizanidine HCl, Oxybutynin HCl, Rofecoxib, Ibuprofen, Promethazine Theoclate, prednisone, Indomethacin, Glyburide, Fentanyl citrate, Griseofulvin, Hydrochlorothiazide, Crystallized Paracetamol, and Nimesulide are few examples of drugs that has been formulated as fast-dissolving drug delivery system.

1.5.3 Tablet Strength and Porosity

Many attempts for fast-disintegrating behavior have been reported by lyophilizing or molding, and compressing wet powders to construct highly porous structure. When the ODT is orally applied, the drug substance has to be dissolved so that it can be absorbed. Dissolution process consists of various processes, e.g., wetting, disintegration, and dissolution. ODTs which generally contains several excipients are involved in a complex series of dissolution process that begins when the solvent contacts the solid and penetrates the tablet matrix.

The fabrication of lyophilized ODTs is based on creating a porous matrix by subliming the water from pre-frozen aqueous formulation of the drug containing matrix-forming agents and other excipients such as lyoprotectants, preservatives, and flavors. The ODTs comprise of two component frameworks of lyophilized matrix system that work together to ensure the development of a successful formulation. The first component is water-soluble polymers such as gelatin, dextran, alginate, and maltodextrin.

This component maintains the shape and provides mechanical strength to the tablets (binder). The second constituent is matrix-supporting/disintegration-enhancing agents such as sucrose and mannitol, which acts by cementing the porous frame work, provided by the water-soluble polymer and accelerates the disintegration of the ODT. Although there is wide availability of literature describing the preparation of RDTs by lyophilization, the number of matrix-supporting/disintegration-enhancing agents used has been limited to saccharides and polyols, with majority of the work dedicated to the inclusion of mannitol. This is primarily because the incorporation of these matrix-forming agents requires fulfillment of stringent characteristics such as reasonable drying time, stability during freeze-drying process, as well as formation of elegant tablets with short disintegration time and adequate mechanical properties.

1.5.4 Moisture Sensitivity

Hygroscopicity is of course, an important characteristic of a powder. It can be shown, roughly, for a fairly soluble compound that the hygroscopicity is related to its solubility. ODTs should have low sensitivity to humidity. This problem can be especially challenging because many highly water-soluble excipients are used in formulation to enhance fast-dissolving properties as well as to create good mouth feel. Those highly water-soluble excipients are susceptible to moisture; some will even deliquesce at high humidity. A good package design or other strategy should be created to protect ODTs from various environmental conditions.

1.5.5 Aqueous solubility: Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

1.5.6 Size of tablet: It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

1.5.7 Mouth feel: ODTs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the ODTs should be as small as possible. Moreover addition of flavors and cooling agents like menthol improve the mouth feel.

1.5.8 Sensitivity to environmental conditions: ODTs should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in ODTs are meant to dissolve in minimum quantity of water.

1.6 DRUG CANDIDATES SUITABLE FOR ORO DISPERSABLE TABLETS (ODTS):-

Several factors must be considered while selecting an appropriate drug candidate for development of orally fast disintegrating dosage forms.

- Drugs which require controlled or sustained release are unsuitable candidates of fast dissolving oral dosage forms.
- Drugs which are very bitter or otherwise unacceptable taste because taste masking cannot be achieved.
- Patients with Sjogre's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for ODT formulations.
- Drugs with a short half-life and frequent dosing.
- Patients who concurrently take anticholinergic medications may not be the best candidates for these drugs.
- The drugs which have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form. E.g. selegiline, apomorphine, buspirone etc.
- The drugs that produce a significant amount of toxic metabolites mediated by first pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pre-gastric GIT.
- Drugs having ability to diffuse and partition into the epithelium of the upper GIT ($\log P > 1$, or preferable > 2); and those able to permeate oral mucosal tissue are considered ideal for FDT formulations.

1.7. TECHNOLOGIES USED TO MANUFACTURE ORODISPERSIBLE TABLETS^[12]

The technologies used to manufacture mouth dissolving tablets can be classified as:

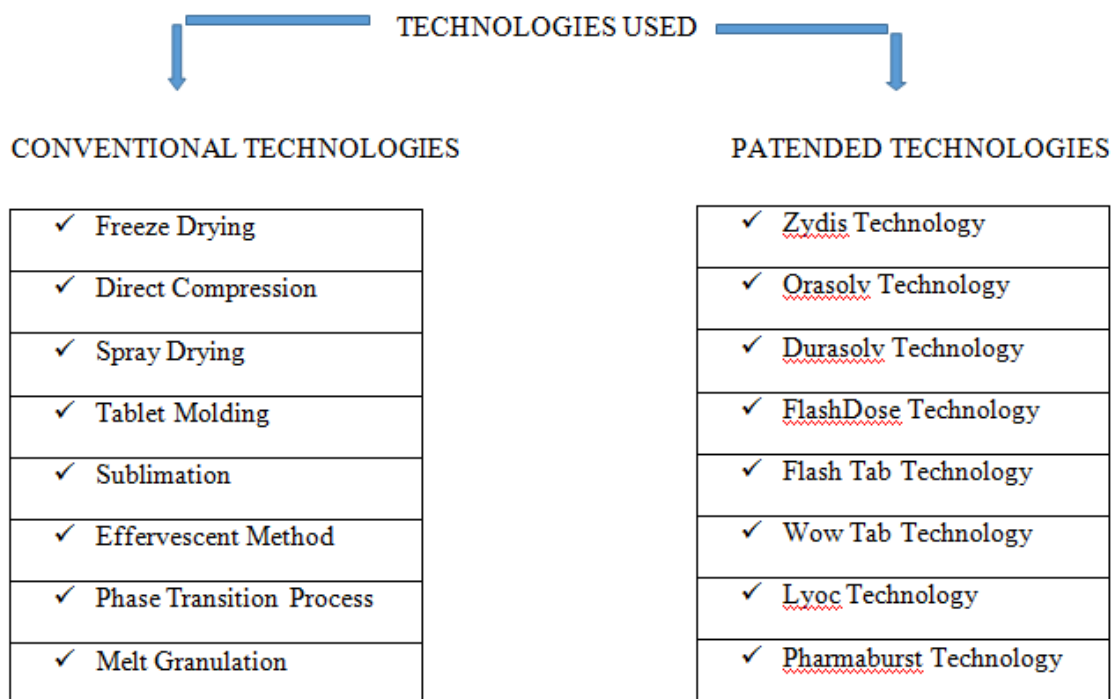


Figure:-1: Technologies Used To Manufacture Orodispersible Tablets.

TECHNIQUES FOR “ODT’s” PREPARATION

Many techniques are used for the preparation of fast disintegrating tablets which are shown in table 1.

Table 1: Various Techniques for “ODT’s” Preparation.

S. No	Techniques	Method and characteristics of prepared ODTs
1	Disintegrant addition	The basic principle involved in formulating oral disintegrating tablets by disintegrates addition technique is addition of super disintegrants in optimum concentration so as to achieve mouth dissolving along with the good mouth feel. Sodium starch glycolate, cross povidone and cross carmellose are some of the popular super disintegrants. Characteristics: Similar to conventional tablets with higher % of disintegrants, lower hardness and higher % of friability.
2	Freeze Drying or Lyophilization	Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. The drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is poured into the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing

		tunnel to freeze the drug solution. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. Characteristics: The preparations are highly porous, have high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability.
3	Tablet Molding	In this method, molded tablets are prepared by using water soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air drying. Characteristics: Molded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution.
4	Sublimation	Inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate, hexamethyl enetetramine) were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structure. Characteristics: Porous structure that enhances dissolution by using volatile material or solvent e.g. cyclohexane, benzene etc.
5	Spray-Drying	The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or cross carmellose sodium as disintegrating and an acidic material (e.g. citric acid) and or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution Characteristics: Prepared tablet disintegrates within 20 seconds when immersed in an aqueous medium.
6	Direct Compression	Direct compression method is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Characteristics: It is most cost effective tablet manufacturing technique
7	Mass-Extrusion	This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. Characteristics: The dried product can be used to coat granules of bitter tasting drugs and thereby masking their bitter taste
8	Cotton candy process	Involves the formation of matrix of polysaccharides by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with active ingredients and excipients after re-crystallization and subsequently compressed to FDTs. Characteristics: It can accommodate high doses of drug and offers improved mechanical strength

9	Nanonization	Involves size reduction of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nano crystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into FDTs. Characteristics: It is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).
10	Compaction a)Melt granulation b)Phase-transition process	Prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate not only acts as binder and increase physical resistance of tablet but also helps the disintegration of tablet. Characteristics: It melts in the mouth and solubilizes rapidly leaving no residue. Prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after heating process due to increase of inter particle bond induced by phase transition of lower melting point sugar alcohol. Characteristics: The compatibility increased and so sufficient hardness gained by the formulation.

1.8) IMPORTANT PATENTED TECHNOLOGIES FOR ORODISPERSABLE TABLETS PREPARATION:-

1.8.1. Zydis technology

Zydis formulation is a unique freeze-dried tablet in which drug is physically entrapped or dissolved within the matrix of fast-dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many materials designed to achieve a number of objectives. To impart strength during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration. Various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse protectants such as glycines prevent the shrinkage of zydis units during freeze drying process or long-term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

1.8.2. Orasolv technology

Orasolv technology has been developed by "CIMA" labs. This technology involves taste masking of active drug. Effervescent disintegrating agent is also used. Conventional blenders and tablet equipments are used for preparation of tablets. Less force of compaction is used for manufacturing to obtain soft and quickly disintegrating tablets. There is a limitation of this technology that soft and fragile tablets are formed, therefore needed to be packed in specially designed pick and place package system.

1.8.3 Durasolv technology

This is one of the suitable technologies to prepare products requiring low amounts of active drug. This technology uses drug, fillers and a lubricant to prepare the tablet. Conventional tableting equipment is used to prepare the tablet. Due to higher force of compaction used, tablets prepared are rigid. Dosage form can be packaged into conventional packaging system like blisters.

1.8.4 Wow tab technology

Wowtab Technology is patented by Yamanouchi Pharmaceutical Co. WOW means "Without Water". The active ingredients may constitute upto 50% w/w of the tablet. In this technique, saccharides of both low and high mouldability are used to prepare the granules. Mould ability is the capacity of a compound to be compressed. Highly mouldable substance has high compressibility and thus shows slow dissolution. The combination of high and low mould ability is used to produce tablets of adequate hardness. Active ingredients are mixed with low mould ability saccharides and then granulated with high mouldability saccharides and then compressed into tablet. The Wow tab product dissolves quickly in 15 s or less. Wow tab product can be packed in both into conventional bottle and blister packs.

1.8.5 Flash tab technology

The Flash tab technology is yet another fast dissolving/disintegrating tablet formulation. Prographarm laboratories have patented the Flash tab technology. It utilizes most of the same excipients as in conventional compressed tablets. A disintegrating agent and a swelling agent are used in combination with coated drug particles in this formulation to produce a tablet that disintegrates in the mouth in less than one minute.

1.8.6 Advatab technology

Advatab tablets disintegrate rapidly in the mouth, typically in less than 30 seconds, to allow for convenient oral drug administration without water. These tablets are especially suited to those patients that experience difficulty in swallowing capsules and tablets. Advatab is distinct from other ODT technologies as it can be combined with Eurand's complimentary particle technologies like its world leading Microcap taste masking technology and its Diffucaps, controlled release technology.

1.8.7 Frosta technology

Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing them at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastic material, water penetration enhancer, and binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of tablet.

1.8.8 Sheafarm Technology

The technology is based on the preparation of floss that is also known as Shearform Matrix, which is produced by subjecting a feed stock containing a sugar carrier by flash heat processing. In this process, the sugar is simultaneously subjected to centrifugal force and to a temperature gradient, which raises the temperature of the mass to create an internal, flow condition, which permits part of it to move with respect of the mass.

The floss so produced is amorphous in nature so it is further chopped and recrystallised by various techniques to provide aciform flow properties and this facilitate blending the recrystallised matrix is then blended with other tablet excipients and an active ingredient. The resulting mixture is compressed into tablet.

1.8.9 Ceform Technology

In ceform technology microspheres containing active ingredient are prepared. The essence of ceform microsphere manufacturing process involves placing a dry powder, containing substantially pure drug material or a special blend of drug materials plus other pharmaceutical compounds, and excipients into a precision engineered and rapidly spinning machine. The centrifugal force of the rotating head of the ceform machine throws the dry drug blend at high speed through small heated openings.

The microspheres are then blended and/or compressed into the pre-selected oral delivery dosage format. The ability to simultaneously process both drug and excipient generates a unique microenvironment in which materials can be incorporated into the microsphere that can alter the characteristics of the drug substance.

1.8.10 Pharmaburst technology

Pharmaburst is a “Quick Dissolve” delivery system patented by SPI Pharma. Pharmaburst is a co-processed excipient system with specific excipients, which allows rapid disintegration and low adhesion to punch faces mouldability saccharine are used to obtain rapid melting strong tablet. The active ingredient mixes with low mouldability saccharides.

1.8.11 Lyoc tech

This is patented technology of Laboratories L. Lafon, MaisonsAlfort, France. It utilizes a freeze-drying process but differ from Zydis in that the product is frozen on the freeze dryer shelves. To prevent inhomogeneity by sedimentation during this process, these formulations require a large proportion of undissolved inert filler (mannitol), to increase the viscosity of the inprocess suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets with disintegration rates that are comparable with the loosely compressed fast melt formulations.

1.8.12 Dispersible Tablet Technology

Lek in Yugoslavia was issued patents for dispersible tablets of dihydroergotoxine and cimetidine, which were claimed to disintegrate in less than 1 minute when in contact with water at room temperature. Dihydroergotoxine is poorly soluble in water in the free base form. An improved dissolution rate of dihydroergotoxinmethanesulphonate was observed with dispersible tablets containing 0.8-10%, preferably about 4% by weight, of organic acids. One of the essential excipients in the cimetidine formulation was a disintegrating agent. It provides rapid swelling and/or good wetting capability to the tablets and thereby a quick disintegration. A combination of two or more disintegrating agents produced better disintegration results.

1.8.13 Nanocrystal technology^[13-14]

For fast disintegrating tablets, Elan's proprietary Nanocrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can

be accomplished predictably and efficiently using Nanocrystal technology. Nanocrystal particles are small particles of drug substance, typically less than 1000 nanometers (nm) in diameter, which are produced by milling the drug substance using a proprietary wet milling technique.

Nanocrystal Fast dissolving technology provides for:

- Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix.
- Product differentiation based upon a combination of proprietary & patent-protected technology elements.
- Cost-effective manufacturing processes that utilize conventional, scalable unit operations.
- Exceptional durability, enabling use of conventional packaging equipment & formats (bottles &/or blisters).
- Wide range of doses (up to 200mg of API per unit).
- Use of conventional, compendial inactive components.
- Employment of non-moisture sensitive in-actives.

Nanocrystal colloidal dispersions of drug substance are combined with water-soluble GRAS (Generally Regarded as Safe) ingredients, filled into blisters, and lyophilized. The resultant wafers are remarkably robust, yet dissolve in very small quantities of water in seconds. This approach is especially attractive when working with highly potent or hazardous materials because it avoids manufacturing operations (e.g., granulation, blending, and tableting) that generate large quantities of aerosolized powder and present much higher risk of exposure. The freeze-drying approach also enables small quantities of drug to be converted into FDT dosage forms because manufacturing losses are negligible.

1.9 THE NEED FOR DEVELOPMENT OF ORO DISPERSIBLE TABLETS^[15]:-

The need for non-invasive delivery systems persists due to patient's poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

1.9.1 Patient factors:-Fast disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow traditional tablets and capsules with a glass of water. These include the following:

- Geriatric patients mainly suffering from conditions like hand tremors and dysphasia.
- Pediatric patients who are unable to swallow easily because their central nervous system and internal muscles are not developed completely.
- Traveling patients suffering from motion sickness and diarrhea that do not have easy access to water.
- Patients with persistent nausea for a long period of time are unable to swallow. Especially cancer patients after taking their chemotherapy are too nauseous to swallow the H₂ blockers, which are prescribed in order to avoid gastric ulceration. Mentally challenged patients, bedridden patients and psychiatric patients.

1.9.2 Effectiveness factor: -Increased bioavailability and faster onset of action are a major claim of these formulations. Dispersion in saliva in oral cavity causes pre-gastric absorption from some formulations in those cases where the drug dissolves quickly. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pre-gastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo hepatic metabolism. Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, and for drugs that have a substantial fraction of absorption in the oral cavity and pre-gastric segments of GIT.

1.9.3 Manufacturing and marketing factors: As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value-added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form. This leads to increased revenue, while also targeting underserved and undertreated patient populations.

1.10. MECHANISM OF ACTION ORODISPERSIBLE TABLETS

When such tablets are placed in oral cavity, saliva quickly penetrates into the pores to cause rapid tablet disintegration. Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms. Most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs over regular tablets or liquids (>80%). The US Food and Drug Administration Center for Drug Evaluation and Research

(CDER) defines, in the ‘Orange Book’, an ODT as “a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when upon the tongue.

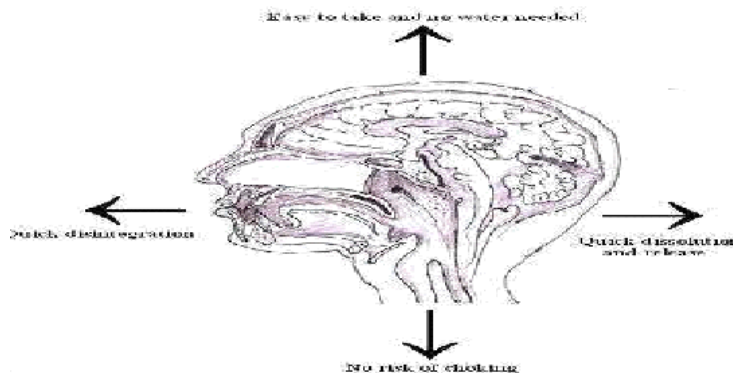


Figure 2: Mechanism of Action of Orodispersible Tablet.

1.11 EXCIPIENTS COMMONLY USED FOR ODT’S PREPARATION

Excipients used in ODTs contain at least one super disintegrants, a diluents, and a lubricant.^[16]

Table 2: Excipients Commonly Used for ODTs Preparation.

Name of the Excipients	Percentage used
Super disintegrants	1-15 %
Binder	5-10 %
Diluents	0-85 %

1.11.1 Super disintegrants^[17-18]

A “Super disintegrants” is an excipient, which is added to tablet or capsule blend to aid in the breakup of the compacted mass, when put into a fluid environment. This is especially important for immediate release product where rapid release of the product is required. These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. The use of super disintegrants is the basic approach in the development of fast disintegrating tablets (ODTs). Super disintegrants plays a major role in the dissolution and disintegration of the tablets. It is essential to choose an optimum concentration of super disintegrants so as to ensure rapid disintegration and high dissolution rates of tablets. Super disintegrants provide rapid disintegration due to combined effect of swelling and water absorption by the formulation. Due to swelling of super disintegrants, the wetted surface of the carrier increases, this promotes the wettability and dispersibility of the system, thus enhancing the disintegration and dissolution. The optimum concentration of the

super disintegrant can be selected according to the critical concentration of the disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the super disintegrant, where as above this concentration the disintegration time remains almost constant or even increases. Common super disintegrants used in formulation are cross carmellose sodium (Vivasol, Ac-Di-Sol), cross povidone (Polyplasdone), carmellose (NS-300), carmellose calcium (ECG-505), sodium starch glycolate (SSG) etc. Recently few ion exchange resins (e.g. Indion 414) are found to have super disintegrant property and are widely used in pharmaceutical industry.

The ideal characteristics of a disintegrant are:

1. High solubility
2. Good gel formation
3. Good molding and flow properties
4. No tendency to form complexes with the drugs
5. Good hydration capacity

Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment.

There are three methods of incorporating disintegrating agents into the tablet:

1. Internal addition (Intra granular)
2. External addition (Extra granular)
3. Partly Internal and External

In Internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. The disintegrant is incorporated within the granules. When these methods are used, part of disintegrant can be added internally and part externally. This provides immediate disintegrating agent within the granules produces further erosion of the granules to the original powder particles.

In External addition method, the disintegrant is added to the sized granulation with mixing prior to compression. The two-step method usually produces better and more complete disintegration than the usual method of adding the disintegrant to the granulation surface only.^[19]

List of Super Disintegrants^[20-21]

Table 3: List of Super Disintegrants.

Super Disintegrants	Example	Mechanism Of Action	Special Comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol® L-HPC	Cross linked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and Wicking both.	-Swells in two dimensions. -Direct compression or granulation -Starch free
Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	Cross linked PVP	-Swells very little And returns to original size after compression but act by capillary action	-Water insoluble and spongy in nature so get porous tablet
Sodium starch glycolate Explotab® Primo gel®	Cross linked starch	-Swells 7-12 folds in < 30 seconds	-Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF Satialgine®	Cross linked alginic acid	-Rapid swelling in aqueous medium or wicking action	Promote disintegration in both dry or wet granulation
Soy polysaccharides Emcosoy®	Natural super disintegrant		-Does not contain any starch or sugar. Used in nutritional products.
Calcium silicate		Wicking Action	Highly porous, Optimum concentration is b/w 20-40%

1.11.2 Binders

The choice of a binder is critical in a orally - dissolving formulation for achieving the desired sensory and melting characteristics, and for the faster release of active ingredient. Binders can either be liquid, semi solid, solid or mixtures of varying molecular weights such as polyethylene glycol. Main role of Binders is to keep the composition of these fast-melting tablets together during the compression stage.

Binders commonly used are cellulosic polymers, povidones, polyvinyl alcohols, and acrylic polymers. Among the cellulosic polymers it will be advantageous to select ethylcellulose, hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), alone or in admixtures, and the most commonly acrylic polymer used are the ammonio-methacrylate copolymer (Eudragit.RL and RS), polyacrylate (Eudragit NE), and polymethacrylate (Eudragit E). The temperature of the excipient should be preferably around 30–35°C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system.

1.11.3 Diluents

The most common antistatic agents used are colloidal silica (Aerosil), precipitated silica micronized or non- micronized talc, maltodextrins, beta-cyclodextrins, etc. Magnesium stearate, stearic acid, sodium stearyl fumarate, micronized polyoxyethyleneglycol, sodium benzoate are used as lubricant. An additional thickening agent, generating a stabilized suspension, is added to avoid settling of the particles and moreover provide a pleasant mouth feeling. Commonly used Diluents are most commonly selected from cellulose derivatives and preferably microcrystalline cellulose, starches, lactose, polyols and preferably mannitol.

1.12 MECHANISM OF ACTION OF SUPER DISINTEGRANTS^[22-27]

The tablet breaks to primary particles by one or more of the mechanisms listed below: -

(a) Porosity and capillary action (Wicking)

Capillary action is always the first step in tablet disintegration. Suitable aqueous medium into which tablet is placed, penetrates into the tablet and replaces the air adsorbed on the particles there by weakens the intermolecular bond and breaks the tablet into fine particles.

Water uptake by tablet depends upon hydrophilicity of the drug /excipients and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

b) Swelling

The general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is to penetrate in the tablet and disintegration is again slows down.

(c) Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegrating attempts to explain the swelling of tablet made with non swellable disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non swelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

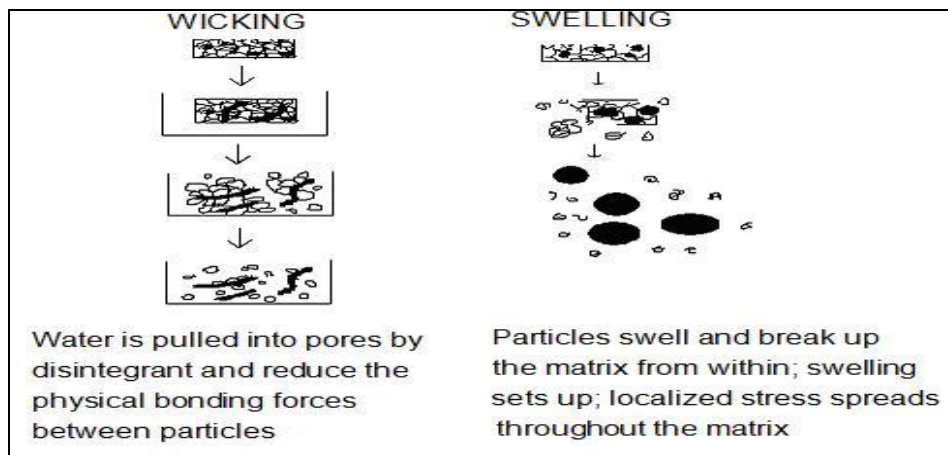


Figure 3: Mechanism of Action of Wicking and Swelling.

(d) Due to deformation: (Elastic recovery)

Most materials, which undergo a plastic deformation during compression, try to return to their initial shape as soon as possible (stored potential energy). In the tablet matrix, there is no means to recover the former shape. But as soon as water penetrates into the tablet matrix and the forces, which keep the particles together, are diminished, those particles have the ability to expand back. After compression, these particles are plastically deformed. After penetration of water into the tablet, these particles return back to their initial shape.

(e) Due to release of gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or orally disintegrating tablet, as these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in two separate fractions of formulation.

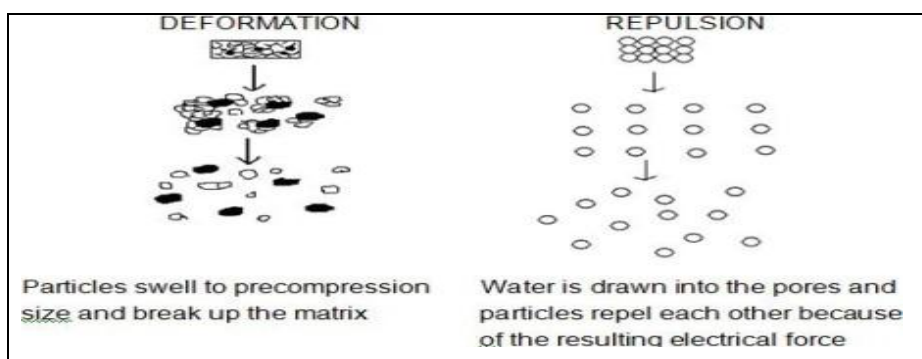


Figure 4: Mechanism of Action of Repulsion and Deformation.

(f) By enzymatic reaction

Here, enzymes present in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration. Actually, due to swelling, pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

(g) Because of heat of wetting (air expansion)

When disintegrants with exothermic properties gets wetted localized stress is generated due to capillary air expansion, which helps in disintegration of the tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

1.13 SALIENT FEATURES OF ORO DISPERSIBLE TABLETS:

- Ease of Administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.
- The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.

Marketed Products of Orodispersible Tablets:**Table 4: Marketed products of Orodispersible tablets.**

Brand name	Active Drug	Manufacturer Company
Benadryl	orally melt Diphenhydramine	Pfizer
Benadryl	Fast melt Diphenhydramine	Warner Lambert
Cibalginadue	FAST Ibuprofen	Novartis Consumer Health
Domray MD	Domperidone	Ray Remedies
Dolib MD	Rofecoxib	Panacea

Feldene	meltPiroxicam	Pfizer
Febrectol	Paracetamol	Prographarm
Imodium Instant	melts Loperamide Hcl	Janssen
Kemstro	Baclofen	Schwarz Pharma
Maxalt-MLT	Rizatriptan Benzoate	Merck
Mosid MT	Mosapride	Torrent
Nulev	Hyoscyamine sulfate	Schwarz Pharma
Nimulid MD	Nimusulide	Panacea
Olanex	InstabOlanzepine	Ranbaxy
Pepcid ODT	Famotidin	Merck

Various Starch Used in Odt's

Table 5: Various starch used in ODTs.

Starch crops	Starch contents
Sweet potato	10-30%
Potato	10-30%
Cassava	50-60%
Sorghum	65-75%
Wheat	60-80%
Rice	70-78%
Beans	40-60%

1.14. EXTRACTION METHODS OF STARCH:-

1.14.1. Tuberos Crop Starch Production

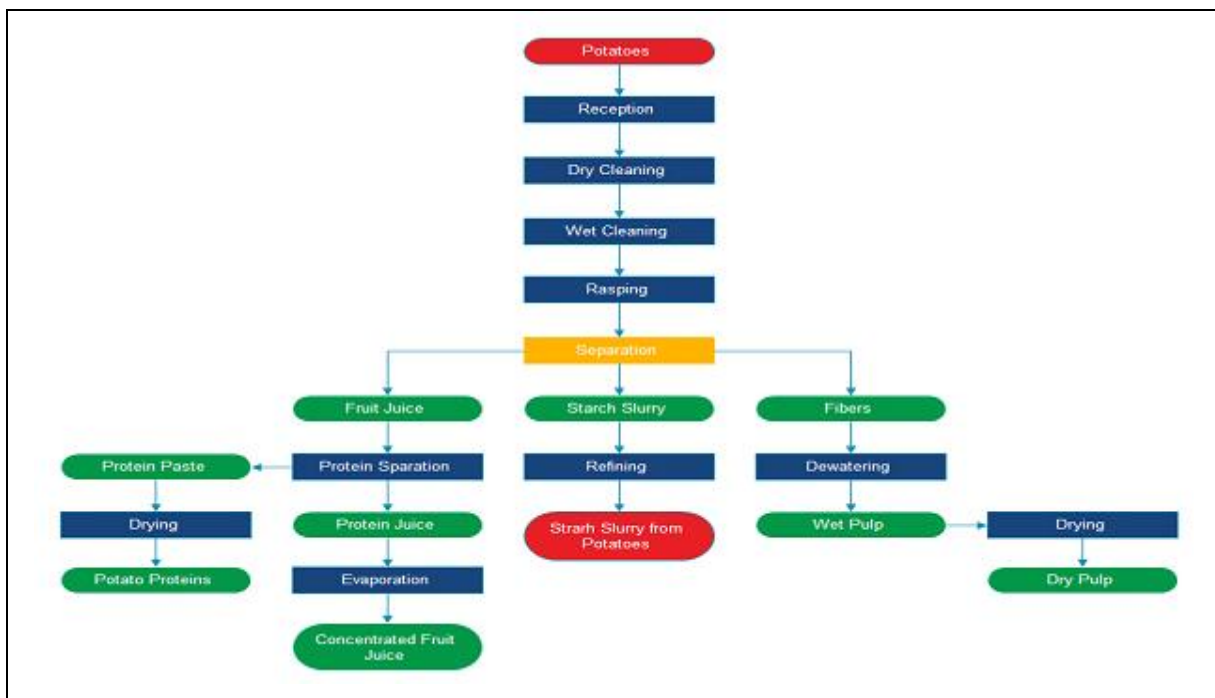


Figure 5: Tuberos Crop Starch Production.

1.14.2. WHEAT CROP STARCH PRODUCTION

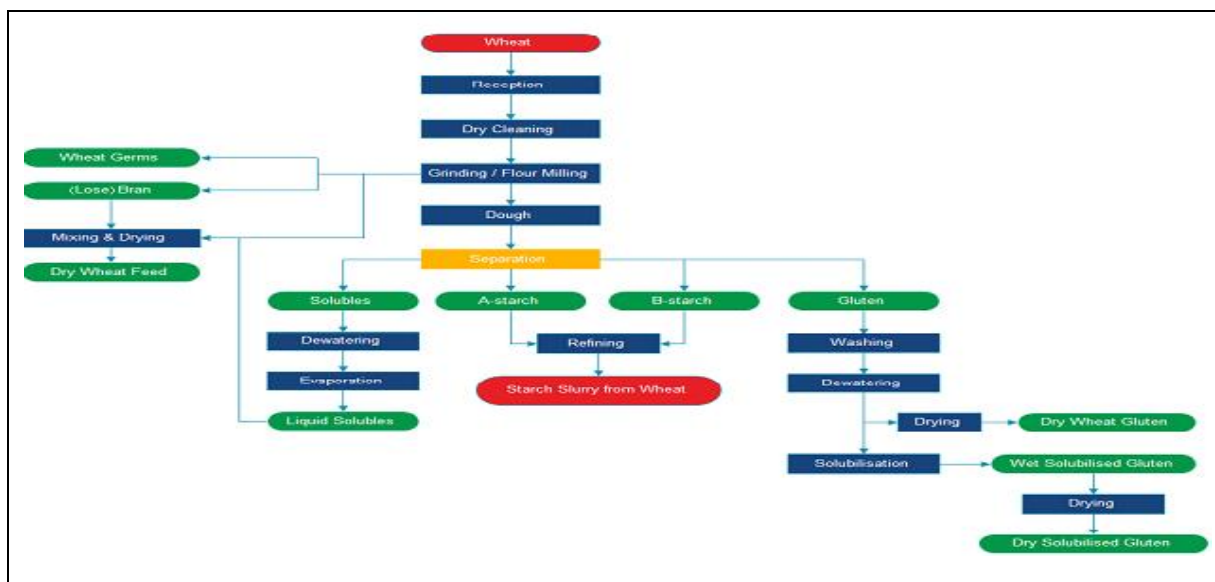


Figure 6: Wheat Crop Starch Production.

1.15 METHODS OF MODIFICATION OF STARCH^[28-35]

1.15.1. Chemical Modification of Starch

The chemical modification is done by addition of a new chemical or functional groups in starch without using any physical alteration in the shape and size of the molecule. The glucose units in the starch consists amylose and amylopectin. The amylase and amylopectin have three reactive hydroxyl groups which plays the major sites for chemical modification in starch. The chemical modification alters the physical behavior of starch including retrogradation, salting, and gelatinization that work by stabilizing the intermolecular and intramolecular bonding of starch granules.

The following are the methods for chemical modification of starch:

- Oxidation by different oxidizing agents
- Etherification by addition of some hydroxyethyl moieties on hydroxyl groups of starch
- Etherification by addition of some hydroxypropyl moieties on hydroxyl groups of starch
- Etherification by addition of some carboxymethyl moieties on hydroxyl groups of starch
- Esterification by condensation of some fatty acids with active hydroxyl groups of starch
- Esterification by condensation of some other carboxylic acids with active hydroxyl groups of starch
- Esterification by condensation of some phosphates with active hydroxyl groups of starch
- Cationization by introducing some cationic molecules

- Cross-linking by addition of various cross-linkers
- Graft-polymerization of starch with synthetic polymers.

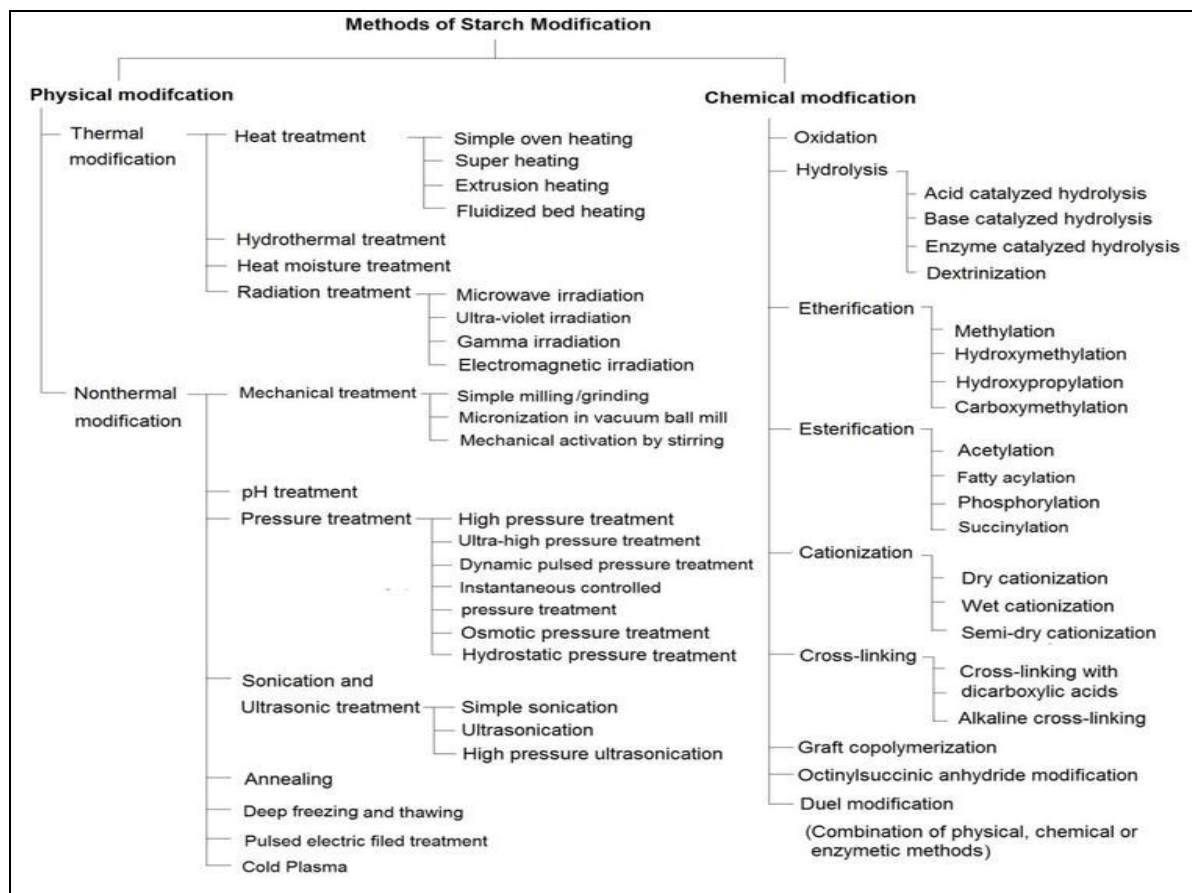


Figure 7: Methods of Modification of Starch.

METHODS OF CHEMICAL MODIFICATION OF STARCH:-

Table 6:- Chemical Modifications of Starch.

MODIFICATION METHOD	TREATMENT	CHANGE IN STRUCTURE	CHANGE IN PROPERTIES
Oxidation	In oxidation the carbonyl and carbonyl group are added to native starch with the help of an oxidizing agent	It leads to depolymerization of starch which results in retardation in recrystallization. This is due to the involvement of carbonyl and carbonyl groups	The modification leads to increase in the stability, clarity and binding properties but it decreases the starch dispersion viscosity.
Stabilization by addition of a polymer	The modification leads to increase in the stability, clarity and binding properties but it decreases the starch dispersion	It increases the starch structural stability but reduces the retrogradation.	It improves the freeze-thaw stability and also increases the shelf life of starch-based food products.

	viscosity.		
Hydroxyethylation	Hydroxyethyl group is introduced into the starch.	.The granular structure changes.	.Drug binding capacity of anti cancer drugs and other drugs increases.
Hydroxypropylation	Hydroxyethyl group is introduced into the starch.	It causes the disturbance in inter- and intra-molecular hydrogen bonds and weakens the starch granular structure. It leads to the free movement of starch chains in amorphous regions.	It improves the peak viscosity, binding capacity of water, swelling power, solubility and digestibility of enzymes of starch. It increases the clarity of paste and freeze–thaw stability. But it reduces the gelatinization parameters, gelatinization enthalpy and transition temperatures. It also reduces the gel hardness and gel adhesiveness.
Carboxymethylation	Hydroxyl groups in the starch is substituted with carboxymethyl group.	It leads to addition of the lipophilic groups on to the starch molecule.	It leads to the improvement of starch stability in aqueous media, and also decreases the ability of recrystallizing and inhibits the heat damage and inhibits the damage from microorganisms.
Acetylation	It involves the reaction of hydroxyl group of polymeric starch with the acetyl group.	It delays the crystallization or retrogradation in the starch granules.	It leads to prevention of the formation of intramolecular hydrogen bonds and increases the viscosity of granules and swelling capacity of granules. It also leads to reduction of the pasting temperature and solubility.
Fatty acylation	Fatty acids reacts with starch.	The formation of amylose-fatty acyl complexes takes place.	Changes in the optical activity and thermal behavior of starch is observed.
Phosphorylation	Phosphate group add some starch hydroxyl groups.	It leads to the formation of monophosphate starch or diphosphate starch. The stearic hindrance increases and inhibits the linearity of molecular chains.	It enhances the viscosity, textural properties, clarity of paste and Freeze-Thaw stability of starch. It also provides resistance to low pH, high temperature, and high shear. It also decreases the gelatinization temperature.
Succinylation	Starch is treated with Octinylsuccinic anhydride.	The derivatization of starch with alkenyl succinic anhydrides.	The modification leads to the swelling volume, peak viscosity, hot paste viscosity,

			and cool paste viscosity but reduces the temperature of gelatinization and hardness of gel. It also enhances the production of slow-digesting and resistant starch.
Cationization	Starch is treated with various cationic molecules.	Involvement of amino, ammonium, imino, phosphonium or sulfonium groups leads to the positive ionic charge to starch.	Improves the solubility, stability, dispersibility, and starch clarity.
Dry cationization	By dry heating the citric acid gets converted to anhydride. In the absence of liquid phase the cationic molecules are sprayed on dried starch during extrusion.	It leads to the formation of cross-linked starch citrate.	The granular structure of starch gets altered and enhances the adsorption properties.
Wet cationization	With cationic molecules homogenous and heterogenous reactions of starch occur with the help of a liquid medium.	Leads to the formation of cross-linked starch.	It enhances the viscosity but decreases the temperature of paste.
Semi-dry cationization	It involves mixing of starch with cationic molecules and involves thermal reaction.	Leads to starch cationic cross-linking.	It leads to a very high degree of substitutions in starch granules.
Cross-linking (Formation of inter and intramolecular bridges)	Etherification and esterification of granules with cross-linking polymers by reacting with a mixture (99:1) of sodium trimetaphosphate and sodium tripolyphosphate or other cross-linkers in an aqueous alkaline slurry containing sodium sulfate.	It changes or decreases the amorphous chains mobility in the starch granule. It introduces the inter- and intra-molecular bonds with multifunctional small molecules with hydroxyl groups on starch to strengthen the granules against various factors. It enhances the ordering of internal granule structure and stability.	It reduces the solubility of starch in water which in turn decreases its interaction with lipids, moisture, and proteins. It also causes reduction in viscosity, swelling capacity, digestibility, rate of retrogradation, the peak temperature of relaxation endotherm and enthalpy of starch. It enhances the temperature of gelatinization, glass transition temperature, melting enthalpy, free volume of starch chains,

			relaxation enthalpy and stability of starch to high temperature.
Acid cross-linking	Starch reacts with acids	-	It enhances the temperature of gelatinization and also the breadth of the gelatinization endotherm.
Graft copolymerization	Synthetic polymers such as poly (ethylene terephthalate), polyethylene, polypropylene, polyvinyl chloride, and polystyrene are copolymerized with starch.	Starch structure changes from homopolymer to heteropolymer.	Leads to changes in physical properties and also starch reactivity.
Dual modification (Modification using the combination of different physical and chemical methods)	Modification is done using the combination of microwave and ultrasound irradiation and esterification of carboxymethyl cold-water-soluble starch with octenyl succinic anhydride.	-	It decrease the esterification time and starch production with better emulsifying and surfactant properties, good freeze-thaw stability.
Cross linking with hydroxypropylation or acetylation	Cross-linking in combination with hydroxypropylation or acetylation.	-	Slow-digesting and resistant starch production increases.

In cationic modifications the secondary and tertiary ammonium, imino, amino, sulfuric acid and phosphate groups react with starch hydroxyl groups. Due to this the dielectric constant of starch granules increases. It is used as additive in the textile industry, in paper and cosmetic industry due to low price, rapid degradation and more bioavailability.

Cross-linking involves the covalent interaction between the starch molecules. The reagents are used as copolymers in starch include sodium trimetaphosphate, sodium tripyrophosphate, epichlorohydrin and phosphoryl chloride. It is useful in the food industry and also used to making of plastics due to involvement of resistant properties.

The addition of anhydrous acetyl group or vinyl acetate to starch granules in the presence of sodium hydroxide and potassium hydroxide is known as esterification. Acetylated starch will have more importance at the industrial level. Industrial level it is used as thickener, stabilizer, adherent and encapsulator.

1.15.2. Physical Modification

Morphology and three-dimensional structure changes of starch occurs by the influence of physical factors like milling, moisture, temperature, pressure, pH, radiation, pulse-electric field, ultrasonic waves, etc. it leads to the variation in particle size, surface properties, solubility index and also functional properties like water absorption, swelling capacity, pasting and gelation ability of starch. The physical modifications have direct influence on quality, selectivity and suitability of the modified starch for various nutritional, pharmaceutical and industrial formulations. Various studies conducted on the physical modification of starch using various methods.

The mostly used methods of physical modification involves

- Superheating of starch
- Thermal inhibition treatment
- UV and gamma irradiation
- Microwave treatment
- High pressure treatment
- Osmotic pressure treatment
- Instantaneous controlled pressure treatment
- Mechanical activation by stirring ball mill
- Treatment by pulsed electric field
- Micronization in vacuum ball mill
- Annealing and freeze–thaw treatment

METHODS OF PHYSICAL MODIFICATION OF STARCH:-

Table 7: Physical Modifications of Starch.

Modification method	Treatment	Change in starch structure	Change in starch properties
Thermal modification			
<i>Heating treatments</i>			
Gentle heating	Starch is heated at low temperature (45–65°C)	Slight changes occur in starch structure and difference in amylopectin to amylose ratio occurs.	No effect on the physicommechanical properties of starch.
Superheating	Starch is heated at relatively high temperature (180–220°C)	Formation of easily spreadable gel particles with a creamy texture on cooling.	Enhances the gelatinization and starch pasting properties.

Extrusion heating	Mechanical force is applied in low-temperature environment.	Leads to the degradation of amylose and amylopectin of the starch polymer. This is due to random chain-splitting. It also leads to a high degree of granule disruption with complete loss of crystallinity	It decreases the swelling power and viscosity and but enhances the water solubility and also starch digestibility.
Hydrothermal treatment	Starch is heated with an aqueous medium.	Leads to physical reorganization of starch granules	Enhances the granule size, mobility, and stability which is useful in easy digestion by amylase. And also enhances the starch gelatinization properties.
Heat-moisture treatment	Heat and moisture applied. The moisture is limited amount. The moisture levels: 22–27% and high temperature above the glass-transition temperature: 100–120°C for a specified length of time: 1–24 h	Causes change in size, shape and granular and crystalline structure of starch. It leads to a partial or complete conversion of the B-type crystalline starch to A-type. It also leads to destruction of helical structures within the amorphous regions of starch granules. It causes the molecular degradation of starch and improves the degree of polarization.	It reduces the leaching of amylose, peak viscosity, and swelling capacity and enhances the solubility, thermal stability, gelatinization temperatures, pasting temperature, pasting time, interaction properties and susceptibility of starch to chemical and enzymatic attack (α -amylase and acid hydrolysis).
Radiation treatment			
Microwave irradiation	microwave radiation is applied at different ranges of moisture and temperature to influence starch dielectric constant..	Increases the granular crystallinity and surface morphology of starch.	Microwave treatment enhances the water and oil holding capacity, emulsifying activity, swelling capacity, solubility, and gelling ability. It also improves the pasting temperature and paste viscosity. It decreases the peak viscosity and gelatinization, and the degree of relative crystallinity
Ultraviolet (UV) irradiation	Starch granules exposed to UV light.	Leads to free radical-induced cross-linking and depolymerization, oxidative photodegradation, and dextrinization in starch.	UV treatment Influences the physical, chemical and functional properties of starch.
Gamma irradiation	Exposure of starch granules to various doses of high energy gamma	Gamma irradiation causes the breakage of the amylopectin chains at the amorphous regions and decreases the	The exposure to gamma radiation decreases the pasting viscosity, and enthalpy change of starch and molecular weight and gyration radius of amylopectin. It increases

	radiation.	amylopectin to amylose ratio. It also causes the radiolysis and radio-depolymerization of starch	the susceptibility of starch towards amylase. It also improved the rheological properties such as gelatinization viscosity, swelling power, and solubility.
Non-thermal modification			
pH treatment	Addition of some acid or base to change the pH of the medium.	A high pH results in partial degradation of starch granules with a decrease in molar size and radius of gyration. A low pH results in hydrolysis of starch particularly in the amorphous region of granules and decreases the molecular weight of the starch.	Increase in pH improves the solubility, swelling power, and compression properties. Low pH treatment improves the gelation properties of starch.
Moisture treatment		Moisture acts as plasticizer and anti-plasticizer for starch films for different properties	It causes a plasticizing effect on calorimetric glass transition temperature, linear expansion, tensile modulus, and water vapor permeability while an anti-plasticizing effect on mechanical properties i.e. tensile strength and toughness.
Mechanical treatment			
Simple milling/grinding	It involves the grinding of starch by physical forces	It decreased the crystalline/amorphous ratio, crystallinity, content of double helix of starch. It also results in a rapid increase and then a gradual decrease in surface parameters.	It reduces the viscosity and increases the susceptibility of physical and chemical factors to starch. It increases water-binding capacity, adsorptive capacity, and reactivity of starch.
Micronization in vacuum ball mill		It damages the B-type starch granules, results in loss of the granular order and double-helix content and reductions in crystallinity. It also causes depolymerization of starch polymer molecules.	Changes the rheological properties of starch. It increases the water adsorption, iodine binding capacity, granule swelling, solubility and susceptibility of starch to amylase. It decreases the viscosity, and elasticity of paste.
Mechanical activation by stirring	Application of mechanical force on starch by stirring ball mill.	The treatment results in the degradation of the crystal structure to amorphous particles and formation of an agglomerate of the	It reduces the gelatinization temperature and enthalpy, shear-thinning, and apparent viscosity of starch resulting in enhancement of cold-water solubility of the starch.

		resulting amorphous particles.	
Pressure treatment			
High-pressure treatment	Treatment of starch under pressure < 400 MPa.	It exerts a pressure and time-dependent effect on the microstructure of starch. It causes melting of amylopectin crystals and loss of birefringence.	The pressure treatment causes changes in rheological properties of starch. It increases the hardness and chewiness and improves the freeze-thaw stability of the starch gels.
Ultra-high pressure treatment	Treatment of starch under pressure > 400 MPa.	It distorts in the crystalline region and transits A-type crystalline starch to B-type.	It increases the swelling of starch granules and restricts the amylose leaching. It lowers the gelatinization temperature.
Instantaneous controlled pressure treatment		The treatment increases the median volume diameter in cold water.	It decreases the gelatinization enthalpy and birefringence under polarized light.
Osmotic pressure treatment	Heating of starch in a hypertonic (saturated) solution of sodium sulfate at 100–120°C across the semipermeable membrane	It causes distortion in the shapes of starch granules and changes the B-type crystalline starch to A-type.	This modification increases the gelatinization temperature.
Hydrostatic pressure treatment	Application of high pressure ranging from 400 to 900 MPa.	It causes the disintegration and retrogradation of starch granules.	It retards the swelling of granules or reduces viscosity with preserving the taste and nutrient of starch
Ultrasound treatment			
Ultra-sonication	Treatment of starch with ultrasonic waves.	It distorts the starch granules	It increases the solubility, viscosity and swelling capacity of granules and reduces the pasting ability and digestibility of starch. It also increases the gelatinization temperature and enthalpy and decreases the solubility.
High-pressure ultra-sonication	The treatment of ultrasound waves to native starch granules. at 24KHz to 360KHz frequency	It distorts in the crystalline region of the starch granules.	It decreases the enthalpy of gelatinization, consistency coefficient, crystallinity and molecular weight of starch granules.
Annealing	Modification of starch in the presence of intermediate water contents	It increases interaction between the amylose-amylopectin and amylose-amylose chains and the crystalline	Decreases the amylose leaching and swelling of granules and increases thermal stability gelatinization temperatures, and susceptibility towards α -amylase.

	(40–50% w/w) or excess water more than 65% w/w at temperatures lower than the onset temperature of gelatinization	perfection. It enhances the mobility of double-helical chain segments within granules, allows subsequent recrystallization, restructuring, or both of starch chains, enhances molecular order and provides more homogeneity among crystallites	
Thermal inhibition	Dehydration of starch at a high temperature until it becomes anhydrous (<1% moisture)	It results in a decrease in granular size.	It increases the cohesive-texture and stabilizes the viscosity of starch.
Cold plasma	Treatment of starch with low-temperature plasma or glow-discharge plasma.	It causes free radical-induced cross-linking of starch and increases the amylose leaching. It reduces the relative crystallinity due to active plasma species-induced depolymerization.	It influences the physical and functional properties of starch. It increases the pasting and viscosity but decreases the retrogradation tendency.
Pulsed electric field (PEF) treatment	Processing of starch-water suspension in electric field strength of 50 kV/cm.		It reduces enthalpy, gelatinization temperature, enthalpy, viscosity and crystallinity of granules. The granule diameters increase with increase in the field strength.
Freezing	Freezing the starch at very low temperature (sub-zero levels)	Reversible structural disorder on starch granules,	It causes the change in the texture and gelatinization properties and increase in retrogradation.
Freeze–Thaw treatment	Heating of starch at high temperature (59–79°C) flowed by freezing and defrosting.	An increase in the number of Free-Thaw cycles changes the complex modulus and phase angle of the starch.	Affects the rheological properties of starch. Increases the swelling power, viscosity, and thermal stability of starch. It also influences the surface properties of the starch granules.
Dual modification	Treatment of starch with a combination of different physical factors.		
Heat-moisture treatment-	Heat-moisture	No significant damage of	Increase in enthalpy.

annealing	treatment followed by annealing.	individual treatment on the structure of starch granules has been observed. Heat-moisture-annealing treatment resulted in disruption of crystalline structure.	
Annealing-sonication and Sonication-annealing	Annealing followed by sonication and vice versa.	Both treatments promote a synergic behavior on crystallite collapse and result in a decrease in relative crystallinity. The later also results in irregular surface morphologies and granule disintegration.	Both increase the pasting viscosity

2. AIM & OBJECTIVE:-

2.1 AIM OF PRESENT STUDY:-

Difficulty in swallowing (dysphagia) is a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with those groups. Other categories that experience problems in using conventional oral dosage forms include the mentally ill, uncooperative and patients suffering from nausea, motion sickness, sudden episodes of allergic attack or coughing. Sometimes it may be difficult to swallow conventional products due to non-availability of water. These problems led to the development of a novel type of solid oral dosage form called orodispersible tablet, which disintegrates/dissolves rapidly in saliva without the need of drinking water.

The benefits in terms of patient compliance, rapid onset of action, increased bioavailability and good stability make these tablets popular as a dosage form of choice in the current market. Some drugs are in such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.

The basic approach used in the development of the ODTs is the use of superdisintegrants. Many approaches have been developed to manufacture ODTs. These include vacuum drying direct compression, lyophilization and molding. The direct compression method is inexpensive and convenient for producing tablets of sufficient mechanical strength.

In the present study, orodispersible tablets of Gingerol, are designed by using natural superdisintegrants (*Musa paradisiaca* starch/green banana starch), modified *Musa paradisiaca* starch using Glutamic acid (starch glutamate) and synthetic superdisintegrants namely Sodium starch glycolate (SSG) in three different varying concentrations of 2%, 4% and 6%.

The designed tablets were evaluated for thickness, hardness, friability, weight variation, *in vitro* dispersion time, wetting time, water absorption ratio, disintegration time, drug content uniformity, *in vitro* dissolution rate (in pH 6.8 phosphate buffer), and drug excipient interactions (FTIR spectroscopy).

Antiemetics are the agents which can block nausea and vomiting sensations, which are frequently encountered with chemotherapy, radiation therapy, and post operative inducing nausea and vomiting. Gingerol is a selective serotonin 5-HT receptor antagonist indicated for the prevention of nausea and vomiting and reported to be well absorbed from the gastrointestinal tract.

2.2 OBJECTIVE OF THE STUDY: -

The objective of the present study is to develop an Gingerol Orodispersible tablets.

- The concept of orodispersible drug delivery system is to provide patient with conventional means of taking their medication.
- In some cases such as motion sickness, sudden episodes of allergic attacks or coughing and unavailability of water, swallowing conventional tablets may be difficult.
- Such problems can be resolved by means of orodispersible tablets when put on tongue these tablets disintegrate and dissolve rapidly in saliva without need of drinking water.
- Some drugs are absorbed from the mouth, pharynx and oesophagus as saliva passes down into the stomach.
- In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form.

2.3 NEED FOR THE STUDY:

The tablet is the most widely used dosage form existing today because of its convenience in terms of self-administration, compactness and ease in manufacturing. However, geriatric, pediatric and mentally ill patients experience difficulty in swallowing tablets, leading to poor patient compliance and thereby, in one or the other way a therapeutic failure. To overcome

these problems, scientists have developed innovative drug delivery system known as Orodispersible/ disintegrating tablets which are novel types of tablets that dissolve/ disintegrate/ disperse in saliva within few seconds without water. These are also called as melt-in-mouth tablets, repimelts, porous tablets, oro dispersible, quick dissolving or rapid disintegrating tablets.

Orodispersible tablets are defined as “a solid dosage form containing medicinal substances, which disintegrates rapidly, usually with a matter of seconds, when placed upon the tongue. It provides good stability, accurate dosing, easy manufacturing, and small packing size and easy handle. Easy of swallowing without aid of water Rapid onset of action, enhanced dissolution rate, increased gastric absorption, improved oral bioavailability, improved patient compliance, convenient to administer during travelling or working without need of water.

2.4 ANTI-EMETIC DRUGS IN ORO-DISPERSIBLE TABLET:

2.4.1 Emesis: Emesis is not a disease, but is only indications of altered physiological functions. Vomiting is a forceful action accomplished by a downward contraction of the diaphragm. At the same time, the abdominal muscles tighten against a relaxed stomach with an open sphincter. The contents of the stomach are propelled up and out.

2.4.2 Rational of Selecting Anti-emetic Drug for Fast Dissolving Tablet

Retention of the administered anti-emetic oral doses and its subsequent absorption during anti-emetic therapy is critically affected by recurrent emesis, a process coordinated by vomiting centre in lateral reticular formation of the medulla receiving inputs from the chemoreceptor trigger zone and other neural sites.^[36] Vomiting induced by chemotherapy, motion sickness, pregnancy, migraine, physiological processes like impaired gastric emptying and other gastric disturbances will also affect drug retention and absorption. Retention of oral dose is therefore, a prerequisite for absorption to prevent emesis. For drug with low bioavailability, partial drug loss by emesis will result in therapeutic failure. Such anti-emetic drug, after oral dosing undergoes extensive gastric and first pass effect. This results in low bioavailability which therefore, will not minimize the rate of vomiting. In general, emesis is preceded with nausea and in such condition it is difficult to administer drug with a glass of water; hence it is beneficial to administer such drugs as fast dissolving tablets. Fast dissolving tablet of anti-emetic drugs are designed for rapid and complete absorption in the body and for achieve therapeutic success.

Pathophysiology of Emesis

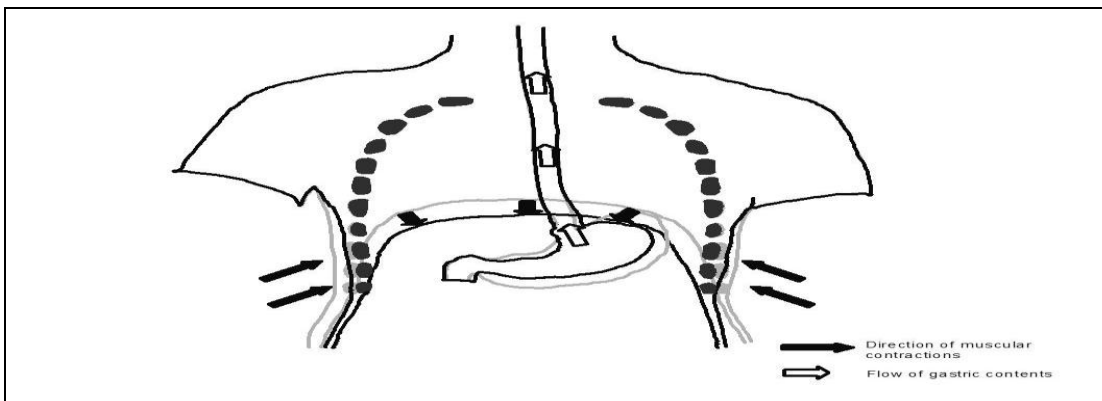


Figure 8: Pathophysiology of Emesis.

2.4.3 Drug Treatment of Nausea and Vomiting

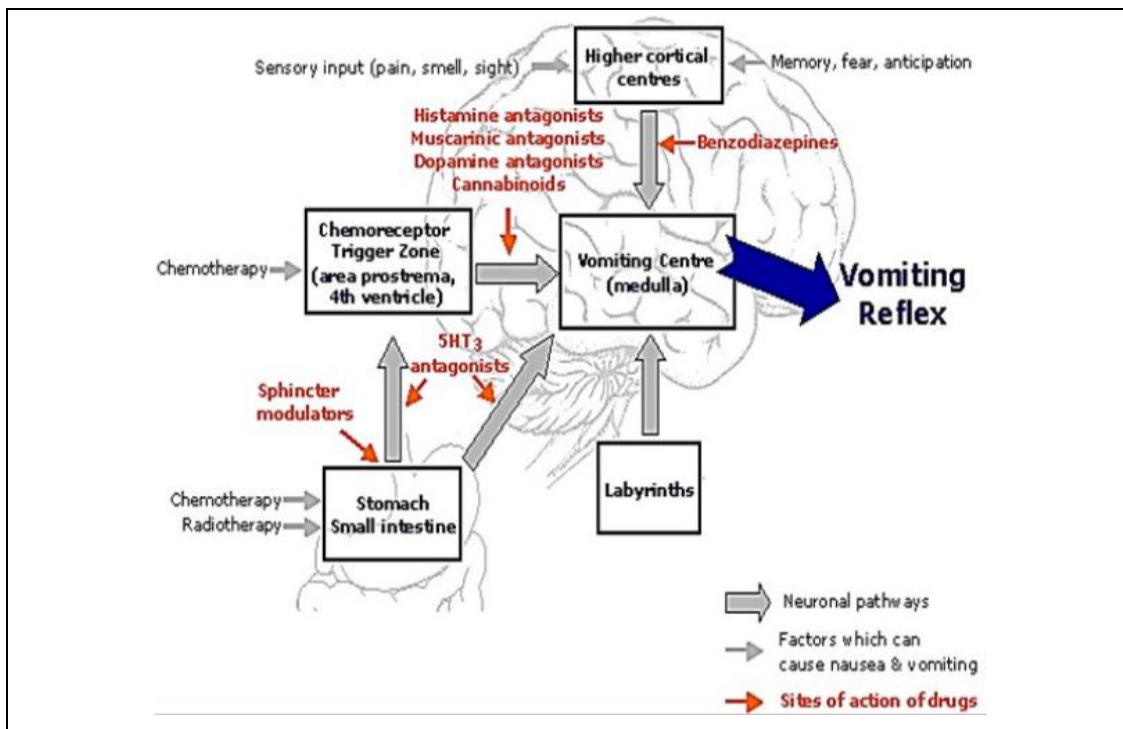


Figure 9: Drug Treatment of Nausea and Vomiting.

2.4.4 Selected Anti-emetic Drug for Oro-dispersible Tablet

Gingerol is specific anti-emetic drug prescribed in all cases of nausea and vomiting (chemotherapy, motion sickness, pregnancy, migraine, physiological processes like impaired gastric emptying and other gastric disturbances). This drug is tasteless molecules and has low bioavailability, low dose and lesser side effects than other anti-emetic drugs.

3. PLAN OF WORK:-

The present work was carried out to prepare and evaluate Gingerol orodispersible tablets

using different superdisintegrants (Natural and synthetic) in various concentrations.

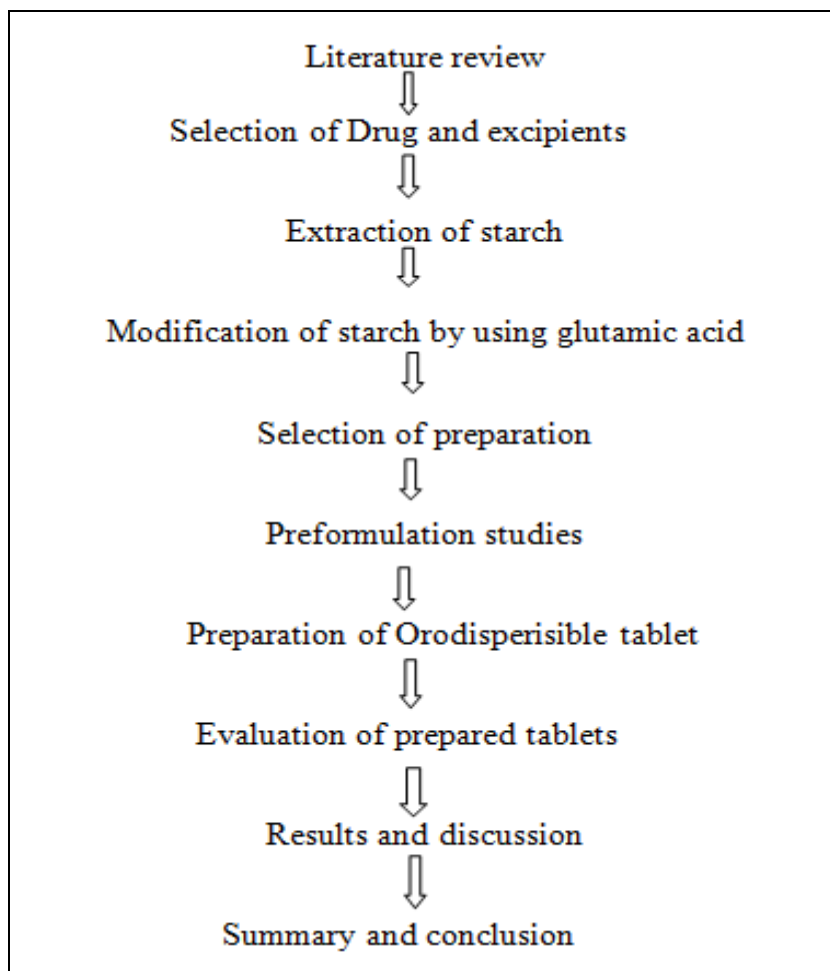
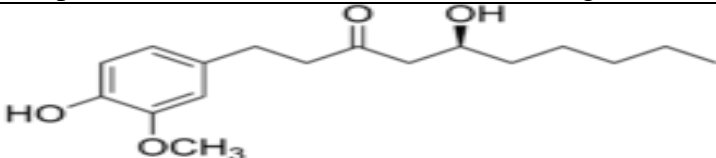


Figure 10: Plan of work.

4. DRUG PROFILE:-

4.1 GINGEROL^[37]

Table 8: Drug Profile of Gingerol.

Name	Gingerol (from ginger)
Description	It is normally found as a pungent yellow oil in the ginger rhizome, but can also form a low-melting crystalline solid. This chemical compound is found in all members of the Zingiberaceae family
Structure	 <p>Figure 11: Structure of Gingerol</p>
Synonyms	<ul style="list-style-type: none"> • (6)-gingerol • 10-gingerol • 6-gingerol • Gingerol
Brand names	Zingiber

	Focalgin-B B-Nexa
Category	Anti emetic
Molecular weight	294.4
Chemical formula	C ₁₇ H ₂₆ O ₄
Iupac name	(5S)-5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)decan-3-one
Absorption	This pungent component of ginger is absorbed rapidly with a maximum plasma concentration of 4.24 µg mL ⁻¹ after 10 min of oral dosing (240 mg kg ⁻¹ of a ginger extract containing 53% of [6]-gingerol)
Metabolism	Although the metabolites derived from gingerol were not detected in the urine, the ethyl acetate extract of the urine after enzymatic hydrolysis was shown to contain six minor metabolites.
Route of elimination	The total cumulative amount of 1 excreted in the bile and 2-7 in the urine during 60 h after the oral administration of [6]-gingerol were approximately 48% and 16% of the dose, respectively. The excretion of 2-7 in the urine decreased after gut sterilization.
Half life	Gingerol conjugates began to appear 30 minutes after oral dosing, reaching their T _{max} between 45 to 120 minutes, with elimination half-lives ranging from 75 to 120 minutes at the 2.0 g dose.
Indication	Ginger is an herbal supplement, which can be used as a natural remedy in treatment of antiemetic, carminative, stimulant and also as an anti-inflammatory. It can be effective in treatment of dyspepsia, migraine headache, morning sickness, nausea (chemo induced), post-operative nausea and/or vomiting, osteoarthritis, respiratory infections, rheumatoid arthritis <ul style="list-style-type: none"> • Demonstrated antiemetic efficacy in pregnancy, postoperative nausea and vomiting and vertigo. It is possibly ineffective for motion sickness. • Insufficient reliable data to rate use in chemotherapy induced nausea and vomiting, migraine headache, and rheumatoid arthritis.
Mechanism of action	Gingerol has been traditionally used to treat gastrointestinal symptoms, nausea and emesis. Moreover, nausea and emesis are common side effects of chemotherapy. The activation of vagal afferent mediated by serotonin (5-HT) is crucial in the mechanism of emesis. Gingerol inhibited emetic signal transmission in vagal afferent neurons by suppressing the 5-HT receptor, and 6-shogaol had the strongest inhibitory efficacy. Furthermore, ginger extract alleviated chemotherapy-induced nausea and emesis by suppressing the activation of 5-HT receptors in enteric neurons.
Drug interactions	<ul style="list-style-type: none"> • Abciximab • Anagrelide • Anamu • Cilostazol • Clopidogrel • Danshen • Devil's claw • Dipyridamole

	<ul style="list-style-type: none"> • Eptifibatide • Green tea • Prasugrel • Ticlopidine • Tirofiban
Side effects	<ul style="list-style-type: none"> • Cardiac arrhythmias (if overdosed) • Central nervous system depression (if overdosed) • Dermatitis (with topical use) • Diarrhea

5. EXICIPIENT PROFILE:-

5.1. Natural Starch (*Musa Paradisiaca*)

Synonym

- *Musa asapiantum*.
- Edible banana.
- Edible fruit.
- *Musa acuminata*
- *Musa sapientum* L
- Plantain

Description

The fruit is variable in size, colour, and firmness, but is usually elongated and curved, with soft flesh rich in starch covered with a rind, which may be green, yellow, red, purple, or brown when ripe. The fruits grow upward in clusters near the top of the plant. Almost all modern edible seedless (parthenocarp) bananas come from two wild species – *Musa acuminata* and *Musa balbisiana*. The scientific names of most cultivated bananas are *Musa acuminata*, *Musa balbisiana*, and *Musa × paradisiaca* for the hybrid *Musa acuminata* × *M. balbisiana*, depending on their genomic constitution. The old scientific name for this hybrid, *Musa sapientum*, is no longer used.

Active constituents

Musa paradisiaca is rich in many bioactive compounds, such as carotenoids, flavonoids, phenolics, amines, vitamin C, and vitamin E having antioxidant activities to provide many human health benefits.

Pharmaceutical uses

- Acts as super disintegrating agent in oral disintegrating tablets.

- Used in anti emetic ODTs
- Substitute for synthetic starch.

Side effects or toxicity: Side effects to *Musa paradisiaca* are rare but may include bloating, gas, cramping, softer stools, nausea, and vomiting. In very high doses, bananas might cause high blood levels of potassium. Some people are allergic to musaparadisica.

Dosage: *Musa paradisiaca* Linn. is a popular Indian medicinal plant belonging to the Musaceae family was administered in the dose of 10 and 20 mg/kg orally.

Warnings/ Indications: Use of other drugs or over the counter products at the same time, the effects of *Musa Paradisiaca* may change. This may increase your risk for side-effects or cause the drug not to work properly. Drugs, vitamins, and herbal supplements may interact with *Musa paradisiaca*, so prevent or manage drug interactions. *Musa Paradisiaca* may interact also interact with the alcohol.

Total ash: not more than 15.10%

Acid soluble ash: not more than 2.61%

Water soluble ash: not more than 3.79%

Swell ratio: 2.12

5.2. Sodium Starch Glycolate

Synonym: Carboxymethyl starch sodium salt, carboxymethyl ether, monosodium salt.

Molecular weight: The molecular weight is typically 5 10⁵ –1 10⁶.

Empirical formula: C₂H₃NaO₃

Structural formula:

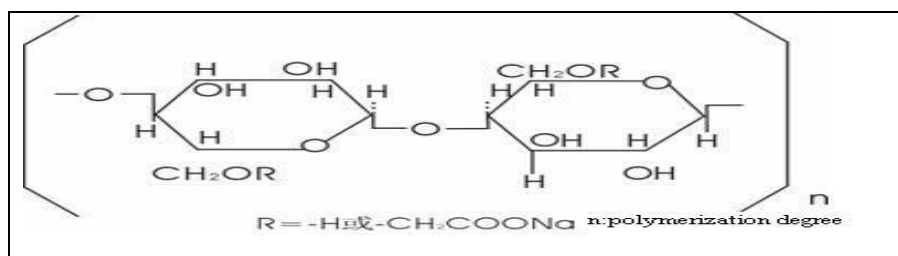


Figure 12: Structure of Sodium Starch Glycolate.

Category: Carbohydrates & Derivatives

Description: It is a white to off-white, tasteless, odorless, relatively free flowing powder.

Density: 0.945 g/cc

Solubility: Practically insoluble in methylenechloride. It gives a translucent suspension in water.

Stability and storage

It 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.

Safety: Sodium starch glycolate is widely used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. However, oral ingestion of large quantities may be harmful.

Applications

- Used in oral pharmaceuticals as a disintegrant in capsules.
- Used in direct-compression or wet-granulation processes.
- Used as a suspending vehicle
- Act as adissolution enhancing agent.

5.3. Micro Crystalline Cellulose

Synonyms

Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystallin e Cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

Nonproprietary names

- BP: Microcrystalline cellulose
- JP: Microcrystalline cellulose
- PhEur: Cellulosummicrocristallinum
- USPNF: Microcrystalline cellulose.

Chemical Name: Cellulose.

Empirical Formula: (C₆H₁₀O₅)

Molecular Weight: 220 gm/mole

Structural Formula

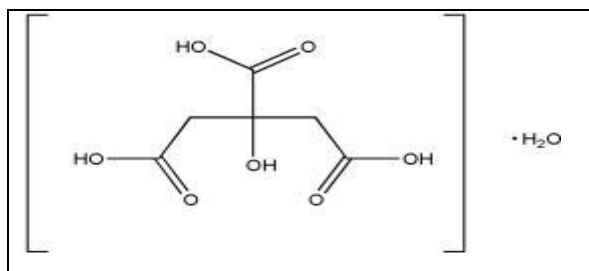


Figure 13: Structure of Microcrystalline Cellulose.

Functional Category

- Adsorbent;
- suspending agent;
- Tablet and capsule diluents.

Applications

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

Appearance

- Microcrystalline cellulose is purified; partially depolymerized 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.

Typical Properties

Acidity/alkalinity: pH = 5.0-7.0 (1% w/v aqueous solution)

Density: 1.512-1.668 g/cm³

Melting point: Chars at 260-270 °C

Solubility: slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Incompatibilities

- Citric acid is incompatible with potassium tartar ate, alkali andalkaline earth carbonates and bicarbonates, acetates, and sulfides. Incompatibilities also include oxidizing agents, bases, reducing agents, and nitrates.
- It is potentially explosive in combination with metal nitrates. On storage, sucrose may crystallize from syrups in the presence of citric acid.

Safety

- Microcrystalline cellulose is widely used in oral pharmaceutical formulationsand food products and is generally regarded as a relatively nontoxic and nonirritant material. Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential.
- Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.

5.4. Mannitol

Synonym: Cordycepic acid, Emprove, manna sugar, D-mannite, peralitol.

Chemical Name: D-mannitol

Molecular Formula: C₆H₁₄O₆

Structure:

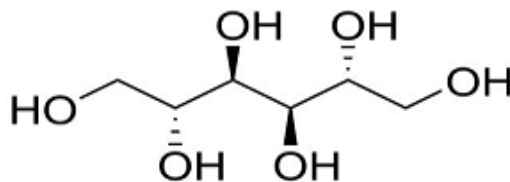


Figure 14: Structure of Mannitol.

- In the UK, the occupational exposure limits for cellulose have been set at 10 mg/m³ long-term (8-hour TWA) for total inhalable dust and 4 mg/m³ for respirable dust; the short-term limit for total inhalable dust has been set at 20 mg/m³.

Description

It is a hexahydric alcohol related to mannose and isomeric with alcohol

It occurs as white, odourless, crystalline powder or free flowing granules.

It has a sweet taste, approximately as sweet as glucose and half sweet as sucrose and imparts a cooling sensation in mouth.

Solubility: 1 part 5.5 in water, 1 part 18 in glycerine and 1 part 83 in ethanol at 20°C.

Pharmaceutical applications

- In pharmaceutical preparations it is primarily used as a diluent (10 – 90 % w/w) in tablet formulations where it is of particular value since it is not hygroscopic and may thus be used with moisture sensitive active ingredients.
- Mannitol may be used in direct compression tablet applications for which the granular and spray dried forms are available.
- It is used in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness and mouth feel.

5.5. Sodium Lauryl Sulphate

Synonyms: Sodium lauryl sulphate.

Non-proprietary name: BP. Sodium lauryl sulphate.

Description: White to off- white powder.

Solubility: Partly water-soluble and partly oil-soluble.

Empirical formula: C₁₂H₂₅NaO₄S

Structure:

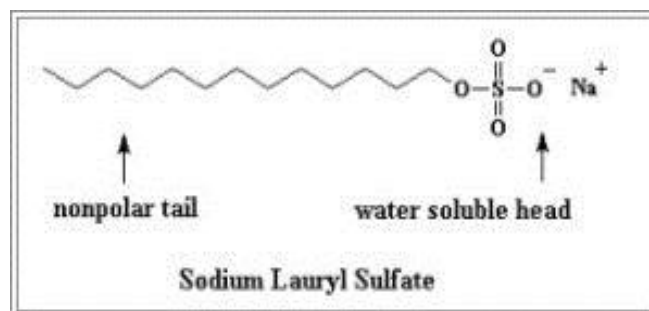


Figure 15: Structure of Sodium Lauryl Sulphate.

Molecular weight: 288.gm/mole.

Functional category: Sodium lauryl sulphate is a surfactant.

Applications

- Anionic surfactant;
- detergent;
- emulsifying agent;

- skin penetrant; tablet and capsule lubricant;
- Wetting agent.

5.6. Magnesium Stearate

Synonyms: Magnesium salt; Magnesium octadecanoate.

Non-proprietary names: BP: Magnesium stearate.

Chemical name: Octadecanoic acid magnesium salt

Empirical formula: $C_{36}H_{70}MgO_4$

Molecular weight: 591.34 g/mole

Structural formula: $[CH_3(CH_2)_{16}COO]_2Mg$.

Structure:

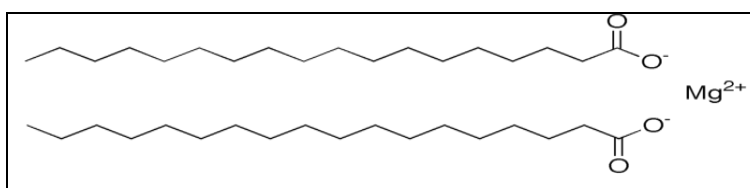


Figure 16: Structure of Magnesium Stearate.

Functional category: As lubricant for capsule and tablet.

Applications:

- It is also principally used as a lubricant in tablet and capsule manufacture at concentrations ranging from 0.25% to 5.0% w/w. Sometimes it is used in barrier creams.

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

Stability and storage condition: Magnesium stearate should be stored in a well-closed package in a cool and dry place.

5.7. ASPARTAME

Synonyms: 3-amino-N(methoxycarbonylphenethyl)succinamic acid; APM; aspartyl phenylamine methyl ester; NutraSweet; Pal Sweet; Pal Sweet Diet.

Nonproprietary Names: BP: Aspartame

Chemical Name: L-Aspartyl-L-phenylalanine 1-methyl ester

Empirical Formula: $C_{14}H_{18}N_2O_5$

Molecular Weight: 294.31 g/mol

Structural Formula:

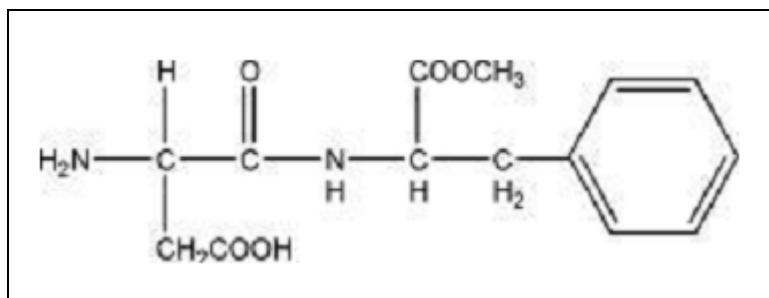


Figure 17: Structure of Aspartame.

Functional Category: Sweetening agent.

Applications

- 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. Therapeutically, aspartame has also been used in the treatment of sickle cell anemia.

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

Melting point: 246–247°C.

Solubility: Slightly soluble in ethanol (95%); sparingly soluble in water. At 20°C the solubility is 1% w/v at the isoelectric point (pH 5.2). Solubility increases at higher temperature and at more acidic pH, e.g., at pH 2 and 20°C solubility is 10% w/v.

Stability and Storage Conditions: Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl-L-phenylalanine and 3-benzyl-6-carboxymethyl-2,5-diketopiperazine. A third-degradation product is also known, L-aspartyl-L-phenylalanine methyl ester.

5.8. Talc

Synonyms: Magnesium hydrogen meta silicate; hydrous magnesium calcium silicate; hydrous magnesium silicate.

Nonproprietary names: BP: Purified talc, USP: Talc.

Chemical name: Talc

Empirical formula: $Mg_6(Si_2O_5)_4(OH)_4$

Functional category:

- Glidant; tablet and capsule diluent;
- anti-caking agent;
- Tablet and capsule lubricant.

Applications

- Talc is widely used in oral solid dosage formulations, cosmetics and food products as a lubricant.

Solubility: It is almost insoluble in organic fluids, dilute acids and alkalis, and water.

Stability and storage condition: Talc should be stored in a closed package in a cool and dry place.

6. METHODOLOGY

1. Extraction of starch from *Musa paradisiaca*
2. Characterisation of extracted starch
3. Modification of extracted starch.
4. Characterisation of modified starch
5. Drug excipient-compatibility studies.
6. To evaluate pre-compression parameters of powder blend
 - Bulk density.
 - Tapped density.
 - Angle of repose.
 - Carr's index.
 - Hauser ratio
7. To prepare tablets by direct compression method.
8. To evaluate post-compression parameters such as
 - Hardness test
 - Friability test
 - Drug content
 - Weight variation test
 - Wetting time and water absorption ratio

- Water dispersion time
- Disintegration test
- In-vitro Dissolution test.

6.1. EXTRACTION OF STARCH FROM *MUSA PARADISIACA* USING ETHANOL

A method of isolating banana starch from a green banana steps comprising blending a green banana with 95% ethanol for a predetermined amount of time to create a mixture.



Pouring the mixture through a sieve.



Collecting a liquid suspension of the mixture.



Centrifuging the liquid suspension to form white banana starch.



Washing the banana starch with ethanol to isolate the banana starch



It was dried under air and the dried powder was then passed through sieve 120 and stored in air tight container.

6.2. CHARACTERIZATION OF EXTRACTED STARCH^[38-39]:-

1. Solubility

The solubility of extracted starch was performed in various solvents like distilled water, the aqueous buffer of pH 1, 2, 3, 4, 6 and organic solvents such as alcohol, dichloromethane, chloroform, acetone, and petroleum ether. 25mg of extracted starch was added to the 100ml of solvent in which solubility tested in a 250ml conical flask and placed on a rotary shaker for 24hrs.

2. pH

1gm of extracted starch was weighed and dispersed in 100ml distilled water in a beaker (1%w/v). The pH of the aqueous dispersion of extracted starch was measured by using pH meter.

3. Melting point

The open end of the glass capillary melting point tube jabbed into a pile of the extracted starch powder which was placed in a petri dish and packed the powder into the capillary tube,

and then this tube was inserted into the slot of the melting point apparatus and measured the melting point of the extracted starch.

4. Viscosity

One gram of extracted starch was dispersed in 100ml distilled water to the concentration of the 1% w/v aqueous dispersion. Oswald Viscometer was used to measure the viscosity of 1% w/v aqueous dispersion of extracted starch.

5. Swelling index

Extracted starch (200mg) was added to two different measuring cylinders containing 10ml distilled water and light liquid paraffin. Then the measuring cylinders were allowed to stand for 12hr. The volumes of the residue in the measuring cylinders were noted. The swelling index (S.I) of the material was calculated as follows.

$$\text{Swelling index} = \frac{\text{vol of residue in distilled water} - \text{vol of residue in light liq. Paraffin}}{\text{Vol of residue in light liq. paraffin}}$$

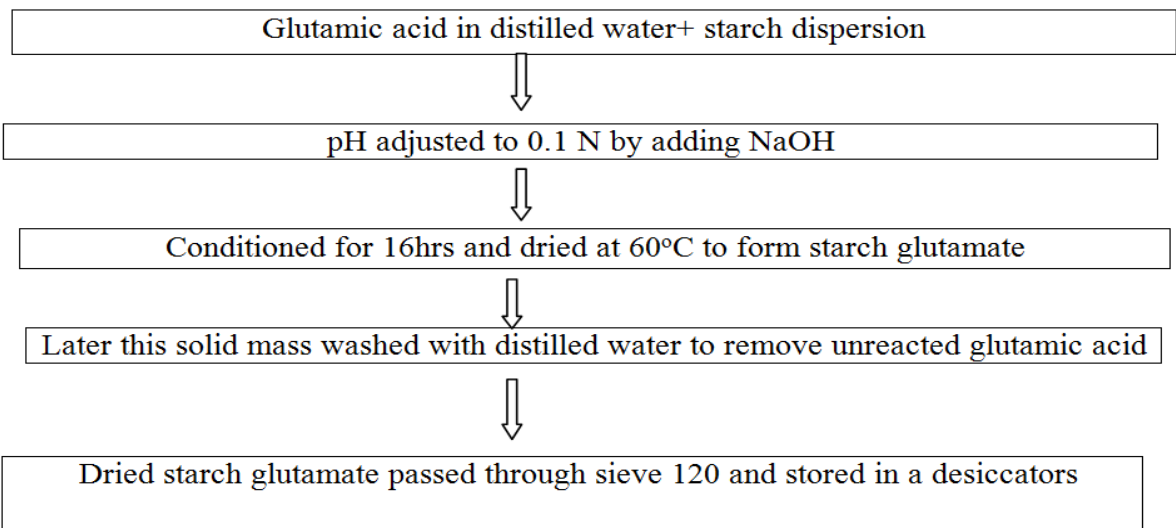
6. Gelling property

The evaluation of the gelling property (gelatinization) of the prepared extracted starch and starch was done by heating 7% w/v dispersion of each in distilled water at 100°C for 30min.

7. Moisture absorption

By performing moisture absorption studies hygroscopic nature of the extracted starch was evaluated in a closed desiccator at 84% relative humidity and at room temperature.

6.3. MODIFICATION OF EXTRACTED STARCH:



6.4. CHARACTERIZATION OF MODIFIED STARCH:

1. Solubility

The solubility of starch glutamate was tested in various solvents like distilled water, the aqueous buffer of pH 1, 2, 3, 4, 6 and organic solvents such as alcohol, dichloromethane, chloroform, acetone, and petroleum ether. 25mg of starch glutamate was added to the 100ml of solvent in which solubility tested in a 250ml conical flask and placed on a rotary shaker for 24hrs.

2. pH

1gm of starch glutamate was weighed and dispersed in 100ml distilled water in a beaker (1%w/v). The pH of the aqueous dispersion of starch glutamate was measured by using pH meter.

3. Melting point

The open end of the glass capillary melting point tube jabbed into a pile of the starch glutamate powder which was placed in a petri dish and packed the powder into the capillary tube, and then this tube was inserted into the slot of the melting point apparatus and measured the melting point of the starch glutamate

4. Viscosity

One gram of starch glutamate was dispersed in 100ml distilled water to the concentration of the 1% w/v aqueous dispersion. Oswald Viscometer was used to measure the viscosity of 1% w/v aqueous dispersion of starch glutamate.

5. Swelling index

Starch glutamate (200mg) was added to two different measuring cylinders containing 10ml distilled water and light liquid paraffin. Then the measuring cylinders were allowed to stand for 12hr. The volumes of the residue in the measuring cylinders were noted. The swelling index (S.I) of the material was calculated as follows.

$$\text{Swelling index} = \frac{\text{vol of residue in distilled water} - \text{vol of residue in light liq. Paraffin}}{\text{Vol of residue in light liq. paraffin}}$$

6. Gelling property

The evaluation of the gelling property (gelatinization) of the prepared starch glutamate and starch was done by heating 7% w/v dispersion of each in distilled water at 100°C for 30min.

7. Moisture absorption

By performing moisture absorption studies hygroscopic nature of the starch glutamate was evaluated in a closed desiccator at 84% relative humidity and at room temperature.

6.5. DRUG EXCIPIENT- COMPATIBILITY STUDIES:

This was carried out check the compatibility between gingerol and superdisintegrants namely extracted natural *Musa paradisiaca* starch, modified starch (starch glutamate), and synthetic starch sodium starch glycolate. It was therefore necessary to confirm that drug is not interacting with excipients under experimental conditions and shelf life. It was carried out by fir analysis.

FOURIER TRANSFORM INFRARED SPECTROSCOPY

The infrared (IR) spectra were recorded using an FTIR by the KBr pellet method and spectra were recorded in the wavelength region between 4000 and 400 cm^{-1} .

The spectra obtained for gingerol, superdisintegrants and physical mixtures of gingerol with superdisintegrants were compared. Dissappearance of gingerol peaks or shifting of peak in any of the spectra was studied.

6.6. PRE COMPRESSION PARAMETERS OF POWDER BLEND:

Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form. Hence, the following preformulation studies were performed on the obtained sample of drug.

A) Bulk Density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and initial weight was noted. This

initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in gm/ml and is given by

$$\text{Bulk density (D}_b\text{)} = \text{Mass (M)} / \text{Bulk volume (V}_b\text{)}$$

Where, M is the mass of powder, V_b is the bulk volume of the powder.

B) Tapped density (D_t)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in gm/ml and is given by

$$\text{Tapped density (D}_t\text{)} = \text{Mass (M)} / \text{Tapped volume (V}_t\text{)}$$

Where, M is the mass of powder; V_t is the tapped volume of the powder.

C) Angle of repose (Θ)

The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following formula:

$$\text{Tan } \Theta = h/r \quad \Theta = \text{tan}^{-1} (h/r)$$

Where Θ is the angle of repose, h is the height in cm and r is the radius.

Relationship between Angle of Repose and Flow Properties

Table 9: Relationship between Angle of Repose and Flow Properties.

Angle of repose(θ)	Type of flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

D) Carr's Index % compressibility: It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, popular and fast method of predicting powder flow characteristics. It is based on the apparent bulk density and the tapped density, the percentage compressibility of the the bulk drug was determined by the following formula.

$$\text{Carr's index} = \text{Tapped Density} - \text{Bulk density}$$

Bulk density**Relationship between Carr's Index and Flow Property****Table 10: Relationship between Carr's index and flow property.**

Carr's index	Type of flow
5-15	Excellent
12-15	Good
18-21	Fair
23-30	Poor
33-38	Very poor
>40	Extremely poor

H) Hausner's ratio

The ratio of the tapped density to bulk density is called as hausner ratio. It is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \text{Tapped density (D}_t\text{)} / \text{Bulk density (D}_b\text{)}$$

Lower hausner ratio (1.25) indicates better flow properties than higher ones (1.25)

Scale of Flowability Based on Hausner's Ratio**Table 11: Scale of Flowability Based on Hausner's Ratio.**

HAUSNER'S RATIO	TYPE OF FLOW
Less than 1.25	Good flow
1.25 – 1.5	Moderate
More than 1.5	Poor flow

Specifications of Precompression Parameters**Table: 12: Specifications of Precompression parameters.**

Flow Character	Carr's index	Hauser's ratio	Angle of repose [⁰]
Excellent	<10	1.00-1.11	25-30
Good	11-15	1.12-1.18	31-35
Fair (aid not needed)	16-20	1.19-1.25	36-40
Passable (may hang up)	21-25	1.26-1.34	41-45
Poor (agitate/vibrate)	26-31	1.35-1.45	46-55
Very poor	32-37	1.46-1.59	56-65
Very, very poor	>38	>1.60	.>66

6.7. PREPARATION OF GINGEROL ORODISPERSIBL TABLETS

Orodispersible tablets containing 100 mg Gingerol were prepared by direct compression method using formula given in table-13. Avicel and mannitol were used as directly compressible diluents. The drug and other excipients were passed through # 60 mesh sieves separately for ensuring better mixing. The drug and directly compressible excipients were thoroughly mixed in a mortar to get a uniform powder and then to the above blend, the other

ingredients were mixed in geometrical order but Magnesium stearate and purified talc were added at the last and mixed for further two minutes. The blend was compressed using 8 mm flat round punches to get tablets of 300 mg weight on 10-station rotary tablet machine. Before compression, the surface of die and punch were lubricated with Magnesium stearate. A batch of 60 tablets was prepared for all the designed formulations.

Table 13: Formulation Table of Gingerol Orodispersible Tablets.

Formulation Code	GIOD T1	GIODT 2	GIOD T3	GIOD T4	GIOD T5	GIOD T6	GIOD T7	GIOD T8	GIODT 9
<i>Ingredients(Mg)</i>									
Gingerol	100	100	100	100	100	100	100	100	100
Modified <i>Musa Paradisiaca</i> Starch	6	12	18	-	-	-	-	-	-
<i>Musa Paradisiaca</i> Starch	-	-	-	6	12	18	-	-	-
Sodium Starch Glycolate	-	-	-	-	-	-	6	12	18
Microcrystalline Cellulose	82	78	74	82	78	74	82	78	74
D.Mannitol	87	85	83	87	85	83	87	85	83
Sodium Lauryl Sulphate	2	2	2	2	2	2	2	2	2
Magnesium Stearate	6	6	6	6	6	6	6	6	6
Aspartamine	1	1	1	1	1	1	1	1	1
Talc	15	15	15	15	15	15	15	15	15
Mixed Fruit Flavour	1	1	1	1	1	1	1	1	1

Total Tablet Weight= 300 mg

6.8. EVALUATION OF ORODISPERSIBLE TABLETS OF GINGEROL:

6.8.1. PREPARATION OF STANDARD CURVE FOR GINGEROL:-

a) Preparation of pH 6.8 buffer (phosphate buffer)

27.218 gm of potassium dihydrogen orthophosphate was dissolved in 1000 ml of distilled water. And prepare 0.1 N sodium hydroxide solution. Then from this Potassium dihydrogen orthophosphate solution 250 ml was taken and mixed with 112 ml of 0.1 N Sodium hydroxide solutions. Finally, to make up 1000 ml by using distilled water.

b) Construction of Standard Curve for Gingerol

100 mg of Gingerol was accurately weighed and dissolved in small portion of phosphate buffer pH6.8 in a 100 ml of volumetric flask and the volume was made upto 100 ml with

buffer. This is the primary stock solution. From the primary stock solution 10 ml was accurately pipette out and transferred into a 100 ml volumetric flask. Then the volume was made upto 100 ml with buffer. From the secondary stock solution aliquots equivalent to 2, 4, 6,8,10 mcg were prepared by using 2ml, 4ml, 6ml, 8ml, and 10 ml and transferred into a 10 ml volumetric flask and diluted upto 10ml with buffer. The absorbance of above set solutions was against the phosphate buffer pH 6.8 as blank at 279nm. Then calibration curve was plotted taking concentration on X-axis and absorbance on Y-axis.

6.8.2. POST COMPRESSION PARAMETERS ^[39]:

A. General appearance

Five tablets from different batches were randomly selected and organoleptic properties such as colour, odour, shape were evaluated.

B. Thickness and diameter

Thickness and diameter of tablets was determined using Screw gauge. Five tablets from each batch were used and an average value was calculated.

C. Weight variation

Twenty tablets were taken and their weights were determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. Average weight was compared with the individual weight and the percentage deviation of individual tablet was calculated.

Weight Variation Limit as Per IP

Table 14: Weight Variation Limit As Per IP.

Average weight of Tablet	Percentage Deviation
80 mg or less	± 10%
More than 80 mg but less than 250 mg	± 7.5%
250 mg or more	± 5%

D. Hardness: For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester.

E. Friability: The friability of the tablet was measured by using Rochefriabillator (Electro lab, India). Twenty reweighed tablets were rotated at 25 rpm for 4 rpm and dropping the tablets at a height of 6 inches at each revolution and the tablets were subjected to 100

revolutions. The tablets were then dedusted using soft muslin cloth and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets was measured as per the following formula.

$$\text{Percentage friability} = (\text{Initial weight} - \text{final weight} / \text{Initial weight}) \times 100$$

F. Drug content: Ten tablets from each batch were weighed and powdered. The required amount of the powder equivalent to 4 mg of Gingerol was dissolved in 100 ml of phosphate buffer pH6.8. From this solution 1 ml was taken and made up to 100 ml by using phosphate buffer pH6.8 and the solution was filtered by using whatmann filter paper. The solution was analysed for drug content at 279nm using UV visible spectrophotometer.

G. *In vitro* dispersion time: *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 10ml of simulated saliva fluid of pH 6.8. After dropping a tablet in the simulated saliva fluid, the tablet started to swell quickly, broke and followed by dispersed. Five tablets from each formulation were randomly selected and *in vitro* dispersion time was performed and it was expressed in seconds.^[49]

H. Wetting time: Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place.

A piece of tissue paper folded double was placed in a petri plate (internal diameter is 6.5cm) containing 6ml of purified water. A tablet having a small amount of Eosine dye powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time.

I. Water absorption ratio

A piece of double folded tissue paper was kept in a petri dish (internal diameter 5.5 cm) containing 6 ml of purified water. The weight of tablet before keeping in petri-dish was noted as (W_b) and after completely wetted tablet in petriplate was noted as (W_a). The wetted tablet was removed and reweighed. Water absorption ratio, R was determined according to the following equation.

$$R = 100 (W_a - W_b) / W_b$$

Where, W_b and W_a are before and after water absorption, respectively.

J. Disintegration time

Disintegration time was measured using disintegration test apparatus. A tablet was placed in each six tubes of the basket. The basket with the bottom surface is made up of stainless – steel screen (mesh no.10) was immersed in pH 6.8 phosphate buffer solution maintained at 37°C as the disintegration fluid and the paddle at 100rpm as stirring element was used. The time taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

K. In vitro dissolution test

In vitro dissolution of the Orodispersible tablets was studied in USP XXIII type-II dissolution test apparatus (Electro lab, model: TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5° C as dissolution medium. One tablet was used in each test. Aliquots of dissolution medium were withdrawn at specified intervals of time and analyzed for drug content by measuring the absorbance at 279 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent of the drug released was calculated and plotted against time.

Dissolution Condition

Apparatus	: USP XX111 paddle apparatus 2.
RPM	: 50
Medium	: Phosphate buffer (pH 6.8)
Sampling Interval	: Every 5 minute.
Sampling Volume	: 5 ml.

7. RESULTS AND DISCUSSION:-

7.1. EXTRACTION OF STARCH FROM *MUSA PARADISIACA* USING ETHANOL



1. *Musa paradisiaca* (green banana)



2. Chopped banana



3. Blended banana pieces.



4. Filtrate obtained from banana mixture.



5. Centrifugation of filtrate.



6. Starch obtained after drying of solid mass.

Figure 18: Extraction of Starch from *Musa Paradisiaca* Using Ethanol.

7.2. CHARECTERISATION OF EXTRACTED STARCH:-

Table 15: Charecterisation of Extracted Starch.

S.No	Parameter	Observation
1.	Solubility	Insoluble in all aqueous and organic solvents
2.	pH	3.9-4-.6
3.	Melting point	256°C
4.	Viscosity	1.25cps
5.	Swelling index	1100
6.	Gelling property	A gel is formed on heating starch with water.
7.	Moisture absorption	4%

7.3. MODIFICATION OF STARCH

The extracted starch was modified using glutamic acid and the modified starch i.e, starch glutamate was obtained.

7.4. CHARECTERISATION OF MODIFIED STARCH:-

Table 16: Characterisation of Modified Starch.

S.No	Parameter	Observation
1.	Solubility	Insoluble in all aqueous and organic solvents
2.	pH	2.8
3.	Melting point	325°C
4.	Viscosity	1.08 cps
5.	Swelling index	1200
6.	Gelling property	it did not exhibit any gelling property
7.	Moisture absorption	4.4%

7.5. PHYSICAL PROPERTIES OF API

Table 17: Physical Properties of API (Gingerol).

S. No	API Properties	Results
1.	Physical appearance	It is brown Amorphous powder.
2.	Melting point	30-32°C.
3.	Solubility	It is soluble in organic solvents such as Ethanol, DMF

7.6. STANDARD CURVE FOR GINGEROL IN PHOSPHATE BUFFER P^H 6.8:

Table 18: Standard Curve of Gingerol in Phosphate Buffer P^H 6.8.

S. NO	Concentration(µg/ml)	Absorbance at 279 nm
1.	0	0
2.	2	0.083
3.	4	0.167
4.	6	0.248
6.	8	0.324
7.	10	0.401
8.	Correlation	0.9998
9.	Slope	0.040

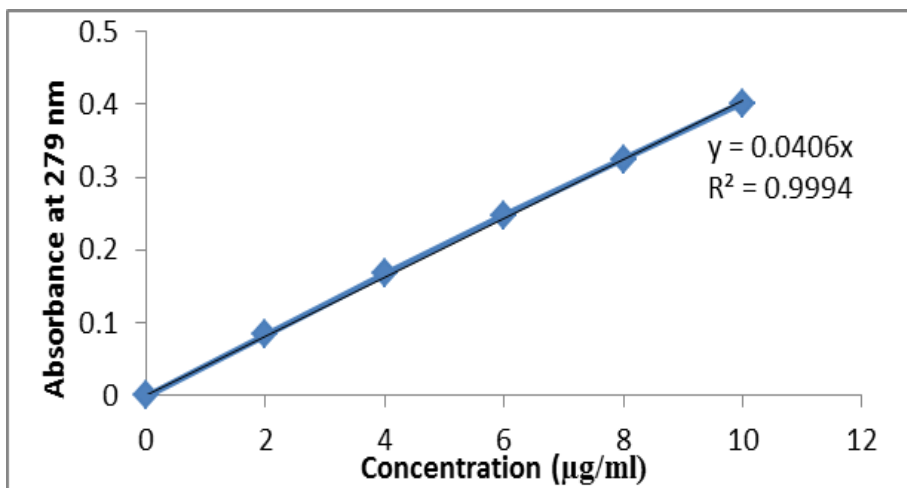


Figure 19:- Standard Curve of Gingerol in Phosphate Buffer P^H 6.8.

7.7. DRUG EXCIPIENT- COMPATIBILITY STUDIES

FTIR SPECTROSCOPY: Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients.

Infrared spectra for drug pure Gingerol and pure drug with natural and synthetic superdisintegrants was determined to check the intactness of the drug in the formulation.

7.7.1. FTIR Spectrum of Gingerol:-

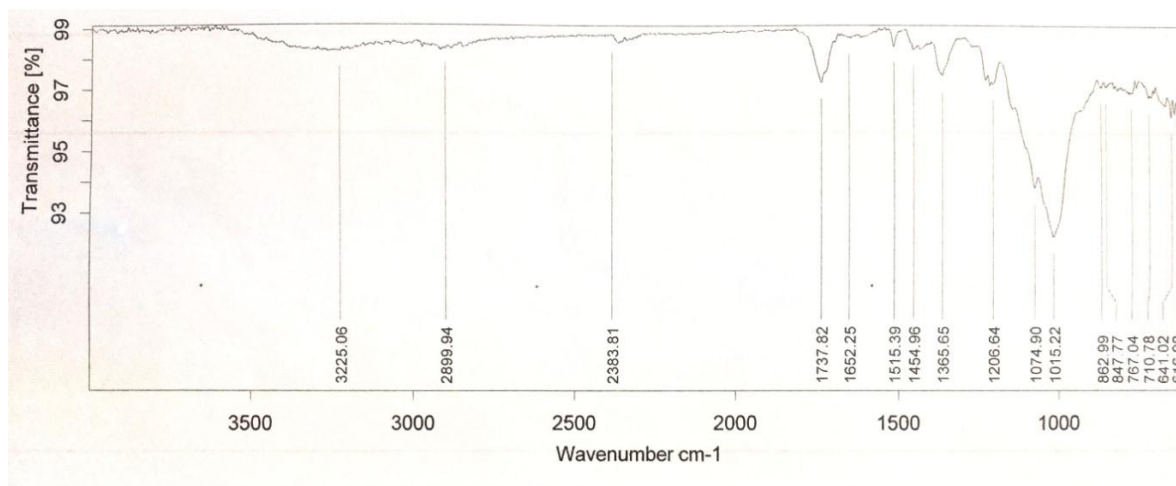


Figure 20: FTIR Spectrum of Gingerol.

7.7.2. FTIR Spectrum of Gingerol with Modified *Musa Paradisiaca* Starch (Starch Glutamate)

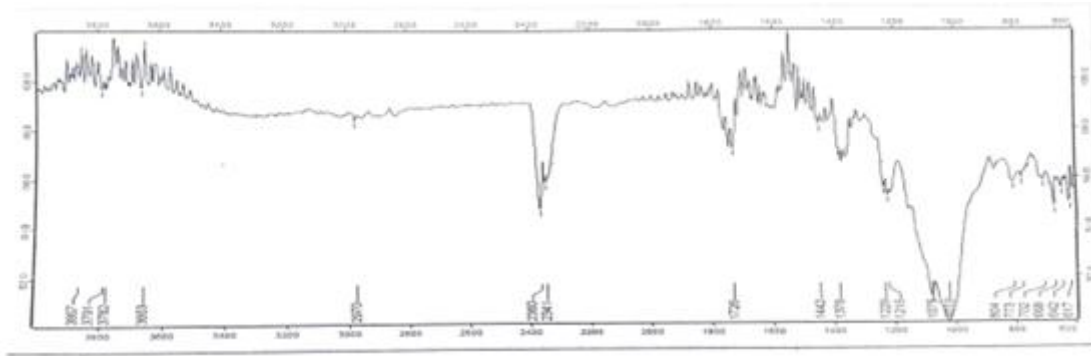


Figure 21: FTIR Spectrum of Gingerol with Modified *Musa paradisiaca* Starch (Starch glutamate).

7.7.3. FTIR Spectrum of Gingerol with Extracted *Musa Paradisiaca* Starch:

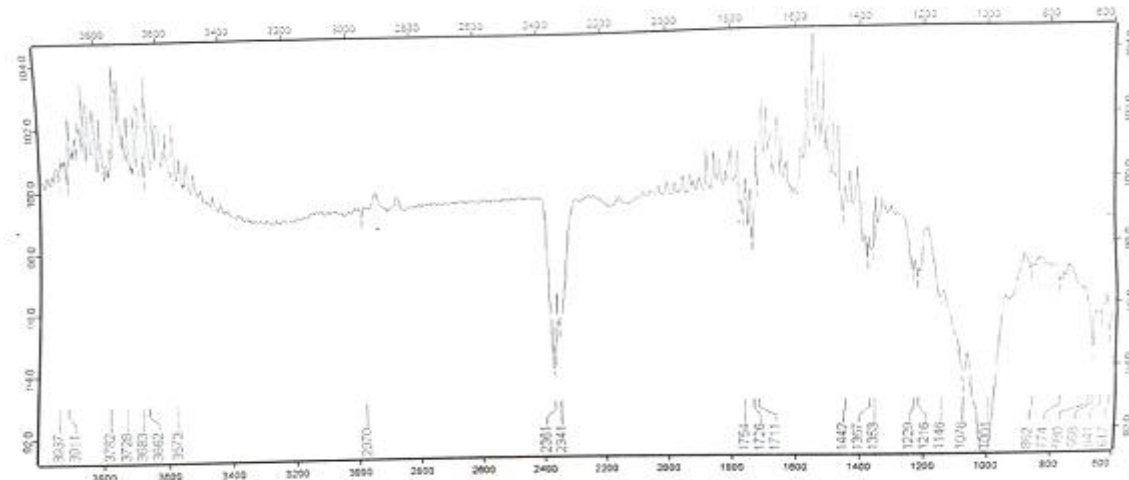


Figure 22: FTIR Spectrum of Gingerol with Extracted *Musa Paradisiaca* Starch.

7.7.4 FTIR Spectrum of Gingerol with Sodium Starch Glycolate

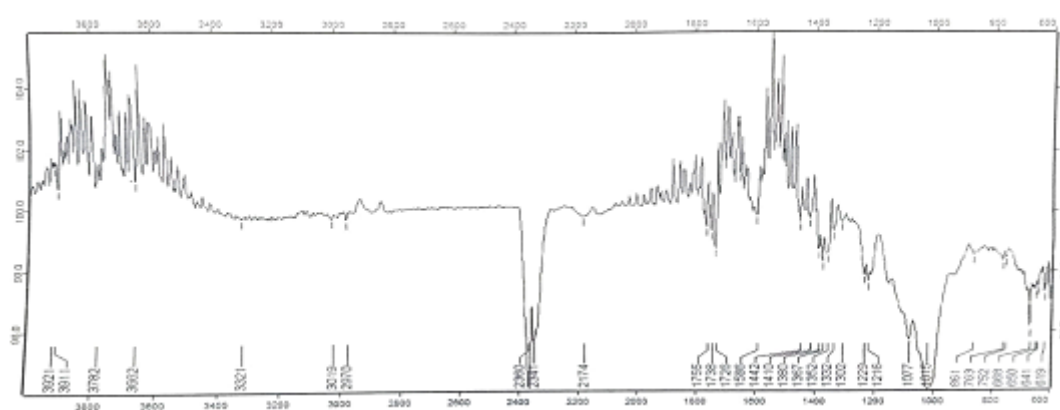


Figure 23: FtirSpectrum of Gingerol with Sodium Starch Glycolate.

The wave number for the characteristic bands in the infrared spectra of pure Gingerol shown as follows:

Characteristic Peaks of Gingerol and Gingerol with Superdisintegrants as follows

Table 19: Characteristic Peaks of Gingerol and Gingerol with Superdisintegrants.

S. No	Functional Group	Theoretical Peaks (cm-1)	Gingerol	Gingerol+modified starch (starch glutamate)	Gingerol+extracted starch	Gingerol+ Sodium starch glycolate
1	C-H(stretch	2700-3300	2899	2970	2970	2970
2	C-O (stretch)	900-1300	1015	1019	1001	1015
3	O-H (stretch)	3000-3700	3225	3663	3662	3662
4	C=O (stretch)	1600-1900	1737	1726	1726	1726
5	C=C (stretch)	1475-1610	1454	1442	1442	1442

Infrared spectra for drug pure Gingerol and pure drug with natural and synthetic superdisintegrants was determined to check the intactness of the drug in the formulation.

The characteristic peaks of the physical mixture of Gingerol and super disintegrants indicated that the super disintegrants did not interfere the peaks of drug confirming its compatibility.

7.8. EVALUATION OF PRE COMPRESSION PARAMETERS OF GINGEROL ORODISPERSIBLE TABLETS (GIODT1-GIODT9):

Table 20: Evaluation of Pre compression parameters of Gingerol Orodispersible tablets (GIODT1-GIODT9)

Formulation Code	PARAMETERS				
	Bulk density (gm/cm ³)	Tapped density (gm/cm ³)	Angle of repose (θ)	Carr's Index (%)	Hausner's Ratio
GIODT1	0.463±0.003	0.543±0.002	24.96±0.051	14.81±0.015	1.18±0.010
GIODT2	0.468±0.005	0.545±0.003	30.31±0.032	14.88±0.085	1.17±0.010
GIODT3	0.471±0.013	0.569±0.006	31.08±0.091	14.30±0.135	1.18±0.010
GIODT4	0.481±0.041	0.561±0.001	28.24±0.250	14.31±0.120	1.15±0.030
GIODT5	0.540±0.010	0.613±0.009	27.25±0.230	11.61±0.162	1.23±0.105
GIODT6	0.552±0.002	0.632±0.010	30.92±0.023	12.51±0.023	1.14±0.001
GIODT7	0.568±0.001	0.663±0.001	29.51±0.022	14.53±0.250	1.12±0.038
GIODT8	0.414±0.005	0.479±0.008	28.83±0.031	14.26±0.300	1.16±0.005
GIODT9	0.395±0.040	0.444±0.005	28.25±0.054	13.17±0.100	1.15±0.015

Blended powder was subjected to pre compression parameters such as bulk density, tapped density, Angle of repose, carr's index & Hausner's ratio and results was found to be 0.395 – 0.568 gm/cm³, 0.444 – 0.663 gm/cm³, 24.96-31.080, 11.61 -14.88 % and 1.1-1.23 respectively.

7.9. PREPARATION OF GINGEROL ORODISPERSIBLE TABLETS USING NATURAL, MODIFIED AND SYNTHETIC SUPERDISINTEGRANTS:

7.9.1 Preparation of Gingerol Orodispersible Tablets with modified *Musa paradisiaca* starch (starch glutamate)



Figure 24: Prepared Gingerol Orodispersible Tablets with Modified *Musa paradisiaca* starch (starch glutamate) (GIODT1-GIODT3).

7.9.2. Preparation of Gingerol Orodispersible Tablets with extracted *Musa paradisiaca* starch



Figure 25: Prepared of Gingerol Orodispersible Tablets with Extracted *Musa paradisiaca* Starch (GIODT4-GIODT6).

7.9.3. Preparation of Gingerol Orodispersible Tablets With Sodium Starch Glycolate



Figure 26: Prepared Gingerol Orodispersible Tablets with Sodium starch glycolate (GIODT7-GIODT9).

7.10. POST COMPRESSION PARAMETERS OF GINGEROL ODT'S

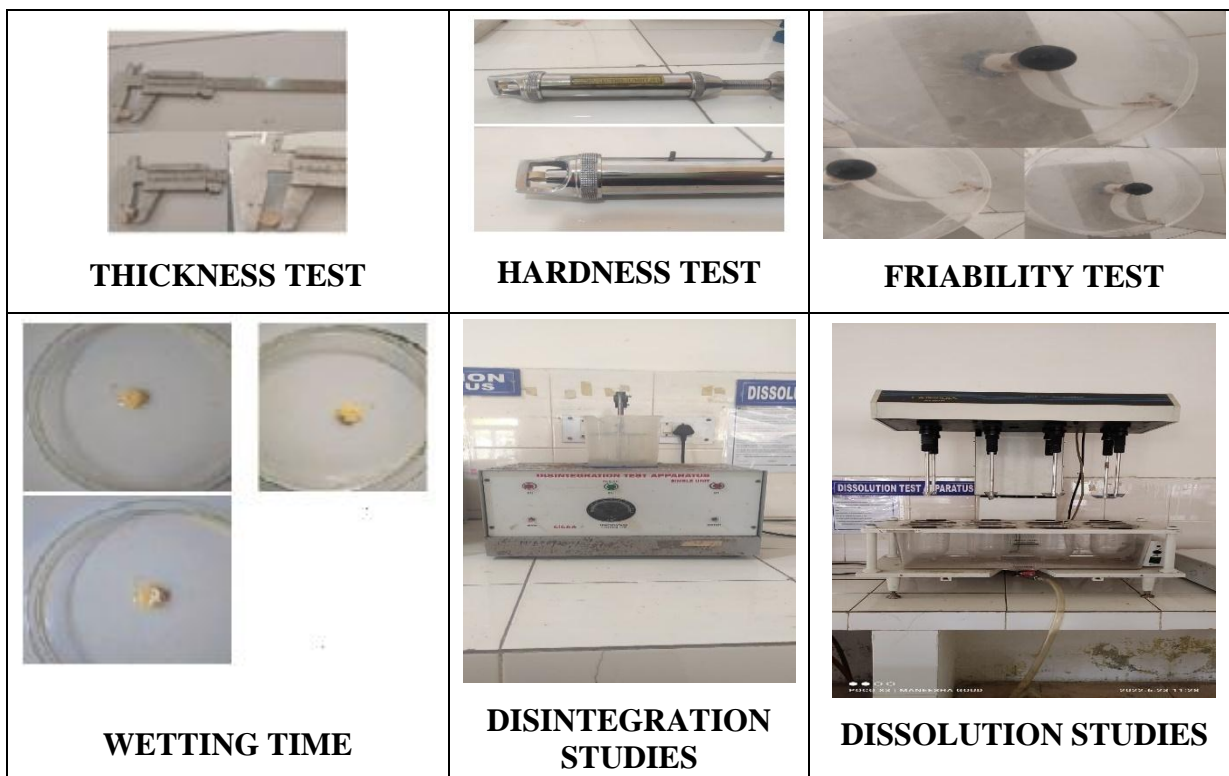


Figure 27: Post Compression Parameters of Gingerol ODT'S.

Table 21: Evaluation of Post compression parameters of Gingerol Orodispersible tablets (GIODT1-GIODT9)

Formulation code	Weight variation(mg)	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)
GIODT1	300.4±0.84	2.87±0.03	2.70±0.10	0.831±0.01
GIODT2	301.2±1.35	2.86±0.01	2.66±0.20	0.781±0.036
GIODT3	300.1±0.06	2.86±0.03	2.50±0.21	0.836±0.07
GIODT4	303.3±0.94	2.84±0.01	2.74±0.17	0.747±0.08
GIODT5	298.1±0.05	2.83±0.01	2.64±0.11	0.814±0.04
GIODT6	299.3±0.94	2.86±0.01	2.54±0.26	0.832±0.01
GIODT7	301.2±0.05	2.84±0.00	2.76±0.25	0.780±0.10
GIODT8	299.9±1.10	2.85±0.01	2.63±0.11	0.907±0.08
GIODT9	300.2±1.30	2.86±0.00	2.59±0.10	0.941±0.04

7.10.1. Weight Variation: The weight variation in all the nine formulations was found to be **298.1±0.05 to 303.3±0.94** mg. Formulations were within pharmacopoeial limits with free flow of the powder blend and demonstrating the efficiency of compression of particles into tablets.

7.10.2. Hardness: The Hardness was maintained to be within **2.50±0.21 to 2.76±0.25**kg/cm² as these tablets are rapidly disintegrating. No variation in the hardness was found which clearly indicates that the proper blending of the mixture for the preparation of Orodispersible tablets. The prepared tablets in all the formulation possess good mechanical strength with sufficient hardness.

7.10.3. Thickness: Thickness of all tablets prepared in the range of **2.83±0.01 to 2.87±0.03** mm was acceptable without much variation.

7.10.4. Percentage Friability: Percentage Friability is below 1% in all the formulation and values obtained lies between **0.747±0.08 to 0.941±0.04%**. It indicated that of good mechanical resistance of the tablets.

Table 22: Evaluation of Post compression parameters of Gingerol Oro dispersible tablets (GIODT1-GIODT9).

Formulation Code	<i>In vitro</i> Dispersion time(sec)	Wetting time(sec)	Disintegration time(sec)	Water absorption ratio	Drug content (%)
GIODT1	32.37±0.40	35.03±0.05	42.73±0.64	83.30±0.81	97.44±0.50
GIODT2	30.16±0.15	27.83±0.73	33.26±0.35	92.06±0.51	98.54±0.48
GIODT3	28.36±0.40	17.66±0.57	21.56±0.45	96.63±0.41	97.37±0.57

GIODT4	40.52±0.44	44.46±0.32	49.13±0.20	82.56±0.58	100.85±0.16
GIODT5	38.56±0.77	36.23±0.25	37.40±0.60	84.70±0.34	99.52±0.17
GIODT6	35.26±0.28	25.63±0.30	28.18±0.23	89.96±0.95	100.48±0.22
GIODT7	60.41±0.17	51.23±0.30	57.63±0.40	71.76±0.68	101.29±0.34
GIODT8	49.37±0.22	38.40±0.36	46.26±0.17	73.36±0.32	102.55±0.48
GIODT9	43.44±0.50	29.30±0.40	34.15±0.17	81.50±0.50	100.15±0.27

7.10.5. Wetting Time: The Wetting time was rapid in formulations prepared with Modified *Musa paradisiaca* starch (starch glutamate) followed by extracted starch and Sodium starch glycolate. The value lies between 17.66±0.57 to 51.23±0.30 sec. Figure.28 depicts the relation between the concentration of superdisintegrants and wetting time. It indicated that as concentration of disintegrant increases the time taken for wetting was reduced. Wetting time is used a parameter to correlate with disintegration time in oral cavity. This is an important criterion for understanding the capacity of disintegrants to swell in the presence of little amount of water.

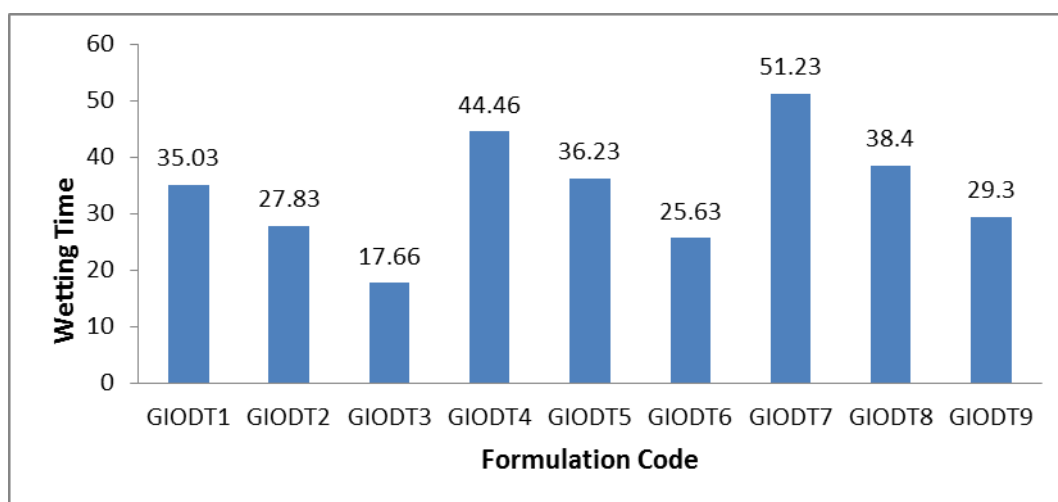


Figure 28: Wetting Time of Gingerol Orodispersible Tablets with *Modified Musa Paradisiaca* Starch (Starch Glutamate), Extracted Starch and Sodium Starch Glycolate in Different Concentrations.

7.10.6. Drug Content

All the prepared tablets were analyzed for drug content and were found in the range of 97.37 to 102.55% was acceptable without much variation.

7.10.7. Dispersion Time

Further the tablets were subjected *in vitro* dispersion in which the time taken by the tablet to produce complete dispersion is measured. The values for all the ten formulations lie between

28.36±0.40 to 60.41±0.17 sec. The *in vitro* dispersion time was rapid in modified *Musa paradisiaca* starch (starch glutamate) followed by extracted starch and Sodium starch glycolate. The comparative results are shown in the following figure 29.

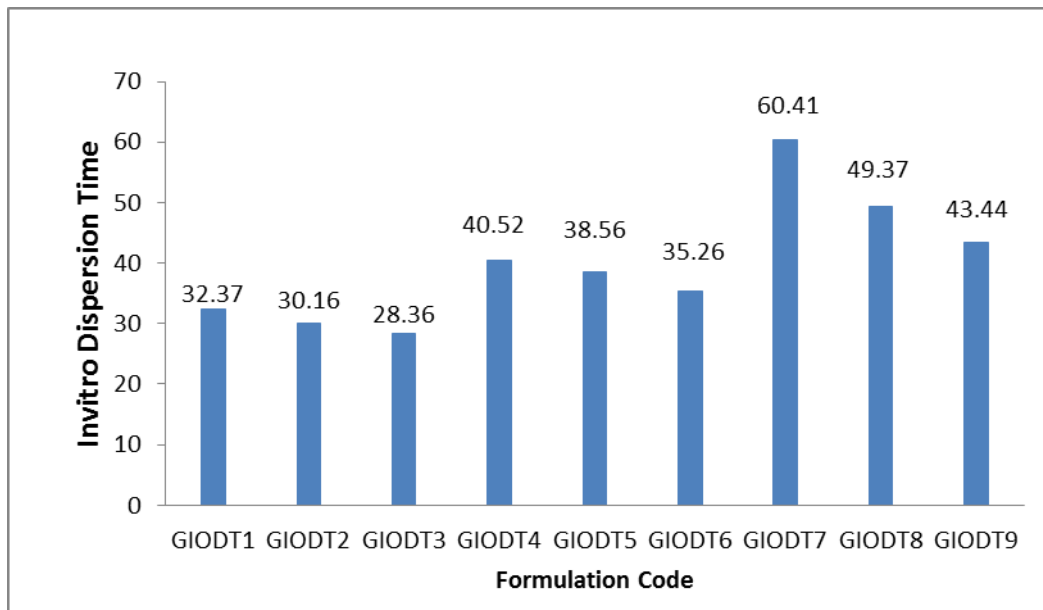


Figure 29: Dispersion Time of Gingerol Orodispersable Tablets with *Modified Musa Paradisiaca* Starch (Starch Glutamate), Extracted Starch and Sodium Starch Glycolate Glycolate in Different Concentrations.

7.10.8. DISINTEGRATION TIME

The disintegration time for the entire formulations lies between 21.56±0.40 to 57.63±0.40 sec. Figure.30. depicts the disintegration behavior of the tablets in water. This rapid disintegration of the oral dispersible tablets was due to penetration of saliva into the pores of the tablets, which leads to the swelling of super disintegrants to create enough hydrodynamic pressure for quick and complete disintegration of the tablet. Batch GIODT3 was selected as best formulation containing modified *Musa paradisiaca* starch (starch glutamate) as superdisintegrant in 6% concentration. It was observed that less disintegration time of 21.56 sec was observed where modified *Musa paradisiaca* starch (starch glutamate) was used as superdisintegrant, may be due to swelling at faster rate upon contact with water and elimination of lump formation after disintegration when compared with extracted starch and sodium starch glycolate.

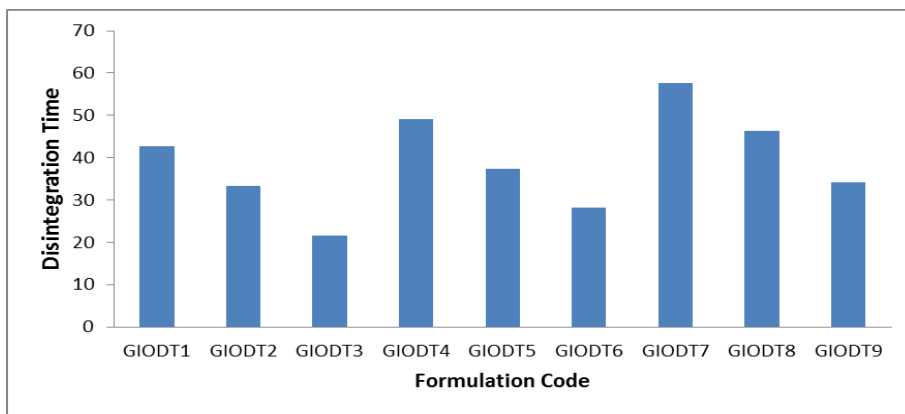


Figure 30: Disintegration Time of Gingerol Orodispersible Tablets with *Modified Musa Paradisiaca* Starch (Starch Glutamate), Extracted Starch and Sodium Starch Glycolate Glycolate in Different Concentrations.

7.10.9. In Vitro Cumulative Drug Release Studies Of Gingerol Oro Dispersible Tablets (GIODT1-GIODT9).

Table 23: % In-Vitro Cumulative Drug Release Data of Gingerol Oro Dispersible Tablets (GIODT1-GIODT9).

TIME(MIN)	% CUMULATIVE DRUG RELEASE								
FORMULATION CODE	GIOD T1	GIOD T2	GIOD T3	GIOD T4	GIOD T5	GIOD T6	GIOD T7	GIOD T8	GIOD T9
0	0	0	0	0	0	0	0	0	0
4	79.50	86.07	87.63	72.43	76.26	78.21	64.06	66.06	69.9
8	85.92	92.55	93.82	75.58	82.21	85.44	67.01	78.35	77.51
12	87.59	93.40	97.66	79.29	86.51	87.73	71.38	84.23	79.51
16	93.82	93.59	99.89	81.28	87.65	89.75	78.80	83.30	84.23
20	92.82	96.76		85.61	88.67	91.88	81.27	85.06	87.13

A. Invitro Cumulative Drug Release Profiles of Gingerol Oro dispersible Tablets (GIODT1, GIODT4 and GIODT7) :-

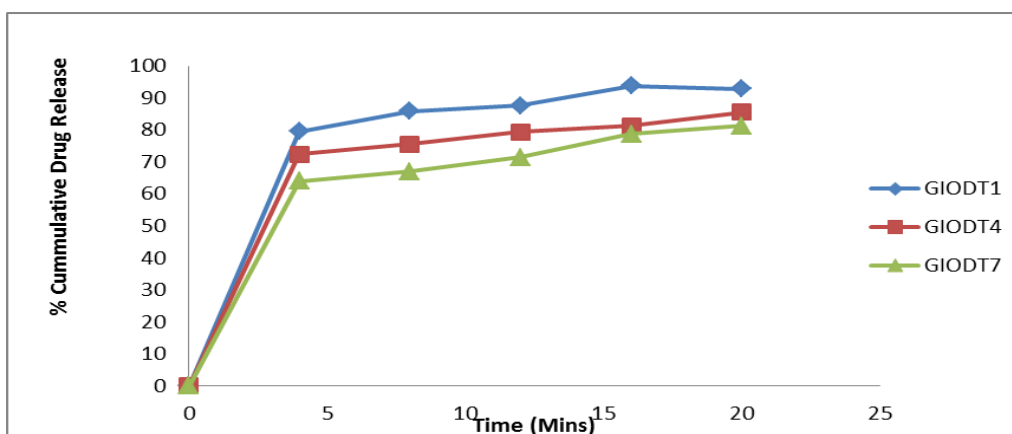


Figure 31: Percentage Cumulative Drug Release Profiles of Formulations (GIODT1, GIODT4 & GIODT7).

B. Invitro Cumulative Drug Release Profiles of Gingerol Oro dispersible Tablets (GIODT2, GIODT5 and GIODT8):

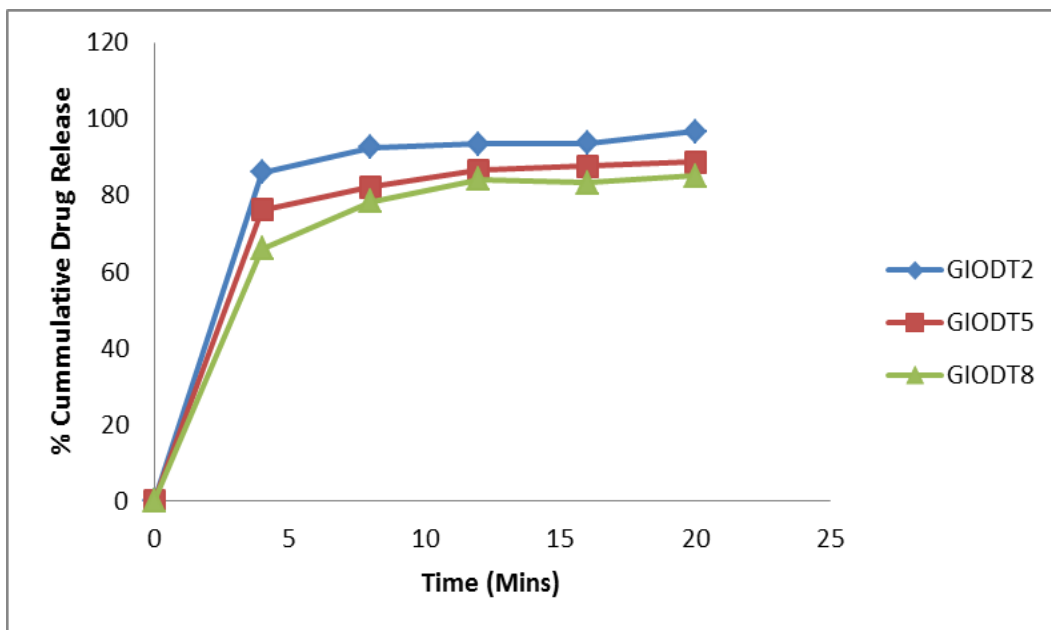


Figure 32: Percentage Cumulative Drug Release Profiles of Formulations (GIODT2, GIODT5&GIODT8).

C. Invitro Cumulative Drug Release Profiles of Gingerol Oro dispersible Tablets (GIODT3, GIODT6 and GIODT9):

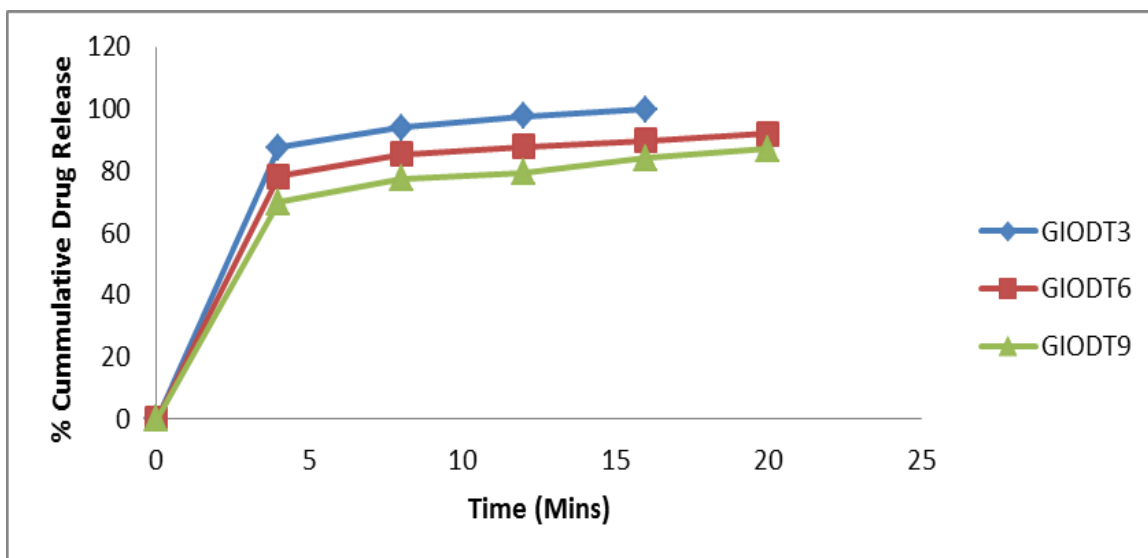


Figure 33: Percentage Cumulative Drug Release Profiles of Formulations (GIODT3, GIODT6&GIODT9).

D. Invitro Cumulative Drug Release Profiles of Gingerol Oro dispersible Tablets (GIODT1- GIODT9):

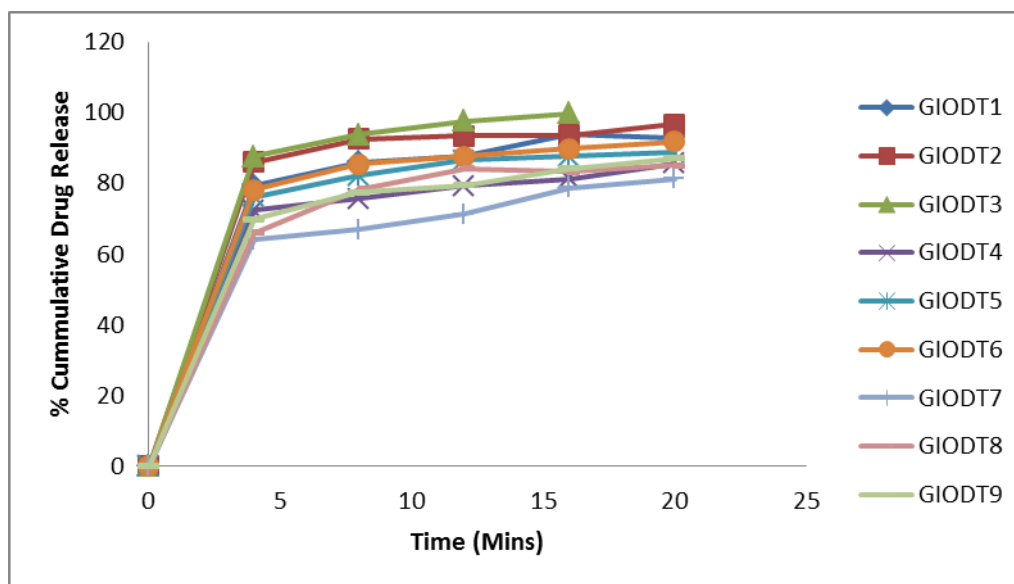


Figure 34: In- Vitro Cumulative Drug Release Profiles of Gingerol Oro Dispersible Tablets (GIODT1- GIODT9).

8. SUMMARY AND CONCLUSION:-

Oro dispersing tablets [ODT's] has increased tremendously over the last decade. The key to ODT formulations is fast disintegration, dissolution, or melting in the mouth and this can be achieved by producing the porous structure of the tablet matrix or adding super disintegrant and/or effervescent excipients. The clinical studies show ODT's can improve patient compliance, provide a rapid onset time of action, and increase bioavailability.

The dosage form was designed by using two natural super disintegrants namely extracted *Musa paradisiaca* starch, Modified *Musa paradisiaca* starch(starch glutamate), and a synthetic super disintegrants sodium starch glycolate along with other excipients. Initially granules were prepared by direct compression method and evaluated for pre-compression parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose.

The formulation blends were compressed as tablets after completion of pre compression parameters. The compatibility studies of drug and excipient was studied by taking FTIR spectra of Gingerol and three super disintegrants i.e., extracted *Musa paradisiaca* starch, Modified *Musa paradisiaca* starch(starch glutamate), and a synthetic super disintegrants sodium starch glycolate. The compressed tablets are evaluated for post compression

parameters such as hardness, thickness, weight variation, friability, drug content, Invitro dispersion time, wetting time, water absorption ratio, disintegration time and in vitro dissolution studies.

Based on the above study following conclusions can be drawn:

- FTIR studies indicated that there are no drug-excipients interactions
- Tablets were prepared by direct compression method and found to be good without any chipping, capping and sticking.
- The hardness of the tablet formulations were found to be in the range of 2.50 -2.76 kg/cm² and friability of the tablet formulations were found to be in the range of 0.747-0.941 %.which indicates the tablet having hard enough with good mechanical strength and have qualified in the official tests.
- The drug content of the tablet formulation was found to be 97.37 - 102.55%.
- The wetting time, Invitro dispersion time and disintegration time of all formulations were found in the range of 17.66 - 51.23 sec ,28.36 - 60.41 sec and 21.56 - 57.63 sec respectively
- Of all the formulations, the tablets formulated with Modified *Musa paradisiaca* starch(GIODT3) showed the least wetting time of 17.66 seconds, which had a direct impact on high water absorption ratio 96.63±0.41%. It was observed that the increased concentration of Modified *Musa paradisiaca* starchdecreased the disintegration time and optimized the drug release. Modified *Musa paradisiaca* starchin the concentration of 6 % acts as a eminent superdisintegrant and disintegrates the tablet within 21.56 seconds fulfilling the criteria of ODT. Further the higher dissolution rate of the GIODT3 formulation 99.89% at the end of 16 min indicated that Modified *Musa paradisiaca* starchhad a better choice among the renowned synthetic super disintegrant like sodium starch glycolate.
- Therefore, among the all formulations (GIODT1-GIODT9), it was observed that formulation-3 has shown better dissolution profile with sufficient wetting capability. So Formulation-3 was found to be the best formulation among others.
- From the results it is concluded, that in comparison with Modified *Musa paradisiaca* starch, *Musa paradisiaca* starch and sodium starch glycolatethe natural super disintegrant i.e., modified*Musa paradisiaca* starchact as a good super disintegrating agent and it showed promising additive anti-emetic activity with Gingerol

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CONFLICT OF INTERESTS

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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