FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF TASTE MASKED NIZATIDINE

Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In partial fulfillment of the requirement for the award of the degree of

MASTER OF PHARMACY

(PHARMACEUTICS)

Submitted By

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MAY - 2012

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LIST OF ABBREVATIONS

µg	-	Microgram
mg	-	Milligram
g	–	Gram
Kg	–	Kilogram
nm	–	Nanometer
cm	–	Centimetre
hrs	–	Hours
min	–	Minute
sec	-	Seconds
ml	–	Millilitre
%	-	Percentage
^{0}C	–	Centigrade
UV	–	Ultra-Violet spectrophotometer
RH	–	Relative humidity
USP	–	United State Pharmacopoeia
IP	–	Indian Pharmacopoeia
BP	–	British Pharmacopoeia
ICH	–	International Conference on Harmonization
#	-	Mesh
Fig	–	Figure
ODT	–	Oro dispersible tablet
HCl	–	Hydrochloric acid

FTIR	–	Fourier transform infrared spectroscopy
SD	-	Superdisintegrants
SSG	–	Sodium starch glycolate
CCS	–	Croscarmellose sodium
CP	–	Cross povidone
F	-	Formulation
SSF	-	Simulated salivary fluid
SGF	-	Simulated gastric fluid

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CERTIFICATE

This is to certify that the work embodied in this thesis entitled **"FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF TASTE MASKED NIZATIDINE"** submitted to The Tamilnadu Dr. M.G.R. Medical University, Chennai, was carried out by **Ms. PAVANI MAKKENA** (Reg.No.26104204) in the Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 in partial fulfillment for the degree of **MASTER OF PHARMACY** in Pharmaceutics under my direct supervision and guidance.

This work is original and has not been submitted in part or full for any other degree or diploma of any university.

Place: Erode **Dr. P.R.RADHIKA, M.Pharm., Ph.D.**

Date: Research Guide

EVALUATION CERTIFICATE

This is to certify that the work embodied in this thesis entitled, **"FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF TASTE MASKED NIZATIDINE"** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, was carried out by Reg. No. **26104204** in the Department of Pharmaceutics, Nandha College of Pharmacy and Research institute, Erode-52 for the partial fulfillment for the award of degree of **MASTER OF PHARMACY** in Pharmaceutics under the supervision and guidance of **Dr.P.R.RADHIKA, M.Pharm., PhD.,** Professor, Department of Pharmaceutics, Nandha College of Pharmacy and Research Institute, Erode- 52.

This work is original and has not been submitted in part or full for any other degree or diploma of this or any other university.

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DECLARATION

The work presented in this thesis entitled **"FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF TASTE MASKED NIZATIDINE"** was carried out by me in the Department of Pharmaceutics, Nandha College of Pharmacy, Erode, under the direct supervision and guidance of **Dr. P.R.RADHIKA, M.Pharm., Ph.D.,** Professor**,** Nandha College of Pharmacy, Erode -52.

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ACKNOWLEDGEMENT

It is moment of gratification and pride to look back with a sense of contentment at a long travelled path, to be able to capture some of the fine moments, to be able to thank infinite number of people, some who were with me from the beginning, some who joined me at some stage during the journey, whose kindness, love and blessing has brought this day. I wish to thank each one of them with all my heart.

It is my great pleasure to thank my eminently esteemed teacher and guide ***Dr. (Mrs.) P.R.Radhika, M.Pharm., Ph.D.,*** *Professor, Dept. of Pharmaceutics, Nandha College of Pharmacy, Erode, for her valuable guidance, keen interest, inspiration, encouragement and moral support throughout my dissertation work.*

I take the opportunity to express my heartfelt gratitude to our principal ***Dr.T.Sivakumar, M.Pharm., Ph.D****., Principal, Nandha College of Pharmacy, Erode, with a deep sense of gratitude for encouragement, co-operation, kind suggestions and providing the best facilities during this work.*

I thank honorable ***Thiru V. Shanmugan, B.Com.,*** *Chairman and* ***Mr.S.Nandhakumar Pradeep, M.B.A.,*** *Secretary, Nandha College of Pharmacy, Erode-52, for providing me the required infrastructure to undergo my study.*

I owe my warmest and humble thanks to ***Dr. Sengotuvelu, M.Pharm., Ph.D.,*** *Head, Dept. of Pharmacology and* ***Prof. R. Rajvel, M.Pharm.,*** *Dept. of Pharmaceutical chemistry, for their immense help throughout the courses of study.*

I also feel pleasure in expressing sincere thanks to respected teachers ***Dr. S. Tamizharasi, M.Pharm., Ph.D.,*** *Head, Dept. of Pharmaceutics****, Prof. Amsa, M.Pharm.,*** *and* ***Prof. K.Raja, M.Pharm.,*** *who constantly supported me in my every needful moment.*

I want to say extremely special thanks to my friends ***A.L.Jayashankar*** *and* ***N.Pavan*** *for providing the necessary help.*

I also express my thanks to our non-teaching staff for providing timely assistance throughout the entire work.

I convey our thanks and gratitude to our college Librarian for providing references in time.

It gives me profound pleasure to express my heartful thanks to my classmates ***Reepa, Sanath, Sibu, Kalpana, Rajnish, Ravi, Praveen, Prakash, Subhash, and Thandav Krishna*** *for their constant inspiration and co-operation.*

Last but not least, I express my heartiest thanks and gratitude to my beloved ***Parents***, ***Sister and Brother*** *for all their support without which my project would be incomplete.*

Besides this, several people have knowingly and unknowingly helped me in the successful completion of this project. I thank every one of them.

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INTRODUCTION

Drug Delivery Systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because of low cost of therapy, ease of administration, accurate dosage, self-medication, pain avoidance, versatility, leading to high levels of patient compliance.

Tablets and capsules are the most popular dosage forms which have wide acceptance up to 50-60% of total dosage forms. Among all conventional dosage forms tablet is the most popular one till today because of ease of administration, compact in nature, easy to manufacture and it can deliver accurate dose. But the main drawback of solid dosage forms is the difficulty in swallowing which is referred as dysphagia in some patients particularly pediatric and geriatric patients. The dysphagia occurs in geriatric patients due to fear of choking, hand tremors and in paediatric patients due to underdeveloped muscular and nervous systems and in schizophrenic patients which leads to poor patient compliance. The difficulty of swallowing also occurs when water is not available, in diarrhoea, coughing during common cold, allergic conditions and bronchial infection and many other medical conditions including stroke, parkinson's disease, AIDS, thyroidectomy, head and neck radiation therapy and other neurological disorders including cerebral palsy and it is also applicable to people who are ill in bed and those active working patients who are busy or travelling, especially those who have no access to water. Improved patient compliance has achieved enormous demand. Consequently demand for their technologies is also increasing many folds. It is always the aim of a scientist or a dosage form designer to enhance the safety of a drug molecule while maintaining its therapeutic efficacy. Recent advances in Novel Drug Delivery Systems (NDDS) aim for the same by formulating a dosage form, convenient to be administered so as to achieve better patient compliance. Pharmaceutical technologists have put in their best efforts to develop a Fast Dissolving Drug Delivery System4, i.e Mouth Dissolving Tablet [1,2].

The US Food and Drug Administration Centre 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 placed upon

the tongue". The significance of these dosage forms is highlighted by the adoption of the term, "Orodispersible Tablet", by the European Pharmacopoeia which describes it as a tablet that can be placed in oral cavity where it disperses rapidly before swallowing [3].

1.1. TABLETS:

Tablets remain popular as oral dosage form because of the advantages, afforded both to the manufacturer [e.g.: simplicity & economy of preparation, stability and convenience in packing, shipping, and dispensing] and the patient [e.g.: accuracy of dosage, compactness, post ability, blandness of taste and ease of administration [4].

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

Types of Tablets:

Tablets are mainly classified into 4 categories according to their route of administration. The following are the 4 groups.

I. Oral tablets for ingestion

a. Standard compressed tablets
b. Multiple compressed tablets
    - Compression coated tablet
    - Layered tablet
    - Inlay tablet
c. Modified Release tablet
d. Delayed action tablet
e. Targeted tablet
    - Floating tablet
    - Colon targeting tablet
f. Chewable tablet
g. Dispersible tablet

II. Tablets used in the oral cavity

a. Lozenges and troches
b. Sublingual tablet

c. Buccal tablet
d. Dental cones
e. Mouth dissolved tablet

III. Tablets administered by other routes

a. Vaginal tablet
b. Implants

IV. Tablets used to prepare solution

a. Effervescent tablet
b. Hypodermic tablet
c. Soluble tablet

1.2. ORODISPERSIBLE TABLETS: (ODTs)

It is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. An orodispersible tablet usually dissolves in the oral cavity within 15 s to 3 min. Orodispersible tablets are also known as mouth-dissolving tablets, melt-in mouth tablets, Fast dissolving tablets, rapimelts, porous tablets, quick dissolving tablet. They have unique property of rapidly disintegrating and/or dissolving and releasing the drug as soon as they come in contact with saliva, thus obviating the requirement of water during administration and they turn into a soft paste or liquid form for easy swallowing, and it is free of risk of choking.

Mainly these tablets are prepared by the use of superdisintegrants such as crosspovidone, croscarmellosesodium, sodium starch glycolate etc. The super disintegrants are added to this formulation to enhance the disintegration of tablet into smaller particles which provides rapid onset of action. Most fast dissolving tablets must include substances to mask the bitter taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients. It has been concluded that faster the dissolution, faster the absorption and onset of action. Some drugs are absorbed from the oral cavity, pharynx and oesophagus as the saliva passes down into the stomach and avoids the first pass metabolism. Thus the bioavailability of drug is significantly more than those observed from conventional tablets dosage form.

Super disintegrants play a major role in the disintegration and dissolution of MDT. Super disintegrants provide quick disintegration due to combined effect of swelling and water

absorption by the formulation which forms a porous structure. The optimum concentration of the superdisintegrant can be selected according to critical concentration of disintegrant. Below this concentration, the tablet disintegration time is inversely proportional to the concentration of the superdisintegrant, whereas if concentration of superdisintegrant is above critical concentration, the disintegration time remains almost constant or even increases [1,2].

Advantages of ODTs [1]:

- Do not require water to swallow the tablet
- It can easily administered to geriatric, paediatric and mentally disabled patients.
- It provides accurate dosing compare to liquids.
- Dissolution and absorption of drug is fast, thus providing rapid onset of action.
- Advantageous over liquid medication in terms of administration as well as transportation.
- Suitable for sustained/controlled release actives.
- It allows high drug loading.
- Bioavailability of drugs is increased as some drugs are absorbed from mouth, pharynx and oesophagus through saliva passing down into the stomach and avoids first pass metabolism and thus reduced dose and side effects.

Limitations [2]:

- The tablets generally have insufficient mechanical strength. Hence, careful handling is required during manufacturing process.
- The tablets may leave unpleasant taste and/or grittiness in oral cavity if not formulated properly.
- Drugs with larger doses are difficult to formulate into FDT e.g. rifampin (600 mg), ethambutol (1000mg) etc.

Ideal properties of ODTs [5]:

- It requires no water for oral administration.
- It should have adequate taste-masking properties.
- It should have pleasant mouth-feel properties, adequate hardness.
- It should leave little or no residue in mouth after oral administration.
- It should be compatible with taste masking.
- It allows high drug loading.

- It should exhibit low sensitivity to environmental conditions such as temperature and humidity.

Approaches to achieve the tablets ODTs [5]:

- Water must rapidly enter into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet.
- Incorporation of an appropriate disintegrating agent or highly water soluble excipients in the tablet formulation.

There are some undermentioned mechanisms by which the tablet is broken down into the smaller particles and then subsequently result a solution or suspension of the drug. The mechanisms are

• High swellability of disintegrants

• Chemical reaction

• Capillary action

Technologies used for manufacturing of ODTs [2,6,7]:

I. Conventional techniques

II. Patented techniques

Conventional techniques:

1. **Freeze drying or lyophilisation:**

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. Finally the blisters are packaged and shipped.

Characteristics: Highly porous, have high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability.

2. **Tablet moulding:**

Water-soluble ingredients with a hydro-alcoholic solvent is used and is moulded into tablets under pressure lower than that used in conventional tablet compression. Then the solvent is removed by air drying.

Characteristics: Moulded tablets are very less compact than compressed tablet porous structure that enhances disintegration/dissolution and finally absorption increased.

3. **Direct compression:**

It is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods.

Characteristics: It is most cost effective tablet manufacturing technique.

4. **Spray drying:**

By hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or crosscarmellose sodium as disintegrating agent and an acidic material (e.g. citric acid) and / or alkali material (e.g. Sodium bicarbonate) to enhance disintegration /dissolution.

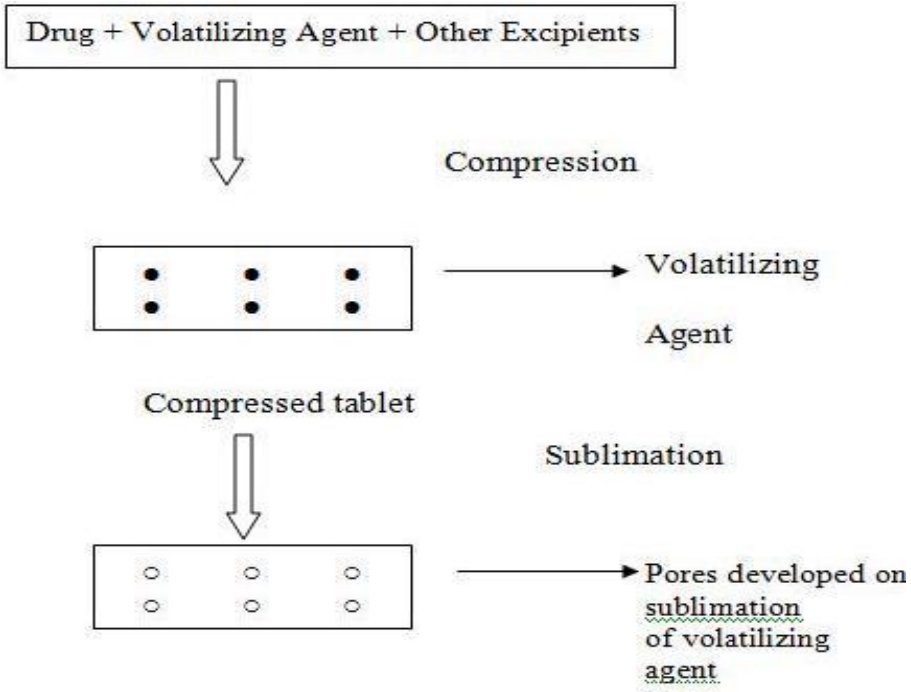
Characteristics: Prepared tablet disintegrates within 20 seconds when immersed in an aqueous medium.

5. **Sublimation:**

Inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate, hexamethylene tetramine 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.

Figure No: 1 Sublimation process



6. **Disintegrant addition method:**

It involves the addition of superdisintegrants in optimum concentration to the formulation to achieve rapid disintegration/dissolution. For e.g. Sodium starch glycolate, crystalline cellulose (AvicelPH-102) and low substituted HPEC, Crosspovidone and crosscarmellose Na.

Characteristics: Similar to conventional tablets with higher % of disintegrants, lower hardness and higher % of friabilty.

7. **Mass extrusion:**

This method involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, methanol and expulsion of softened mass through the extruder or syringe to get a cylindrical shape 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:**

This process is so named as it utilizes a unique spinning mechanism to produce floss-like crystalline structure, which mimic cotton candy. It 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 FDT.

Characteristics: It can accommodate high doses of drug and offers improved mechanical strength.

9. Compaction:

a) Melt granulation:

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. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation

Characteristics: It melts in the mouth and solubilizes rapidly leaving no residue.

b) Phase transition process:

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.

10. Nanonization:

A recently developed nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using a proprietary wet-milling technique. Nanocrystals 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).

11. Fast dissolving films:

A non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, cellulose derivatives, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients are used to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated

micro particles of the drug can be incorporated into the film. This film, when placed in mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form.

Characteristics: The thin films size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavoured after taste.

Patented techniques [7,8]:

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 material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

2. **Orosolv technology:**

   In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable.

3. **Durasolv technology:**

   The tablets made by this technology consist of drug, filler and a lubricant. Tablets are prepared by using conventional punching equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. durasolv is an appropriate technology for product requiring low amounts of active ingredients.

4. **Flashtab technology:**

   Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation and extrusion spheronisation. All the processing utilized conventional tableting technology.

5. **Wowtab technology:**

WOW means "Without Water". In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (eg. lactose, glucose, and mannitol) and granulated with a high mouldability saccharide (eg. Maltose, oligosaccharides) and compressed into tablet.

6. **Oroquick technology:**

The OraQuick fast-dissolving/disintegrating tablet formulation utilizes a patented taste masking technology. It is microsphere technology, known as MicroMask, has superior mouthfeel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production. Also, lower heat of production than alternative fast-dissolving/disinte-grating technologies makes OraQuick appropriate for heat-sensitive drugs. The matrix surrounds and protects the drug powder in microencapsulated particles is more pliable, meaning tablets can be compressed to achieve significant mechanical strength without disrupting taste masking. OraQuick claims quick dissolution in a matter of seconds, with good taste-masking. There are no products using the OraQuick technology currently on the market, but KV Pharmaceutical has products in development such as analgesics, scheduled drugs, cough and cold, psychotropics, and anti-infectives

7. **Flash dose technology:**

Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product launched by biovail corporation. Flash dose tablets consist of self-binding shear form matrix termed as "floss". Shear form matrices are prepared by flash heat processing.

8. **Ziplet technology:**

AdvaTab is distinct from other ODT technologies as it can be combined with Eurand's complimentary particle technologies like its world leading Microcaps® taste-masking technology and its Diffucaps® , controlled release technology. The pairing of AdvaTab with Microcaps creates products that offer the dual advantage of a patient preferred dosage form, together with a superior taste and smooth mouth feel.

Table No: 1 Patented technologies and their brand products [2]

S.No	Technique	Novelty	Patent owner	Drugs used (brand name)
1.	Zydis	First to market, Freeze dried	R.P.Scherer Inc.	Loratidine (Claritin Reditab and Dimetapp Quick Dissolve)
2.	Orosolv	Unique taste-masking, lightly compressed	Cima Labs Inc.	Paracetamol (Tempra Quicklets),Zolmitriptan (Zolmig Repimelt)
3.	Durasolv	Compressed dosage form, Proprietary taste masking.	Cima Labs Inc.	Hyoscyamine Sulfate (NuLev)Zolmitriptan (Zolmig ZMT)
4.	Flashtab	Compressed dosage form containing drug as micro-crystals	Ethypharm	Ibuprofen (Nurofen Flashtab)
5.	Wowtab	Combination of low - mouldability and high - mouldabiity saccharides. Smoothmelt action gives superior mouth feel.	Yamanouchi Pharma Technologies, Inc.	Famotidine (Gaster D)
6.	Oraquick	Uses patented taste masking technology	KV Pharm. Co., Inc.	Hyoscyamine Sulfate ODT
7.	Flashdose	Unique spinning mechanism to produce a floss-like crystalline structure, much like cotton candy.	Fuisz Technology Ltd.	Tramadol HCl (Relivia Flash dose)
8.	Ziplet/ advatab	Incorporation of waterinsoluble inorganic excipients for excellent physical performance	Eurand International	AdvaTab cetrizine, AdvaTab Paracetamol

Table No: 2 Important patented technologies for preparation of ODTs [2]

S.No	Technique	Process involved	Advantages	Disadvantages
1.	Zydis	Lyophilization	Quick dissolution, Self-preserving and increased bioavailability.	Expensive process, poor stability at higher temperature and humidity.
2.	Orosolv	Compressed tablets	Taste-masking is twofold, quick dissolution.	Low mechanical strength.
3.	Durasolv	Molding	Higher mechanical strength than Orasolv, Good rigidity.	Inappropriate with larger dose.
4.	Flashtab	Lyophilization	Only conventional tableting technology	-
5.	Wowtab	Compressed molded tablets	Adequate dissolution rate and hardness.	No significant change in bioavailability.
6.	Oraquick	Micromask taste masking	Faster and efficient production, appropriate for heat-sensitive drugs.	-
7.	Flashdose	Cotton-candy process	High surface area for dissolution	High temperature required to melt the matrix can limit the use of heat-sensitive drugs, sensitive to moisture and humidity.
8.	Ziplet/ advatab	Molding	Good mechanical strength, satisfactory properties can be obtained at high dose (450 mg) and high weight (850 mg).	As soluble component dissolves, rate of water diffusion in to tablet is decreased because of formation of viscous concentrated solution

1.3. SUPERDISINTEGRANTS (SDs) [1]:

Use of superdisintegrants is basic approach in development of ODTs and plays important role like discussed above. The following are some mechanisms through which the SDs shows their action.

Mechanisms of SDs:

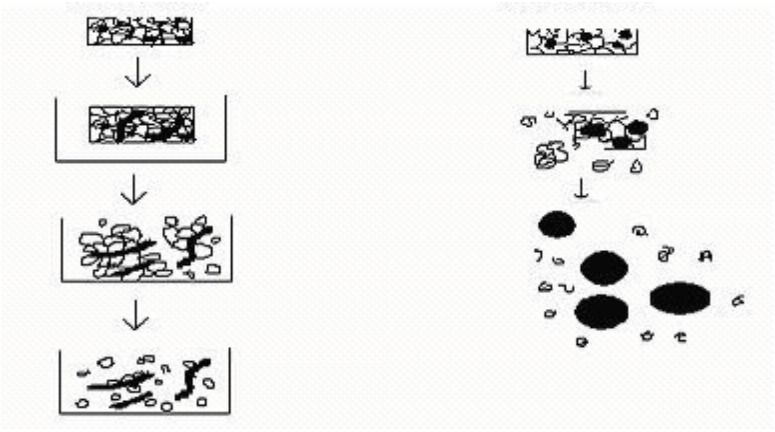
a. By capillary action (wicking):

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug /excipient and on tableting conditions.

b. By swelling:

The most widely accepted 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 unable to penetrate in the tablet and disintegration is again slows down.

Figure No: 2 Disintegration of tablet by wicking and swelling



WICKING	SWELLING
Water is pulled by disintegrant and reduced the physical bonding force between particles	Particles swell and break up the matrix form within

c. 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 tablet. This is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

d. 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 and generates pressure within the tablet due to which the tablet disintegrants. This effervescent mixture is used when pharmacist needs to formulate fast 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 to two separate fraction of formulation.

e. By enzymatic reaction:

Here, enzymes present in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration. But actually the disintegration occurs by swelling.

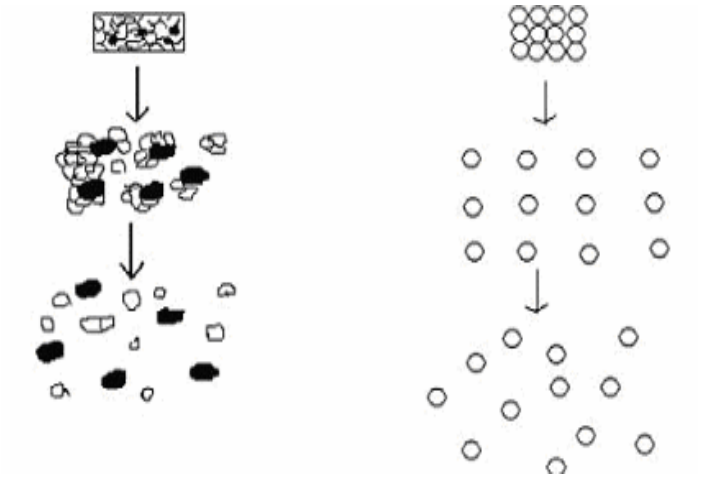
f. Due to disintegrating particle/particle repulsive forces:

Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling 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. This is the swelling of tablet made with non-swellable disintegrants.

g. Due to deformation:

Hess had proved that during tablet compression, disintegranted particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression.

Figure No: 3 Disintegration by deformation and repulsion



DEFORMATION

Particles swell to precompression size and break up matrix

REPULSION

Water is drawn into poresand particles repel each other because of resulting electrical force.

Table No: 3 List of some superdisintegrants used in ODTs preparation [2]

Superdisintegrant	Nature	Properties	Mechanism
Crosspovidone	Crosslinked homo polymer of *N*-vinyl-2-pyrrolidone	Particle size - 100 μm, insoluble in water, gives smoother mouth feel	Both swelling and wicking
Cross carmellose sodium	Cross-linked form of sodium CMC	Particle size 200 mesh, insoluble in water	Swelling
Sodium starch glycolate	Crosslinked low substituted carboxymethyl ether of poly-glucopyranose	Particle size 140 mesh, insoluble in organic solvents, disperses in cold water and settles in the form of a highly saturated layer	Water uptake followed by rapid and enormous swelling
Acrylic acid derivatives 43 (Yang *et al*. 2004)	Poly(acrylic acid) super porous hydrogel	Particle size 106 μm, DT- 15 + 2 S	Wicking action
Effervescent mixture	Citric acid, tartaric acid, sodium bicarbonate	Crystalline nature	Effervescence
Sodium alginate	Sodium salt of alginic acid	Slowly soluble in water, hygroscopic in nature	Swelling
NS-300 43 (Ozeki *et al.* 2003)	Carboxy methyl cellulose	Particle size 106 μm, DT - 20 S	Wicking type
ECG-505 43 (Ozeki *et al*. 2003)	Calcium salt of CMC	Particle size 106 μm, DT - 80S	Swelling type
L-HPC 43 (Ozeki *et al.* 2003)	Low hydroxy propyl cellulose	Particle size 106 μm, DT-90S	Both swelling and wicking

1.4. TASTE MASKING METHODS FOR ODTs [8]:

The drugs are mostly bitter in nature. Taste masking is needed to hide the bitter taste in ODTs formulations which can be achieved by using combination of right flavour and right sweeteners. Methods used in taste masking are given as follows:

a. Incorporation of Sweeteners and Flavours:

Different flavours are used in ODT formulations to mask the bitter taste and give pleasant mouth feel. Most commonly used flavours are mint, orange, strawberry, pineapple, peppermint flavours. Mannitol and aspartame are most widely used excipients in formulating ODTs.

b. Adjustment of pH values:

Many drugs are less soluble at pH different from the pH of the mouth, which are around 5.9. Drugs can be insufficiently solubilized to be available to taste if the equilibrium concentration is below the taste threshold.

c. Effervescent Technique:

The bitter taste of the drugs can be masked as effervescent tablet rapidly disintegrates and carbon dioxide is produced by contact with saliva or aqueous fluid.

d. Spray Drying Technique :

Simple wet granulation method or roller compaction of other excipients. Spray drying can also employed to shroud the drug.

e. Coating of Drug Particles with Inert Agents:

Coating is an extremely useful technique for number of applications in the pharmaceutical field. By using the right type of coating material it is possible to completely mask the taste of a bitter drug, while at the same time, not adversely affecting the intended drug release profile. Any nontoxic polymer that is insoluble at pH 7.4 and soluble at acidic pH would be an acceptable alternative for taste masking.

f. Taste Masking by Formation of Inclusion Complexes:

The complexing agent is capable of masking the bitter taste of the drug by decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste. Mainly involved forces in inclusion complexes are Vander Waals forces. Most widely used complexing agent is Beta-cyclodextrin for inclusion type complexes. It is sweet, nontoxic, cyclic oligosaccharide obtained from starch. Cyclodextrin help to solubilize many drugs.

g. Solid Dispersion System:

Solid dispersion is also called as co precipitates for those preparations obtained by solvent method such as co precipitates of sulphathiazole and povidone. Solid dispersions using insoluble matrices or bland matrices may be used to mask the bitter taste of drugs. Also using them as absorbents on various carriers may increase the stability of certain drugs.

h. Microencapsulation:

Microencapsulation as a process has been defined by Bakan as a means of applying relatively thin coating to small particles of solid, droplets of liquid and dispersion54. This process can be used for masking of bitter tasting drugs microencapsulating drug particles with various coating agents.

i. Mass Extrusion Method (Dispersion coating):

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.

j. Ion Exchange Resin:

When the drug resinates comes into contact with the gastrointestinal fluids, such as the acid of the stomach. The drug is released from resinate directly into solution and then absorbed in the usual way. The resin passes through the GI tract without being absorbed. Examples of drugs where this technique has been successfully demonstrated include ranitidine, risperidone and paroxetine.

LITERATURE REVIEW

Prashant Khemariya *et al* [13]: They prepared mouth dissolving tablets of meloxicam which is a newer selective COX-1 inhibitor. They prepared the tablets by wet granulation procedure and evaluated for % friability, wetting time and disintegration time. They found that sublimation of camphor from tablets resulted in better tablets as compared to the tablets prepared from granules that were exposing to vacuum.

Metker Vishal *et al* [14]: They have developed orodispersible tablets of lornoxicam using kyronT-314 (polacrillin potassium) as a novel superdisintegrant. They are prepared by wet granulation method using Kyron T-314 and menthol as sublimating agent and menthol as sublimating agent for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Prabhakar Reddy Veerareddy *et al* [15]: They have prepared and evaluated the fast dissolving tablets of ketorolac tromethamine using a combined approach of subliming agent and superdisintegrant. FDTs were prepared by direct compression technique. The prepared tablets were dried under vacuum for camphor sublimation that results porous structure in the tablet which results faster disintegration and drug release. They evaluated the tablets for various tests. The porous structure of the tablet was observed under scanning electron microscopy (SEM). Their results showed low weight variation, good hardness, acceptable friability.

Dr. Srinivasa Rao Y *et al* [16]: Designed FDTs of taste-masked ondansetron HCl using eudragit E 100 as a taste masking agent. They used mass extrusion method to prepare taste-masked granules. The drug polymer complexes were tested for drug content,in vitro taste evaluation in SSF of pH 6.2 and drug excipient interaction. They considered a complex as taste masked which did not release drug in SSF and selected the same for the formulation of FDTs. Indion-414 was used as the superdisintegrant.

Uddhav Bagul *et al* [17]: They developed fast melt tablets of levocetirizine dihydrochloride by using sublimation technique which were prepared by direct compression method using different concentrations of spray dried mannitol (Perlitol SD200), menthol and camphor. The sublimation technique is used to increase the porosity of the tablets in which menthol and camphor were used as subliming agents which in turn forms the porous structure on the surface of tablets after sublimation. The in vitro drug release study revealed that

menthol and camphor (1:1) at a concentration of 20 % (Batch – LMD-6)of the total weight of the tablet offer fast release of Levocetirizine dihydrochloride within 5 minutes. These tablets also dissolved within 15-20 seconds in saliva with pleasant taste and smooth mouth feel.

Basawaraj S.Patil *et al* [18]: They prepared fast dissolving tablets of Granisetron hydrochloride by vacuum drying technique using camphor as subliming agent together with croscarmellose sodium, crospovidone, sodium starch glycolate and plantago ovate as superdisintegrants. They have concluded that fast dissolving tablets with improved granisetron hydrochloride dissolution could be prepared by sublimation of tablets containing suitable subliming agent.

Nagendra Kumar D *et al* [19]: They have formulated fexofenadine hydrochloride fast dissolving tablets by sublimation method. In this method, camphor was used as the subliming agent (upto 30% w/w), crospovidone and croscarmellose sodium (2-8% w/w) were used as superdisintegrants. Estimation of fexofenadine hydrochloride in the prepared tablet formulations was carried out by extracting the drug with methanol and measuring the absorbance at 259 nm. Based on *in vitro* dispersion time (approximately 5-14 sec), two promising formulations (one from each super-disintegrant) were tested for *in-vitro* drug release pattern in pH 6.8 phosphate buffer. They found that among the two promising formulations, the formulation (SCP3) containing 8% w/w of crospovidone and 30% w/w camphor as the subliming agent emerged as the overall best formulation (t50%4.3 min) based on drug release characteristics in pH 6.8 phosphate buffer compared to commercial conventional tablet formulation (t50%15 min).

D.G.Umalkar *et al* [20]: They designed mouth dissolving tablet of zopicolon using combination of super-disintegrants i.e.Ac-di-sol (croscarmellose sodium), polyplasdone XL-10, microcrystalline cellulose pH 102 along with directly compressible dextrose to improve mouth feel. The formulation prepared by direct compression method using Ac-di-sol (croscarmellose sodium) 50mg, polyplasdone XL- 10 -25mg, microcrystalline cellulose pH 102- 25mg was found to be better formulation T80% = 5 min based on in-vitro drug release characteristics.

S Furtado *et al* [21]: Developed and characterized the orodispersible tablets of famotidine containing camphor as a subliming agent. Sodium starch glycolate and crosscarmellose sodium were used as superdisintegrants. They evaluated the prepared tablets for various

tests. They observed that the tablets containing subliming agent had a good dissolution profile.

Patel Bipin *et al* [22]: Developed mouth dissolving tablets of cinnarazine which is H1-receptor antagonist and widely used in the treatment of motion sickness, vomiting and vertigo. Mouth dissolving tablets of cinnarizine were prepared by effervescent, superdisintegrant addition and sublimation methods among which superdisintegrant addition method showed lowest disintegration time; hence it was selected for further studies. Further nine batches (B1-B9) were prepared by using crospovidone, croscarmellose sodium and L-HPC in different concentrations such as 5%, 7.5% and 10%. Formulation with 10% L-HPC showed less disintegration time (25.3 seconds) and less wetting time (29.1 seconds) and in-vitro dissolution studies showed total drug release at the end of 6 minutes.

Vijay Tiwari *et al* [23]: They have researched to study fast dissolving tablets of celecoxib using soliddispersion of celecoxib and sorbitol by holt melt extrusion process, and superdisintegrants (sodium starch glycolate), binder (polyvinylpyrrolidone), sweetner (saccharine sodium), flavour (menthol). They have prepared six different formulations of solid dispersion and the batch having the best drug release profile was used for the preparation of nine batches of fast dissolving tablets by direct compression method. It has shown that the batch of solid dispersion containing maximum concentration of sorbitol polymer is showing best drug release and in fast dissolving tablets the batch containing maximum concentration of superdisintegrant is showing the best drug release (99.74% in 30 min). They concluded the bioavailability of celecoxib is increased by fast dissolving dosage form.

Ashwini R.Madgulkar *et al* [24]: Developed novel taste masked mouth-dissolving tablets of tramadol that overcomes principle drawback of such formulation which is inadequate mechanical strength. The crucial aspect in the formulation of mouth-dissolving tablets is to mask the bitter taste and to minimize the disintegration time while maintaining a good mechanical strength of the tablet. They masked the bitter taste of tramadol HCl by forming a complex with an ion exchange resin Tulsion335. The novel combination of a superdisintegrant and a binder that melts near the body temperature was used to formulate mechanically strong tablets that showed fast disintegration. A 32 full factorial design and statistical models were applied to optimize the effect of two factors, i.e., superdisintegrant

(crospovidone) and a mouth-melting binder (Gelucire 39/01). It was observed that the responses, i.e., disintegration time and percent friability were affected by both the factors. The statistical models were validated and can be successfully used to prepare optimized taste masked mouth-dissolving tablets of Tramadol HCl with adequate mechanical strength and rapid disintegration.

Sachin B.Mahamuni *et al* [25]: Formulated fast dissolving tablets which can rapidly disintegrate in the saliva using taste-masked granules of drugs with a bitter taste, promethazine HCl (PM HCl) which were prepared using gastro erodible aminoalkyl methacrylate copolymers (Eudragit E-100) by extrusion method. Fast dissolving tablets were prepared by direct compression method using taste-masked granules and a mixture of excipients containing optimized level of microcrystalline cellulose (Avicel PH-101) and starch. The effect of various superdisintegrants crospovidone (Polyplasdone XL), sodium starch glycolate (Primogel), croscarmellose sodium (Ac-Di-Sol)] was also studied. The dissolution rate was significantly improved with FDT formulated with taste masked granules of PM HCl as compared with unmasked granules. This could be accounted to the effect of Eudragit E-100 on the dissolution profile of PM HCl and also aiding in masking the bitter taste.

Vineet Bharadwaj *et al* [26]: They prepared fast dissolving tablets of amlodipine besylate by sublimation method using camphor as sublimating agent. The tablets are prepared by direct compression method. They used different concentrations (2%, 4%, 6%) of superdisintegrants such as Ac-Di-Sol, sodium starch glycolate, kollidon-CL were used respectively. Amongst all formulations, formulation prepared by 6% Ac-Di-Sol showed least disintegrating time of 11sec and faster dissolution. Formulation F9 was then studied for accelerated stability studies as per ICH guidelines for 60 days that shows no remarkable change in the formulation.

Anupama Kalia *et al* [27]: Mouth dissolving tablets of oxcarbazepine are produced by direct compression method contain crospovidone as a superdisintegrant and aspartame as a sweetener. Solid dispersions of oxcarbazepine with polyvinylpyrrolidone K-30 and polyethylene glycol 6000 in different weight ratios were prepared with a view to increase its water solubility. Oxcarbazepine solid dispersions with polyvinylpyrrolidone K-30 in 1:2 ratios of drug: carrier showed maximum drug release and hence, compressed along with other excipients into mouth dissolving tablet. The results compared for both the

technologies showed that the oxcarbazepine tablets prepared using solid dispersion technology was found to have good technological properties and satisfying and reproducible drug dissolution profiles.

D.Nagendrakumar *et al* [28]: They formulated fast dissolving tablets of granisetron HCl using novel co-processed superdisintegrants consisting of crospovidone and crosscarmellose sodium in the different ratios (1:1, 1:2 & 1:3). Based on *in vitro* dispersion time (approximately 20 sec), promising formulation CP1 was tested for *in vitro* drug release pattern in pH 6.8 Phosphate buffer and short-term stability (at 400C/75% RH for 3 months), drug excipients interaction (IR spectroscopy) were studied. Among the designed formulations, the formulation (CP1) containing 4% w/w of coprocessed superdisintegrant (1:1 mixture of crospovidone and crosscarmellose sodium) emerged as the overall best formulation (t50% 3.0 min) based on drug release characteristics in pH 6.8 phosphate buffer compared to commercial conventional tablet formulation (t50% >15 min).

Shailendra Kumar Singh *et al* [29]: Prepared fast disintegrating combination tablets of omeprazole and domperidone using Mannitol as diluent and sodium saccharin as sweetening agent along with three different levels of disintegrant. They used Kollidon CL, Ac-Di-Sol and SSG as superdisintegrants. The tablets were prepared by direct compression method and evaluated for various tests. Drug content was estimated by using HPLC method and also assay of sample was compared with standard drugs. From the results obtained they concluded that the tablet formulation prepared with 4.76% Ac-Di-Sol showed disintegration time of 15 seconds in vitro and also satisfied the other tests.

Dr. C.S.R. Lakshmi *et al* [30]: They compared the effect of subliming agents on the oral dispersible properties of cinnarazine tablets. The fundamental principle used in the development of oral dispersible tablets by sublimation technique is to maximize pore structure of the tablets the compressed tablets prepared by using water soluble materials like mannitol, does not rapidly disperse in water since it is difficult for water to penetrate into the tablets due to their low porosity. To increase the porosity of the tablets which are prepared by direct compression using Mannitol, subliming agents such as camphor, menthol, ammonium bicarbonate or thymol are to be used. A high porosity was achieved due to the formation of many pores where camphor, menthol, ammonium bicarbonate and thymol particles previously existed in the compressed Mannitol tablets prior to

sublimation of these subliming materials. These compressed tablets which have high porosity rapidly dissolved within 25 seconds.

Suhas M. Kakade et al [31]: Designed mouth dissolving tablets of losartan potassium to improve its dissolution rate and bioavailability which has low bioavailability due to first pass metabolism. Tablets prepared by direct compression and using super disintegrants like polyplasdone XL 10, croscarmellose sodium and explotab in different concentrations. Among all, the formulation containing 5%w/w superdisintegrant polyplasdone XL 10 was considered to be best formulation, which release up to 99.26% in 12 min.

Hindustan Abdul Ahad et al [32]: A novel attempt has been made to develop mouth dissolving tablets of nimesulide by including clove oil as flavouring and local anaesthetic agent on taste buds. The tablets were prepared by direct compression method. The formulated tablets were evaluated for Pre-formulation and post formulation parameters and they were found to be satisfactory. The formulated mouth dissolving tablets possess good drug releasing property, good mouth feel and improved drug availability with better patient compliance.

Siva Prasad Reddy *et al* [33]: A novel attempt has been made to design mouth dissolving tablets of clozapine by inclusion of clove oil as a flavouring agent which also has local anaesthetic action on taste buds of tongue. Additionally stevia leaf powder was included as sweetener which has 400 times sweeter than sucrose. The tablets were prepared by direct compression technique and evaluated for pre compression and post compression properties which were found to be satisfactory.

Srinivas Pannala *et al* [36]: Prepared nizatidine immediate release tablets to deliver a programmed dose of drug intended for excessively secreted gastric acid and for promoting healing of duodenal ulcers thereby spontaneously delivering the drug when exposed into GIT for producing an anti-ulcer effect. These immediate release drug containing core tablets of nizatidine were prepared by wet granulation method. The prepared tablets were evaluated for various tests and stability was tested as per ICH guidelines.

Sachin Sharma *et al* [37]: Formulated mouth dissolving tablets of the ranitidine HCl to improve its bioavailability as it undergoes first pass metabolism and shows only 50% bioavailability. They prepared the tablets using sublimation method using ammonium

bicarbonate as subliming agent and evaluated for various tests. They also prepared other tablets using superdisintegrants sodium starch glycolate and cross carmellose sodium. Finally they reported that the tablets prepared by superdisintegrant addition have better disintegrating properties and release.

P.V.Swamy *et al* [40]: Designed orodispersible tablets of pheniramine by effervescent method with a view to enhance patient compliance. In the effervescent method, mixture of sodium bicarbonate and tartaric acid (each of 12% w/w concentration) were used along with super disintegrants, i.e., pregelatinized starch, sodium starch glycolate, croscarmellose sodium and crospovidone. Based on *in vitro* dispersion time (approximately 60 s), three formulations were tested for *in vitro* drug release pattern (in pH 6.8 phosphate buffer), short-term stability (at 40±2°/75±5% RH for 3 months) and drug-excipient interaction (IR spectroscopy). Among three promising formulations, formulation ECP_4 containing 4% w/w crospovidone and mixture of sodium bicarbonate and tartaric acid (each of 12% w/w) emerged as the overall best formulation ($t_{70\%}$ = 1.65 min) based on the *in vitro* drug release characteristics compared to commercial conventional tablet formulation.

Jyothi Singh *et al* [42]: They formulated orodispersible tablets which can rapidly disintegrate in saliva using taste-masked granules of drug, Tizanidine HCl. They prepared the taste-masked granules using gastro-erodible aminoalkyl methacrylate copolymer (Eudragit E-100) in different ratios by extrusion method. Drug-polymer complexes were tested for drug content and in vitro drug release in simulated salivary fluid (SSF) of pH 6.8. They selected the complex that did not release drug in SSF which has been considered as taste-masked for formulation of ODTs. They also studied the effect of various super disintegrants such as chitosan, Croscarmellose sodium and sodium starch glycolate in formulation of ODTs.

Sunil H. Makwana *et al* [43]: They masked the intensely bitter taste of ondansetron HCl with indion-204 in different ratios by the solvent evaporation and formulated a orodispersible of the taste masked drug. Drug-resin complex were optimized by considering parameters such as optimization of resin concentration, optimization of swelling time, optimization of stirring time, optimization of pH and optimization of temperature on maximum drug loading and they observed the effect of variables on

maximum amount of the drug loading. Resinate was evaluated for taste masking, characterized by X-ray diffraction and IR spectrometer.

Seong Hoon Jeong *et al* [47]: FDTs are prepared by several different methods including crystalline transition, phase transition, sublimation, spray drying, and direct compression. Of these approaches, a conventional tablet compression method is used most widely because of its low cost and ease of manufacturing. Research on FDTs prepared by the compression method has focused on decreasing the dissolution time of the tablets in the mouth, while maintaining sufficiently high mechanical strength to withstand handling during manufacturing, packaging and transportation. The key to developing a successful FDT formulation by the compression method is to select the right excipients and the right processing techniques.

D.R.Brahma Reddy *et al* [49]: Over the past three decades, Rapimelts have gained considerable attention as a preferred alternative to conventional tablets and capsules due to their better patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. Prescription Rapimelts products initially were developed to overcome the difficulty in swallowing conventional tablets with water among pediatric, geriatric and psychiatric patients with dysphagia. Today, Rapimelts are widely available as the over-the-counter drugs for the treatment of allergies and cold and flu. Technologies used for manufacturing of orally disintegrating tablets are either conventional technologies or patented technologies.

Sunil Kumar Jain *et al* [53]: Developed mouth dissolving tablets of ibuprofen by using optimized solid dispersion of the same along with superdisintegrants, which was prepared by using different concentrations of drug and PEG 4000. The prepared solid dispersion formulations were characterized by FT-IR, DSC, XRD and in vitro drug release. From IR and XRD studies, it may be concluded that there is change in crystalline form of drug into amorphous during formation of solid dispersion. From DSC studies, it was predicted that drug was completely dissolved in the carrier.

RESEARCH ENVISASED

OBJECTIVE OF THE WORK:

Recent advances in technology have presented viable dosage alternative for patients who may have difficulty in swallowing tablets or capsules. An orodispersible tablet is one such approach. Orodispersible tablets are an innovative technology, which disperse rapidly, usually in a matter of seconds, without the need for water, providing optimal convenience to the patient. Orodispersible tablets offer many advantages like rapid onset of action, useful for pediatric, geriatric and psychiatric patients, good chemical stability, as well as improved taste.

Most orodispersible tablets must include substances to mask the bitter taste of the active ingredients. This masked ingredient is then swallowed by patient along with the soluble and insoluble excipients. It has been concluded that faster the dissolution, faster the absorption and onset of action .The time of disintegration of orodispersible tablets is generally considered to be less than one minute.

Orodispersible tablet of Nizatidine was developed in present study to get rapid onset of action, to increase bioavailability and to increase patient compliance. Nizatidine is very bitter in taste and if it is incorporated directly in to an orodispersible tablet, the formulation of the dosage will definitely get futile and reduce levels of patient compliance, thereby lowering therapeutic efficacy. So an unpleasant tasting active substance needs to be masked for only a short period of time in the mouth and the throat which requires effective coating for good results. The methacrylate copolymer, Eudragit E100 is very suitable for this purpose which shows excellent taste masking properties even at low film thickness.

Thus the present study has been made to mask the taste of Nizatidine using Eudragit E100 and to formulate orodispersible tablet with good mouth feel so as to prepare a ‘’patient friendly dosage forms’’.

PLAN OF WORK

The present work was carried out to mask the taste and prepare orodispersible tablets of Nizatidine using different superdisintegrants. The following experimental protocol allows a systemic approach to the study.

- Preformulation study
- Preparation of standard curves
- Compatibility study of Nizatidine with excipients
- Masking the bitter taste
    - Preparation of Drug Polymer complex
    - Determination of drug content
    - In Vitro taste evaluation
- Formulation of Orodispersible tablets by using different superdisintegrants
- Evaluation of precompression properties of powder blend
    - Bulk density
    - Tapped density
    - Compressibility index
    - Hausner ratio
    - Angle of repose
- Preparation of Orodispersible tablets
- Evaluation parameters of the Orodispersible tablets
    - Weight variation
    - Thickness
    - Hardness
    - Friability
    - Wetting time
    - In Vitro dispersion time
    - Disintegration time
    - Taste
    - In Vitro dissolution
    - Assay
    - Content uniformity
- Determination of stability of orodispersible tablets as per ICH guide lines

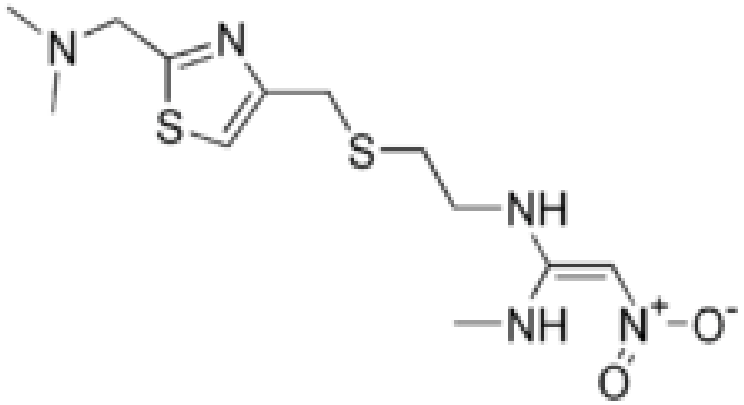
DRUG PROFILE

NIZATIDINE:

Niztidine is an anti-histaminic drug.

Chemical structure:

Fig No.4. Structure of Nizatidine



IUPAC name : N-(2-[(2-[(dimethyl amino) methyl] thiazol-4-yl) methyl thio] ethyl) –N-methyl-2-nitroethene-1,1-diamine.

Molecular formula : $C_{12}H_{21}N_5O_2S_2$

Molecular weight : 331.46 g/mol

Category : Anti-ulcer agent, Histamine H_2 antagonist

PROPERTIES

Description : Off white to brown crystalline powder

Solubility : Freely soluble in water, methanol

Melting point : 203^0C

Half life : 1-2 hrs

Bioavailability : 70%

Plasma protein binding : 35%, mainly to α_1-acid glycoprotein

Volume of distribution : 0.8 to 1.5 L/kg

Onset of action : 30 min

Peak : 0.5 – 3 hrs

Metabolism : Metabolized in the liver to active N-desmethylnizatidine (60% as active as Nizatidine in blocking acid secretion), and inactive Nizatidine N-oxide and nizatidine sulfoxide.

Excretion : Excreted principally in urine.

MECHANISM OF ACTION:

Reversibly and competitively blocks histamine at H_2 receptors, particularly those in gastric parietal cells, antagonising the usual stimulatory effect of endogenous histamine on gastric acid production.

DOSAGE AND ADMINISTRATION:

1. **Duodenal Ulcer:** 300 mg at bedtime or 150 mg twice daily for up to 8 weeks.
2. **Benign Gastric Ulcer:** 300 mg at bedtime or 150 mg twice daily.
3. **Gastroesophageal Reflux Disease:** 150 mg daily (Adults), 150 mg twice daily up to 8 weeks (Children 12 yr of age and older).
4. **Acid Reduction/ Dyspepsia:** 75 mg once or twice daily**.**

INDICATIONS:

Treatment and maintenance of duodenal ulcer, gastroesophageal reflux disease (GERD) (including erosive or ulcerative disease), and benign gastric ulcer; prevention of heartburn, acid indigestion, and sour stomach brought on by consuming food and beverages

CONTRAINDICATIONS:

Hypersensitivity to H_2 antagonists, cirrhosis of the liver, impaired renal or hepatic function.

ADVERSE REACTIONS:

Common adverse effects are head ache and dizziness.

Cardiovascular: Ventricular tachycardia.

CNS : Headache, dizziness, abnormal dreams, nervousness.

Dermatologic : Pruritus.

GI : Abdominal pain, diarrhoea, flatulence, nausea, vomiting.

Hepatic : Elevated liver enzymes.

EUDRAGIT E100 [56]:

Eudragit E100 is a cationic copolymer based on dimethylaminomethyl methacrylate, butyl methacrylate and methyl methacrylate.

Nonproprietary names:

PhEur : Basic Butylated Methacrylate Copolymer

USPNF : Amino Methacrylate Copolymer-NF

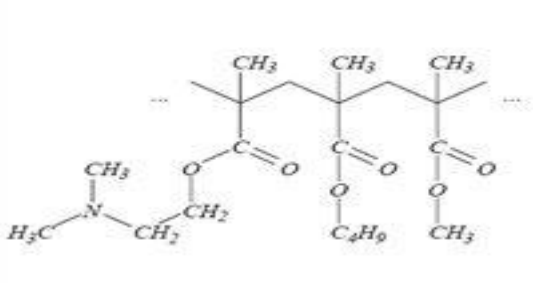
JPE : Aminoalkyl Methacrylate Copolymer E

Physical description:

It consists of colourless to yellow tinged granules with a characterstic amine like odour.

Chemical structure:

Fig No.5. Structure of Eudragit E100



IUPAC name : Poly(butyl methacrylate-co-(2- demethylaminoeethyl) methacrylate-co-methyl methacrylate) 1:2:1

INCI name : Acrylates/ Dimethylaminoethyl Methacrylate Copolymer

Molecular weight: approx. 47,000 g/ mol

Characteristics:

Low viscosity, high pigment binding capacity, good adhesion and low polymer weight gain.

Dissolution:

- Soluble in gastric fluid up to pH 5.0
- Swellable and permeable above pH 5.

Alkali value : 180 mg KOH/ g polymer

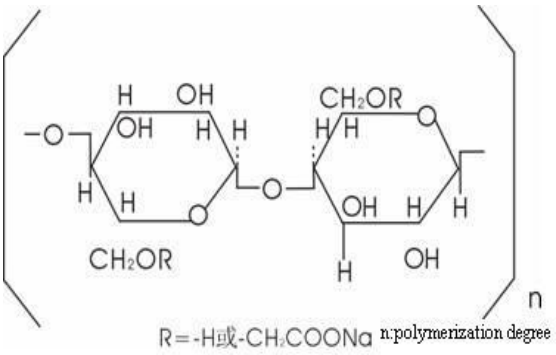
Glass transition temp(Tg) : ~ 48°C

Pharmaceutical applications:

Eudragit E polymers help you to seal sensitive actives and increase patient compliance by masking tastes and odours. Even thin layers of Eudragit provide the desired effect, making it an extremely economical application. Pharma polymers offer various cationic Eudragit E grades for protective coatings.

SODIUM STARCH GLYCOLATE [56] :

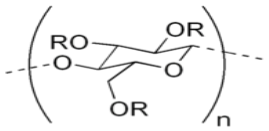
1. **Nonproprietary Names :**
   BP : Sodium Starch Glycollate
   Ph Eur : Carboxymethylamylum natricum
   USPNF : Sodium starch glycolate
2. **Synonyms :**
   Carboxymethyl starch, sodium salt; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.
3. **Chemical Name :**
   Sodium carboxymethyl starch.
4. **Structural Formula :**



5. **Molecular weight :**
   $5\times10^5 - 1\times10^6$
6. **Functional Category :**
   Tablet and capsule disintegrant
7. **Applications in pharmaceutical formulation or technology :**
   Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.
   Sodium starch glycolate has also been investigated for use as a suspending vehicle.
8. **Description :**
   Sodium starch glycolate is a white to off-white, odourless, tasteless, free-flowing powder.
9. **Typical Proprties :**
   Acidity / alkalinity: pH 3.0–5.0 or pH 5.5–7.5 for a 3.3% w/v aqueous dispersion.

CROSCARMELLOSE SODIUM [56]:

1. **Nonproprietary Names :**
   BP : Croscarmellose sodium
   PhEur : Carmellosum natrium conexum
   USPNF : Croscarmellose sodium
2. **Synonyms :**
   Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.
3. **Chemical Name :**
   Cellulose, carboxymethyl ether, sodium salt, crosslinked
4. **Empirical Formula :**
   Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium.
5. **Structural Formula :**

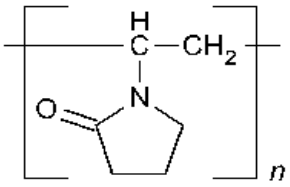


R = H or CH_2CO_2H

6. **Molecular weight :**
   90,000–7,00,000.
7. **Functional category :**
   Tablet and capsule disintegrant.
8. **Applications in pharmaceutical formulation or technology**
   Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets. In tablet formulation croscarmellose sodium may be used in both direct-compression and wet-granulation processes. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant.
   When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra- and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized.
9. **Description :**
   Croscarmellose sodium occurs as an odorless, white or grayish white powder.
10. **Typical properties :**
    Acidity/alkalinity: pH = 5.0–7.0 in aqueous dispersions.
    Density (bulk) : 0.529 g/cm3 for Ac-Di-Sol
    Density (tapped) : 0.819 g/cm3 for Ac-Di-Sol
    Density (true) : 1.543 g/cm3 for Ac-Di-Sol
    Solubility : insoluble in water, although croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

CROSPOVIDONE [56] :

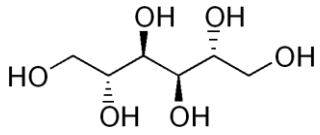
1. **Nonproprietary Names :**
   BP : Crospovidone
   PhEur : Crospovidonum
   USPNF: Crospovidone
2. **Synonyms :**
   Crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.
3. **Chemical Name :**
   1-Ethenyl-2-pyrrolidinone homopolymer
4. **Empirical Formula :**
   The USPNF 23 describes crospovidone as a water-insoluble synthetic crosslinked homopolymer of N-vinyl-2-pyrrolidinone.
5. **Structural Formula :**



6. **Molecular weight :**
   (C6H9NO)n >1 000 000
7. **Functional Category :**
   Tablet disintegrant.
8. **Applications in pharmaceutical formulation or technology :**
   Crospovidone is a tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels.
   Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs.
9. **Description :**
   Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.
10. **Typical properties :**
    Acidity/alkalinity : pH 5.0–8.0 (1% w/v aqueous slurry)
    Density : 1.22 g/cm3
    Solubility : Practically insoluble in water and most common organic solvents.

MANNITOL [56]:

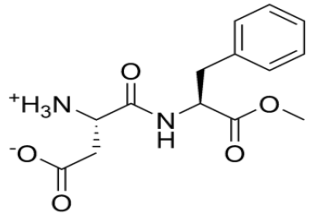
1. **Nonproprietary Names :**
   BP : Mannitol
   JP : D-Mannitol
   PhEur : Mannitolum
   USP : Mannitol
2. **Synonyms :**
   Cordycepic acid; C*PharmMannidex; E421; manna sugar; D-mannite; mannite; Mannogem; Pearlitol.
3. **Chemical Name :**
   D-Mannitol
4. **Emirical Formula :**
   C6H14O6
5. **Molecular weight :**
   182.7
6. **Structural Formula :**



7. **Functional Category :**
   Diluent; diluent for lyphilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.
8. **Applications in pharmaceutical formulation or technology :**
   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.
   Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.
   Given orally, mannitol is not absorbed significantly from the GI tract, but in large doses it can cause osmotic diarrhea.
9. **Description :**
   Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth.
10. **Typical properties :**
    Flowability : Powder is cohesive, granules are free flowing.
    Melting point: 166–168 ^{0}C
    Solubility : Soluble in alkalies

ASPARTAME [56]:

1. **Nonproprietary Names :**
   BP : Aspartame
   PhEur : Aspartamum
   USPNF : Aspartame
2. **Synonyms :**
   3-Amino-N-(a-carboxyphenethyl)succinamic acid N-methyl ester; 3-amino-N-(a-methoxycarbonylphenethyl)succinamic acid; APM; aspartyl phenylamine methyl ester; Canderel;E951; Equal; methyl N-a-L-aspartyl-L-phenylalaninate; NutraSweet; Pal Sweet; Pal Sweet Diet; Sanecta; SC-18862;Tri-Sweet.
3. **Chemical Name :**
   N-a-L-Aspartyl-L-phenylalanine 1-methyl ester
4. **Empirical Formula :**
   C14H18N2O5
5. **Molecular Weight :**
   294.31
6. **Structural Formula :**



7. **Functional Category :**
   Sweetening agent.
8. **Applications in pharmaceutical formulation or technology :**
   Aspartame is used as an intense sweetening agent in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations.The approximate sweetening power is 180–200 times that of sucrose. Aspartame is metabolized in the body and consequently has some nutritive value.
9. **Description :**
   Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.
10. **Typical Properties :**
    Acidity/alkalinity : pH 4.5–6.0 (0.8% w/v aqueous solution).
    Density (tapped) : 0.29 g/cm3
    Density (true) : 1.347 g/cm3
    Solubility : slightly soluble in ethanol (95%); sparingly soluble in water

MAGNESIUM STEARATE [56] :

1. **Nonproprietary Names:**
   BP/JP/USPF : Magnesium stearate.
   Ph Eur : Magnesii stearas.
2. **Synonyms:**
   Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt.
3. **Chemical Name :**
   Octadecanoic acid magnesium salt.
4. **Empirical Formula :**
   C36H70MgO4
5. **Molecular weight :**
   591.34
6. **Structural Formula:**
   $[CH_3(CH_2)_{16}COO]_2Mg$
7. **Functional Category:**
   USP : Tablet and capsule lubricant.
   BP/EP : lubricant, pharmaceutical aid.
   Others : Glidant, anti-adherent.
8. **Applications in pharmaceutical formulation or technology:**
   Tablet and capsule lubricant, glidant or anti-adherent.
9. **Description:**
   Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste.
10. **Typical Properties :**
    Density (bulk) : 0.159 g/cm3
    Density (tapped): 0.286 g/cm3
    Density (true) : 1.092 g/cm3
    Melting range : 117–1508C (commercial samples);
    126–1308C (high purity magnesium stearate).
    Solubility : Practically insoluble in ethanol, ether and water; slightly soluble in warm benzene and ethanol (95%).

TALC [56] :

1. **Nonproprietary Names**
   BP : Purified talc
   JP : Talc
   PhEur : Talcum
   USP : Talc
2. **Synonyms :**
   Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.
3. **Chemical Name :**
   Talc
4. **Empirical Formula :**
   Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$.
5. **Molecular Weight :**
   379.3 g/mol
6. **Functional Category :**
   Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant
7. **Applications in pharmaceutical formulation or technology :**
   Talc was once widely used in oral solid dosage formulations as a lubricant and diluent. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.
8. **Description :**
   Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.
9. **Typical properties :**
   Acidity/alkalinity: pH 7–10 for a 20% w/v aqueous dispersion.
   Solubility : Practically insoluble in dilute acids and alkalis, organic solvents, and water.

MATERIALS AND METHODS

Table No:4 List of materials and their applications in formulation

S.No	Name of the materials	Use in Formulation
1.	Nizatidine	Active ingredient
2.	Eudragit E100	Taste masking agent
3.	Mannitol	Diluent
4.	Sodium starch glycolate	Superdisingrant
5.	Croscarmellose sodium	Superdisingrant
6.	Cross povidone	Superdisingrant
7.	Aspartame	Sweetener
8.	Mint flavour	Flavouring agent
9.	Magnesium stearate	Glidant
10.	Talc	Lubricant

Table No:5 Equipments used for the Research Work

S.No	Insrtuments Used	Manufacturing company
1.	Digital Balance	Shimatzu LB 300
2.	Tablet hardness tester	Pfizer hardness tester
3.	Friability tester	Riche Pharma
4.	Vernier Caliper	Mitutoyo digimatic caliper
5.	Dissolution apparatus USP	Electrolab tablet dissolution apparatus
6.	Double beam UV Spectrophotometer	Shimatzu UV-1800
7.	Rotary tablet punching machine	Cadmach
8.	pH meter	Elico Ll120
9.	FT-IR Spectrophotometer	KBR press model M15

7.1. PREFORMULATION STUDY:

Preformulation studies are the first step in the development of a dosage form. Preformulation study relates to pharmaceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. It is an investigation of physicochemical properties of the drug substance alone and along with excipients which may influence the formulation design, manufacture methods and pharmacokinetic and pharmacodynamic properties of the final product. The following preformulation studies were performed on the obtained sample of drug.

7.1.1. Melting point:

Melting point of the drug was determined by using melting point apparatus. This was compared with the official melting point value of drug.

7.1.2. Drug and Drug-Excipients physical compatibility studies:

To study the physical compatibility of various formulation excipients with Nizatidine, solid admixtures were prepared by mixing the drug with excipients separately in the ratio of 1:1 and were filled in 2 ml glass vials and sealed. And they were kept in stability chamber at room temperature and 30 ± 2^0C/65±5%RH. The samples were withdrawn and analysed for colour change for every 10 days.

7.1.3. Chemical compatibility studies by FT-IR:

IR spectra of drug, polymer and all superdisintegrants alone and along with drug were taken by using KBr pellet method and scanned at a moderate scanning speed between 4000-400 cm^{-1} using FT-IR. The peak values and the possibility of functional groups shown in spectra were compared with standard values.

7.1.4. Determination of Analytical Wavelength(λ_{max}):

A standard stock solution of Nizatidine was prepared by dissolving accurately weighed 5 mg of Nizatidine in water in a 50 ml volumetric flask and the volume was made up to 50 ml with water to obtain a stock solution of 100 µg/ml. From the standard stock solution, 10 ml was pipetted into 100 ml volumetric flask. The volume was made up to 100 ml with water. The resulting solution containing 10 µg/ml was scanned between 200 and 400 nm.

7.1.5. Calibration curve of Nizatidine :

1. Preparation of 0.1N HCl :

85 ml of conc.HCl was pipetted out into 1000 ml of volumetric flask and the volume was made up to 1000 ml with distilled water to prepare 0.1N HCl.

2. Preparation of buffer solution of pH solution:

a. Preparation of 0.2M NaOH solution:

8 g of NaOH was accurately weighed and taken into 1000 ml of volumetric flask. Then it was dissolved in little amount of water and the volume was made up to 1000 ml with distilled water to prepare 0.2M NaOH solution.

b. Preparation of 0.2M potassium di hydrogen phosphate solution:

27.218 g of potassium di hydrogen phosphate was accurately weighed and taken into 1000 ml of volumetric flask. Then it was dissolved in little amount of water and the volume was made up to 1000 ml with distilled water to prepare 0.2M potassium di hydrogen phosphate solution.

3. Calibration curve of Nizatidine in 0.1N HCl:

Accurately weighed quantity of Nizatidine (5 mg) was dissolved in little quantity of 0.1N HCl and volume was made up to 50 ml with the same (100 µg/ml). Then withdraw 1, 2, 3, 4, 5 ml from the above solution in to separate 50 ml volumetric flasks and made up the volume to 50 ml to produce 2, 4, 6, 8, 10 µg/ml respectively. And the absorbances were taken at 315 nm. This procedure was performed in triplicate to validate the calibration curve.

4. Calibration curve of Nizatidine in buffer solution of pH 6.8 :

Accurately weighed quantity of Nizatidine (5 mg) was dissolved in little quantity of pH 6.8 buffer solution and volume was made up to 50 ml with the same (100 µg/ml). Then withdraw 1, 2, 3, 4, 5 ml from the above solution in to separate 50 ml volumetric flasks and made up the volume to 50 ml to produce 2, 4, 6, 8, 10 µg/ml respectively. And the absorbances were taken at 315 nm. This procedure was performed in triplicate to validate the calibration curve.

7.2 TASTE MASKING OF NIZATIDINE:

7.2.1 Introduction:

Nizatidine is an anti-ulcer agent, prescribed extensively both in solid and liquid dosage forms and is extensively bitter resulting in poor patient compliance. Complexation with Eudragit E100 is efficient technique of masking the bitterness.

The purpose of this research was to formulate tasteless complexes of Nizatidine with Eudragit E100 (about polymer).

7.2.2. PREPARATION OF DRUG POLYMER COMPLEX (DPC):

The drug polymer complex (DPC) was prepared by using different ratios of Nizatidine and Eudragit E100 i.e. 1:1, 1:2, 1:3, 1:4 and 1:5 were mixed by using mortar and pestle. The mixture of drug and polymer was slowly added with continuous stirring (600 rpm) into a 500ml of glass beaker containing 10% ethanol till a gel was formed. The gel was manually pressed out using a syringe, on a polycarbonate sheet. After extrusion of the gel, ethanol was allowed to evaporate overnight at room temperature and vacuum dried at -700 mm of Hg at 35^0C for 6 hr. The sample was then grounded in a mortar and pestle, and again vacuum dried under the aforementioned conditions to ensure adequate solvent removal. The prepared taste masked granules was used for further studies.

7.2.3. CHARACTERIZATION OF DPC (Drug polymer complex):

7.2.3.1. Differential Scanning Colorimetery (DSC) Study:

DSC is a technique in which the difference in heat flow between the sample and a reference is recorded versus temperature. DSC thermal analytical profile of a pure chemical represents its product identity. By comparing the DSC curves of a pure drug sample with that of formulation, the presence of an impurity due to the interaction of polymer and drug can be detected in a formulation. The scanning temperature for pure drug and formulation are the same when dynamic measurements are performed, and hence the required heat energy for chemical transformation is directly recorded on a heat flow versus temperature graph. The energy is measured as Joules per kilocalorie. All dynamic DSC studies were carried out on TA instruments Q200 series. The instrument was calibrated using high purity indium metal as standard. The dynamic scans were taken in nitrogen atmosphere at the heating rate of 10ºC/min.

7.2.3.2. Determination of drug content [16]:

DPC equivalent to 75 mg of drug was stirred by using magnetic stirrer with 100 ml of 0.1 N HCl for 60 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper. Further, solution diluted with 0.1 N HCl and the drug content was determined spectrophotometrically at 315 nm. As the concentration of Eudragit E100 increases the drug content of the complex has been increased.

7.2.3.3. In Vitro taste evaluation [16]:

In Vitro taste was evaluated by determining the drug release from the complex into simulated salivary fluid (SSF) (pH 6.8) to predict release of drug in the human saliva. DPC, equivalent to 10 mg of Nizatidine (equivalent to dose 75 mg), was placed to 10 ml screw capped bottles containing SSF and fixed in water bath shaker and shaken for 60 sec at 50 rpm. The amount of drug released was analyzed at 315 nm. As the concentration of the Eudragit E100 increases, the release of the drug from the complex in the SSF has been decreased which indicates that the taste has been masked.

Table No:6 Effect of different concentrations of Drug-Eudragit E100 on drug content and In Vitro taste evaluation.

Drug-polymer ratio	% Drug content*	%Drug dissolved in SSF*	Taste
1:1	98.57±0.42	0.83±0.12	Bitter
1:2	98.62±0.38	0.64±0.06	Bitter
1:3	98.94±0.36	0.37±0.02	Slightly bitter
1:4	99.28±0.15	0.12±0.03	No bitter
1:5	99.46±0.12	ND	No bitter

*Results are the mean of 3 observations ± SD

ND – Not detectable

7.3 FORMULATION OF NIZATIDINE ODTs:

Label claimed : 450 mg

Batch size : 100 tablets

Punch size : 10 mm concave punch

Table No: 7 Formulation of Nizatidine ODTs

Ingredients for one tablet	**F_1 mg**	**F_2 mg**	**F_3 Mg**	**F_4 mg**	**F_5 mg**	**F_6 mg**	**F_7 mg**	**F_8 mg**	**F_9 mg**
DPC (equivalent to 75mg of Nizatidine)	377	377	377	377	377	377	377	377	377
Mannitol	51	46.5	37.5	51	46.5	37.5	51	46.5	37.5
Crosspovidone	9	13.5	22.5	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	9	13.5	22.5	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	9	13.5	22.5
Aspartame	4	4	4	4	4	4	4	4	4
Mint Flavour	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Total weight	450	450	450	450	450	450	450	450	450

DPC – Drug Polymer Complex

7.4 PREPARATION OF TABLETS:

In - House Specification:

The Nizatidine orodispersible tablets should have following criteria.

Table No:8 In house specification of Nizatidine orodispersible tablets

S.No	Parameter	Specification
1.	Theoretical weight per tablet (mg)	450 mg
2.	Average weight of 20 tablets (mg)	450 mg
3.	Uniformity of weight (mg)	450 mg
4.	Thickness (mm)	5.5 mm
5.	Hardness (Kg/cm^2)	3-4 Kg/cm^2
6.	Friability (%)	Not more than 1 %
7.	Disintegration time (sec)	Not more than 3 min
8.	Dissolution (%)	Not less than 80 % in 10 min

In the present study Direct Compression technique was employed for the preparation of orodispersible tablets.

Direct compression is widely used in tableting because it requires fewer processing steps, simpler to validate and improves drug stability when compared with the wet granulation method. Direct compression also eliminates exposure to heat and moisture during processing and is a more economical process. However, the majority of active pharmaceutical ingredients exhibit poor compressibility. Therefore the addition of directly compressible adjuvant is mandatory in such cases.

Directly compressible filler should exhibit good flowability and compactibility. Good flowability is necessary to ensure rapid and uniform die filling, whereas high compactibility is necessary to produce tablets having sufficient mechanical strength.

Precautions:

1. Inspection of cleanliness of the compression machine.
2. Inspection of cleanliness of storage container.
3. Inspection of cleanliness of all the Mechanical stirrers and weighing balance.

MANUFACTURING PROCEDURE:

Step 1: Optimized batch of drug polymer complex equivalent to 75 mg of Nizatidine was used for the ODT preparation.

Step 2: Mannitol, crospovidone/ Croscarmellose sodium/ sodium starch glycolate and aspartame were weighed individually and passed through #40 mesh.

Step 3: All the above sifted excipients were mixed with the optimized DPC and mixed properly for 3 min and mint flavour was added and mixed properly.

Step 4: Finally magnesium stearate and talc were added to the mixture thoroughly for 2 min.

Step 5: The powder blend was compressed by using 10 mm concave punch.

7.5 PRE COMPRESSION STUDIES ON GRANULES:

7.5.1. Bulk density:

It is also called as the poured density. It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the 20 g powder (passed through standard sieve # 20) into a 100 ml measuring cylinder and initial volume was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$$Db = M/ Vb$$

Where, M is the mass of powder

Vb is the bulk volume of the powder.

7.5.2. Tapped density:

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 g/ml and is given by

$$Dt = M / Vt$$

Where, M is the mass of powder

Vt is the tapped volume of the powder.

7.5.3. Angle of repose (θ):

The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder.

It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane and it can be calculated by the following formula.

$$\tan(\theta) = h / r$$

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

Where, **θ** is the angle of repose.

h is the height in cms

r is the radius in cms.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property is given as follows.

Table No.9 Angle of Repose as an Indication of Powder Flow Properties

S.No	Angle of Repose (θ)	Type of Flow
1.	< 20	Excellent
2.	20 – 30	Good
3.	30 – 34	Passable
4.	> 34	Very Poor

7.5.4. Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is give

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where, Dt is the tapped density of the powder and

Db is the bulk density of the powder.

Table No.10 Relationship between % compressibility and flow ability

S.No	% Compressibility	Flow ability
1.	5-12	Excellent
2.	12-16	Good
3.	18-21	Fair Passable
4.	23-35	Poor
5.	33-38	Very Poor
6.	<40	Very Very Poor

7.5.5. Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{Dt}{Db}$$

Where, Dt is the tapped density.

Db is the bulk density.

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

7.6 POST COMPRESSION STUDIES OF TABLETS:

7.6.1. Description:

The general appearance of the tablet like size, shape, and colour should be observed. It must need for consumer acceptance and during storage physical chances may happens it easily matched with description.

7.6.2. Weight variation:

Weigh individually 20 tablets taken at random and determine the average weight. Not more than 2 of the individual weight deviate from the average weight. The percentage deviation limits shown in the following table.

Table No.11 Weight Variation Specification as per IP

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

7.6.3. Thickness:

It can be dimensionally described and controlled. Thickness may affect the hardness, disintegration time and dissolution rate. Tablet thickness of 10 tablets was measured by vernier callipers.

7.6.4. Hardness:

Tablet requires certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packing and shipping. Hardness or tablet crushing strength (fc) is the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm2.

7.6.5. Friability:

The crushing test may not be the best measure of potential behaviour during handling and packaging. The resistance to surface abrasion may be a more relevant parameter. Friability of each batch was measure in "Electro lab Friabilator". Five preweighed tablets were rotated at 25 rpm for 4 min, the tablets were then re weighed and the percentage of weight loss was calculated. It should be less than 1%.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Rapidly Disintegrating Property:

To evaluate the tablets for their rapid disintegration properties, following tests were carried out.

7.6.6. Wetting time:

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipients.

The procedure for wetting time is as follows, a piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water containing eosin (water soluble dye). The tablet was placed on the paper and the time for complete wetting of

the tablet was measured in seconds. This has been repeated three times for each formulation to get accurate value.

7.6.7. Modified disintegration test:

The standard procedure of performing disintegration test for these dosage forms has several limitations and they do not suffice the measurement of very short disintegration times. The disintegration time for ODT needs to be modified as disintegration is required without water, thus the test should mimic disintegration in salivary contents. For this purpose, a petridish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the centre of petridish and the time for the tablet to completely disintegrate into fine particles was noted.

7.6.8. Water absorption Ratio:

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation,

$$R=10(wa/wb)$$

where, Wb is weight of tablet before water absorption

Wa is weight of tablet after water absorption.

7.6.9. In Vitro dispersion time:

Tablet was added to 10 ml of SSF (phosphate buffer solution) ph 6.8 at 37+0.5ºc, time required for complete dispersion of a Tablet was measured.

7.6.10. In Vitro drug release:

In Vitro dissolution test was carried out by triplicate method using USP Type II (paddle type) apparatus. 900 ml of SGF (0.1N HCl) to maintain ph 1.2 was used as dissolution medium, and the paddle was rotated at 50 rpm for 1hr at a temperature of 37^0C. Sampling was done at regular intervals and was replaced by 0.1N HCl after each sampling interval. The samples are then analysed spectrophotometrically at 315 nm.

7.6.11. Content uniformity test:

Standard solution: Prepare a solution of Nizatidine in water having a known concentration of about 0.9 µg/ml.

Sample solution: 20 tablets were randomly selected from the prepared batch and triturated to get fine powder. Powder equivalent to total weight of the tablet was taken and dissolved in beaker containing small amount of water and shake for some time. Filter the

solution to 500 ml volumetric flask and make up the volume with water. And add 1 ml of this solution to 100 ml volumetric flask and make up the volume with water. Take the absorbance at 315 nm using water as a blank for background correction.

7.6.12. Stability study:

FDA and ICH specifies, the guidelines for stability testing of a new drug product, as a technical requirement for the registration of a pharmaceuticals for human use.

The ICH triplicate guidelines have established that long term stability testing should be done at 25^0C / 60% RH for 12 months. Accelerated stability testing should be done at 40^0C / 75% RH for six months. Stability testing at intermediate storage condition should be done at 30^0C / 65%RH. Different storage conditions and periods of stability testing are shown in the Table No.12.

Table No.12 ICH Guidelines for stability study

Study	Storage condition	Duration
Long term	25^0C±2^0C, 60%±5% RH	12 months
Intermediate	30^0C± 2^0C, 65%± 5% RH	6 months
Accelerated temperature	40^0C± 2^0C, 75%± 5% RH	6 months

In the present work, stability study was carried out for Nizatidine ODT of desirable formulation of 75 mg label claim.

Any ideal dosage form apart from other dosage form requirement should provide consistency of drug content and release throughout its shelf life.

RESULTS AND DISCUSSION

8.1. PREFORMULATION STUDIES:

The overall objective of Preformulation studies is to generate useful information to the formulator on developing stable and bioavailable dosage forms that can be mass produced.

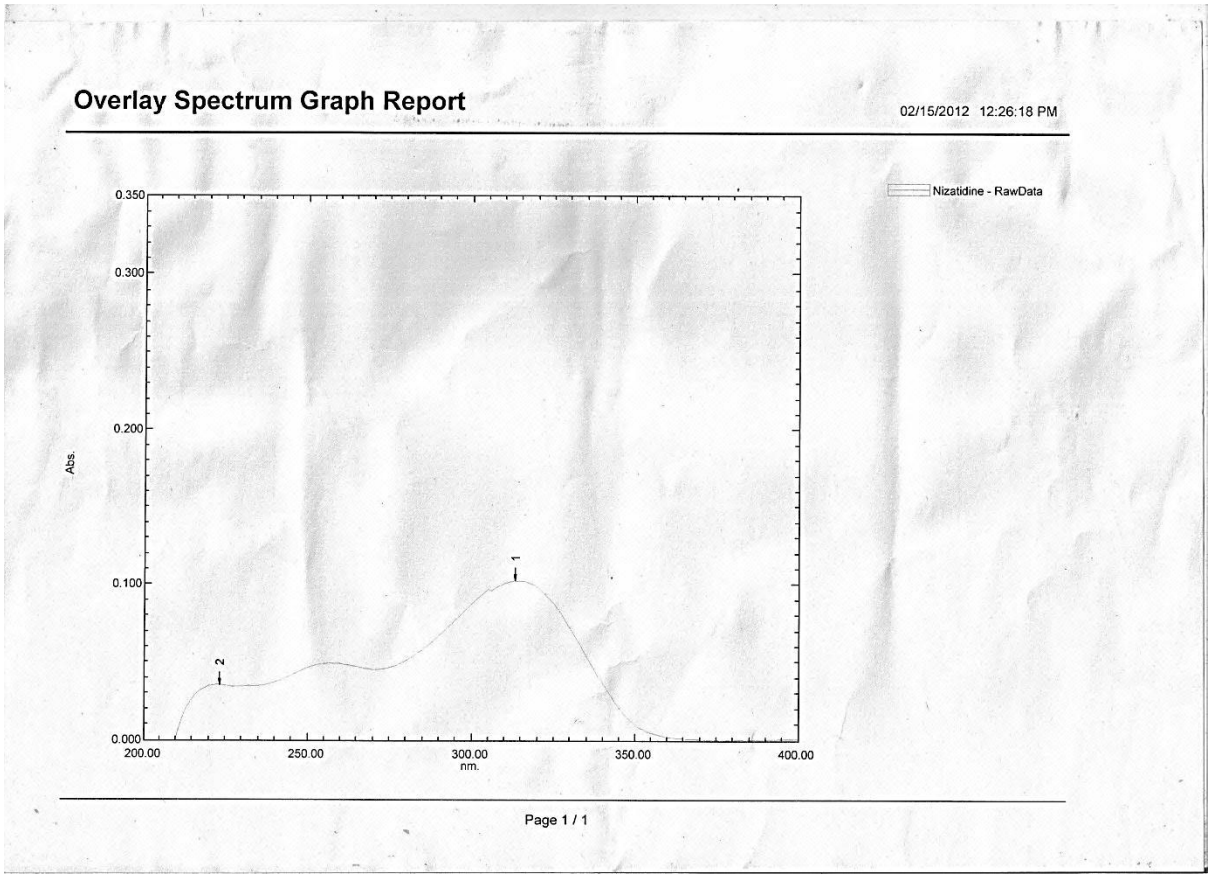
8.1.1. Determination of melting point of Nizatidine:

Melting point of Nizatidine was determined by capillary method and was found to be 132.7^0C which is in the range specified in the official limits.

8.1.2. Determination of analytical wavelength (λ_{max}) of Nizatidine:

By using UV-Spectrophotometer Nizatidine drug solution in water was scanned between the range of 200-400 nm using water as the blank and a sharp peak was observed at 315 nm which reports that the analytical wavelength is 315 nm. The value found was lies in the range specified in official monograph and it has shown in Fig No.6.

Fig No.6. λ_{max} of Nizatidine



8.1.3. Physical compatibility studies of drug and excipients:

Physical compatibility study of drug and excipients is necessary for the stable and effective solid dosage form which is performed on visual basis. The study reveals that the drug, polymer and other excipients were physically compatible with one another as there was no change in physical description. The results have been illustrated in Table No.13.

8.1.4. Chemical compatibility studies by FTIR:

The IR spectral analysis of the Nizatidine, polymer and other excipients was carried out by using KBr pellet method and the spectra were shown from Fig No.7 to Fig No.15. All the characteristic peaks appear for the pure Nizatidine and its physical mixture indicating no interaction between Nizatidine and excipients.

Table No.13 Physical compatibility studies of drug and excipients

S.No	Drug + Excipients	Description at initial day	RT, 35±2^{0}C/65±5% RH IN days		
			10th	20th	30th
1.	NZ	Off white to brown crystalline powder	NC	NC	NC
2.	EE100	Colourless to yellow tinged granules	NC	NC	NC
3.	CP	White, crystalline powder	NC	NC	NC
4.	CCS	White or greyish white powder	NC	NC	NC
5.	SSG	White, free-flowing hygroscopic powder	NC	NC	NC
6.	NZ + EE100	Off white to brown free flowing powder	NC	NC	NC
7.	MNT	Free flowing white crystalline powder	NC	NC	NC
8.	APT	Off white, crystalline powder	NC	NC	NC
9.	MF	Yellow colour liquid	NC	NC	NC
10.	Mg.S	White, crystalline powder	NC	NC	NC
11.	Talc	White or greyish white powder	NC	NC	NC
12.	NZ + CP	Off white to yellow powder	NC	NC	NC
13.	NZ + CCS	Off white to yellow powder	NC	NC	NC
14.	NZ + SSG	Off white to yellow powder	NC	NC	NC
15.	NZ + ALL	Off white to yellow free flowing powder	NC	NC	NC

NZ – Nizatidine, **EE100 –** Eudragit E100, **CP** – Crosspovidone, **CCS –** Croscarmellose sodium, **SSG –** Sodium starch glycolate, **MNT** – Mannitol, **APT –** Aspertame, **MF –** Mint flavour, **Mg. S –** Magnesium stearate, **NC** – No change.

Chemical compatibility studies by FT-IR:

Fig No.7. Nizatidine

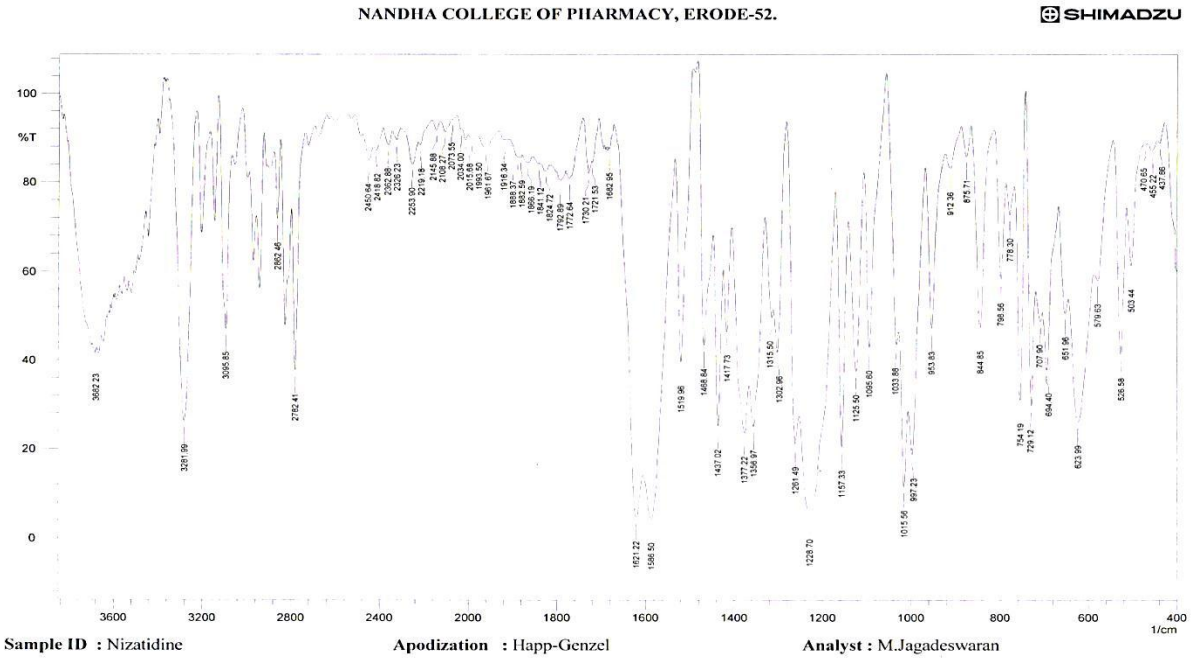


Fig No.8.Eudragit E100

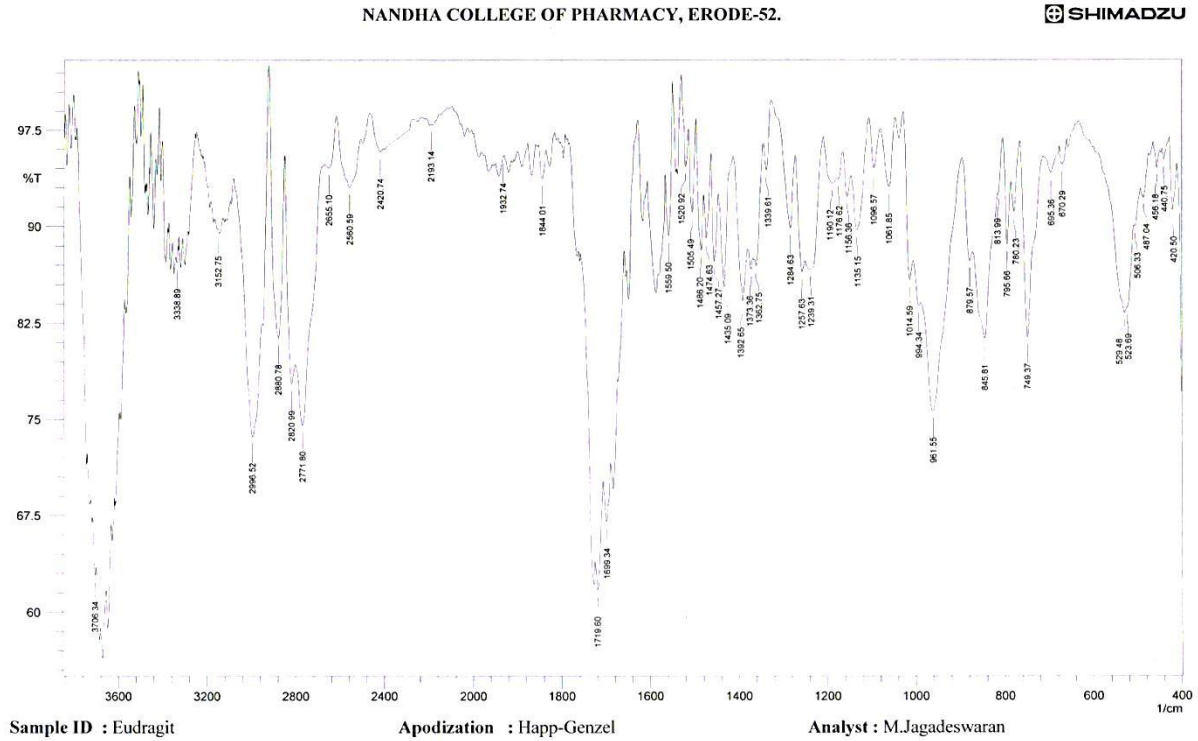


Fig No.9. Nizatidine + Eudragit E100

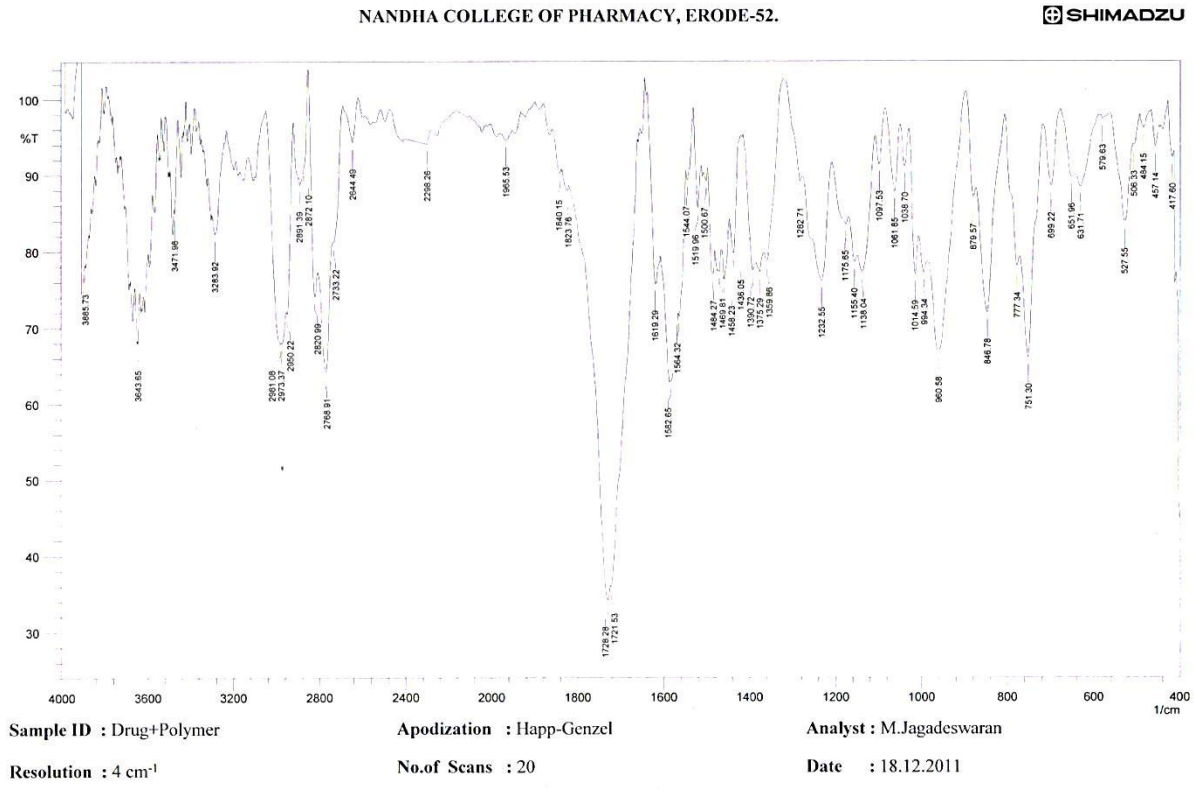


Fig No.10.Crospovidone

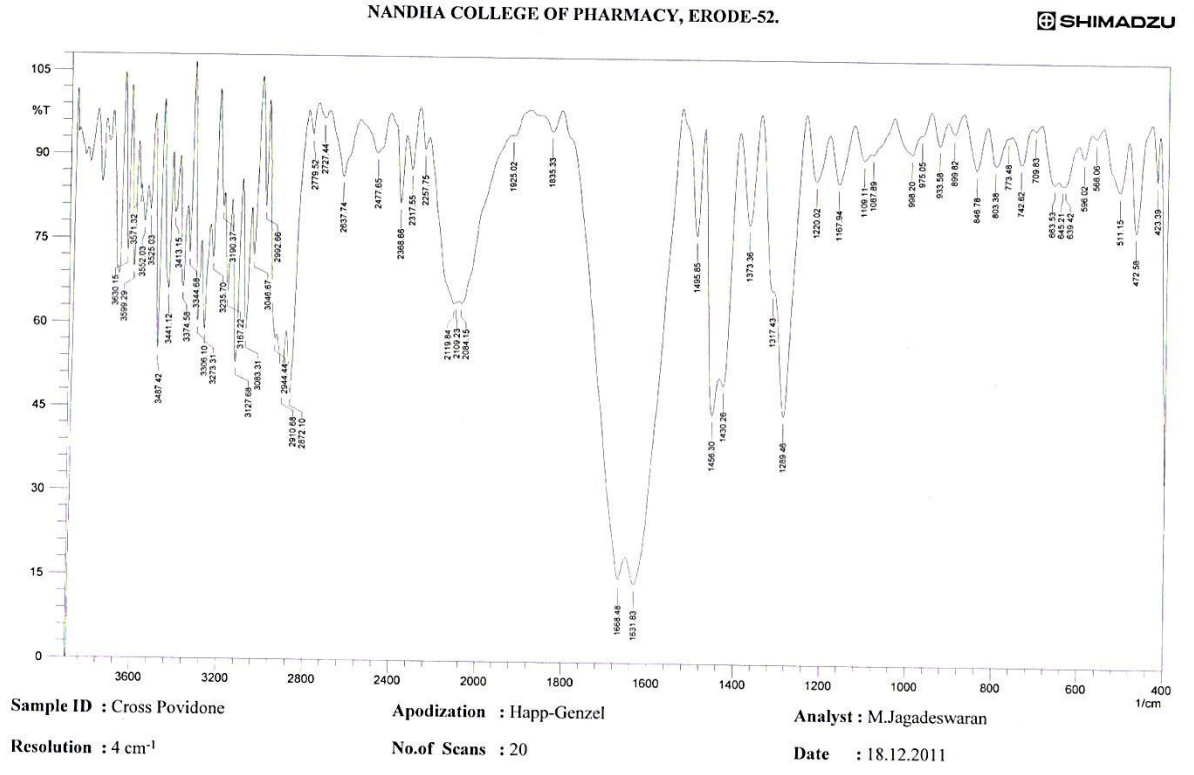


Fig No.11. Cros carmellose sodium

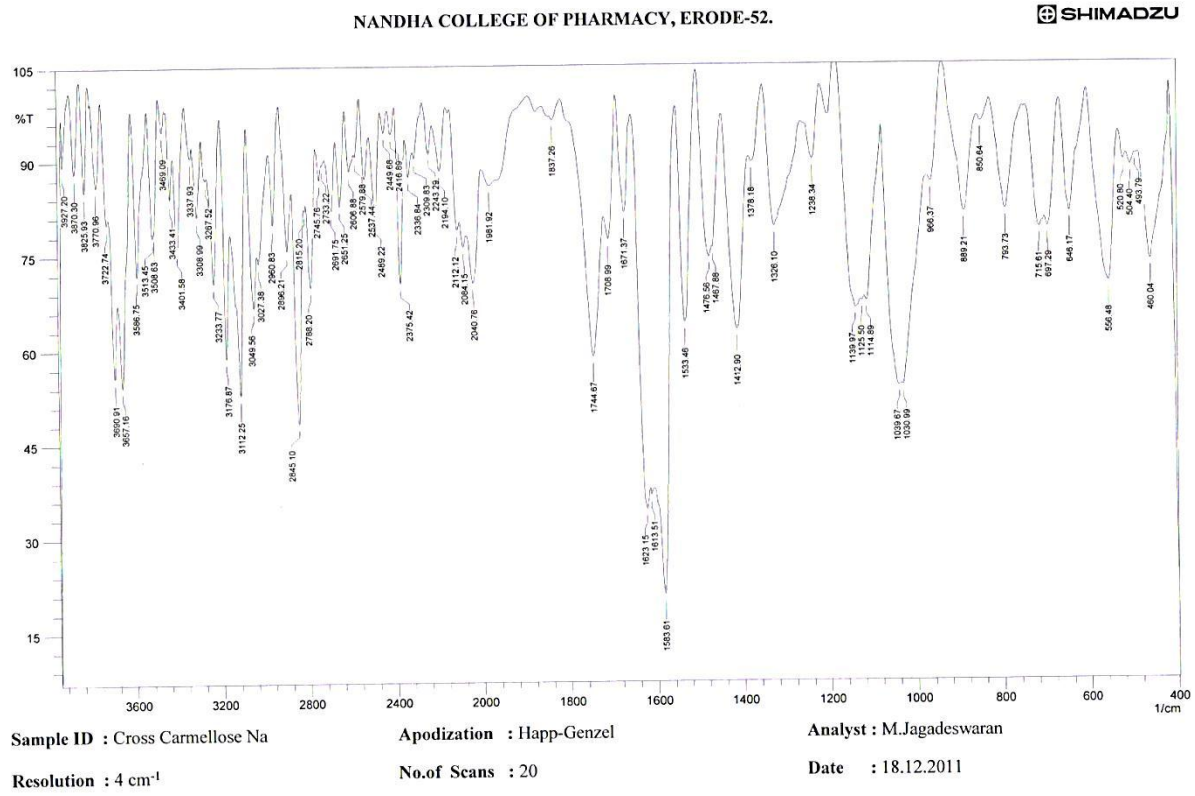


Fig No.12. Sodium starch glycolate

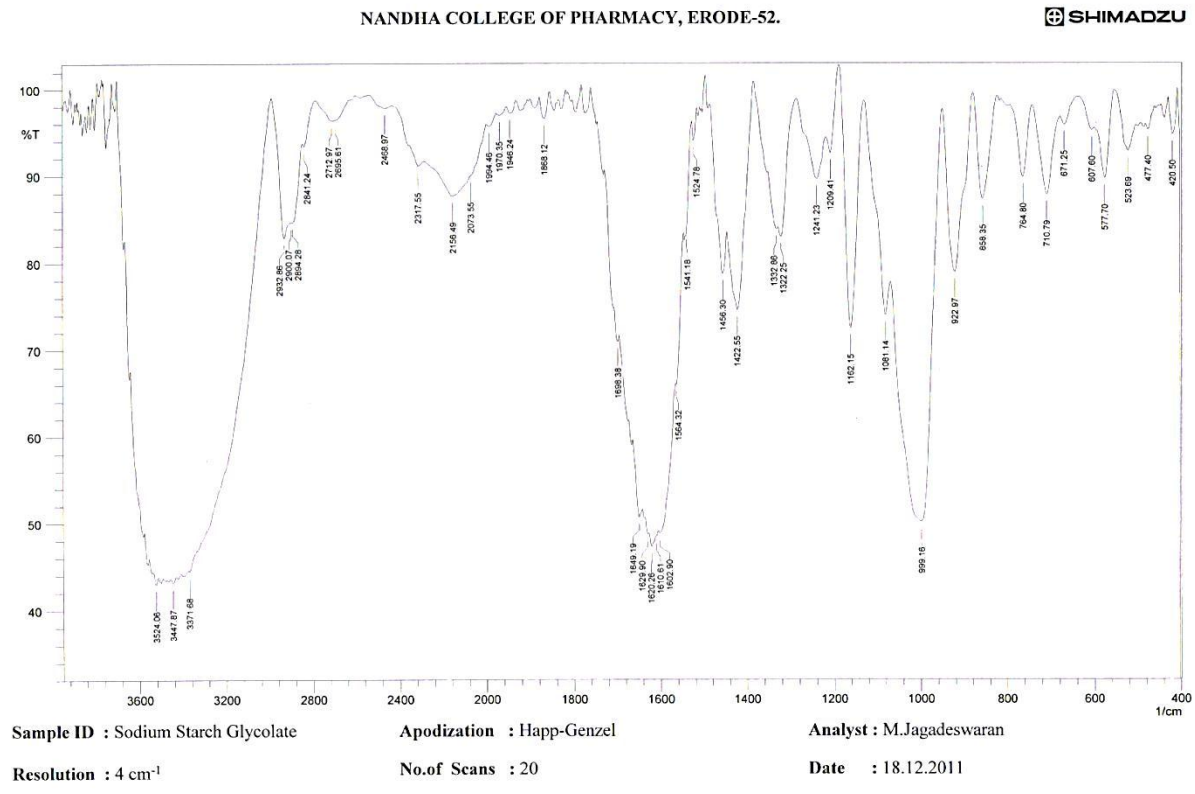


Fig No.13. Nizatidine + Crospovidone

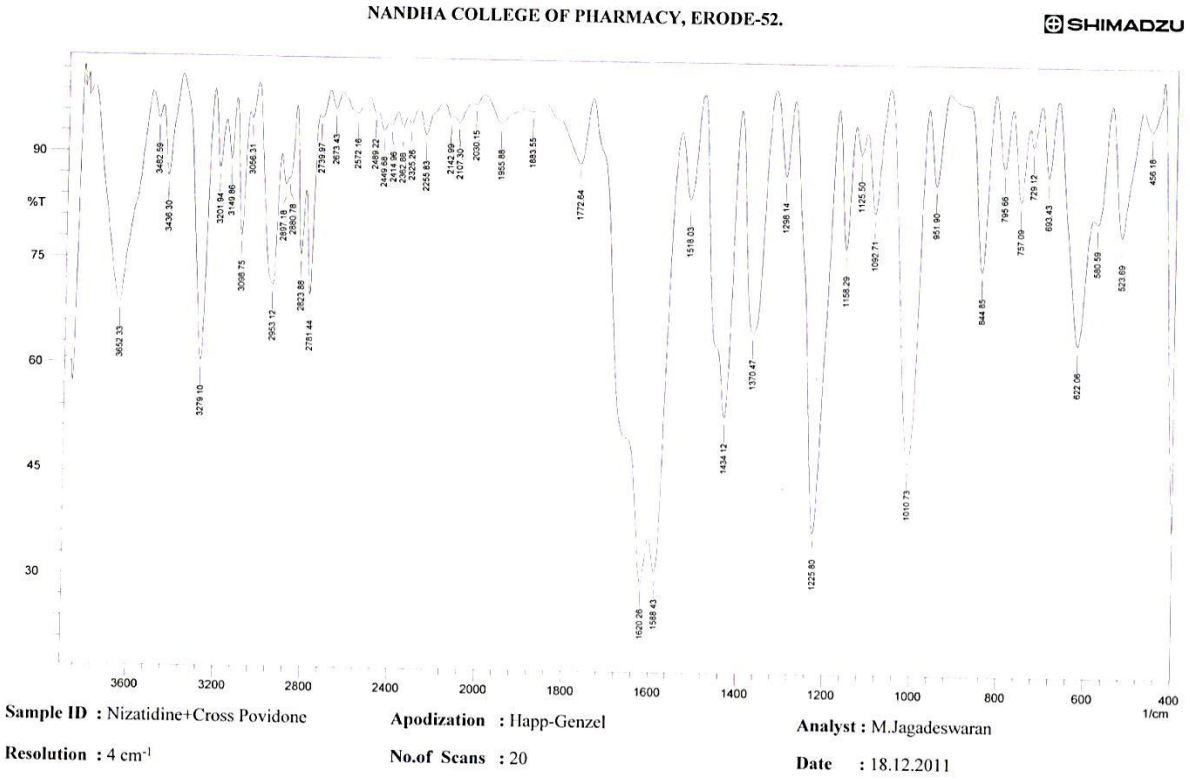


Fig No.14. Nizatidine + Croscarmellose sodium

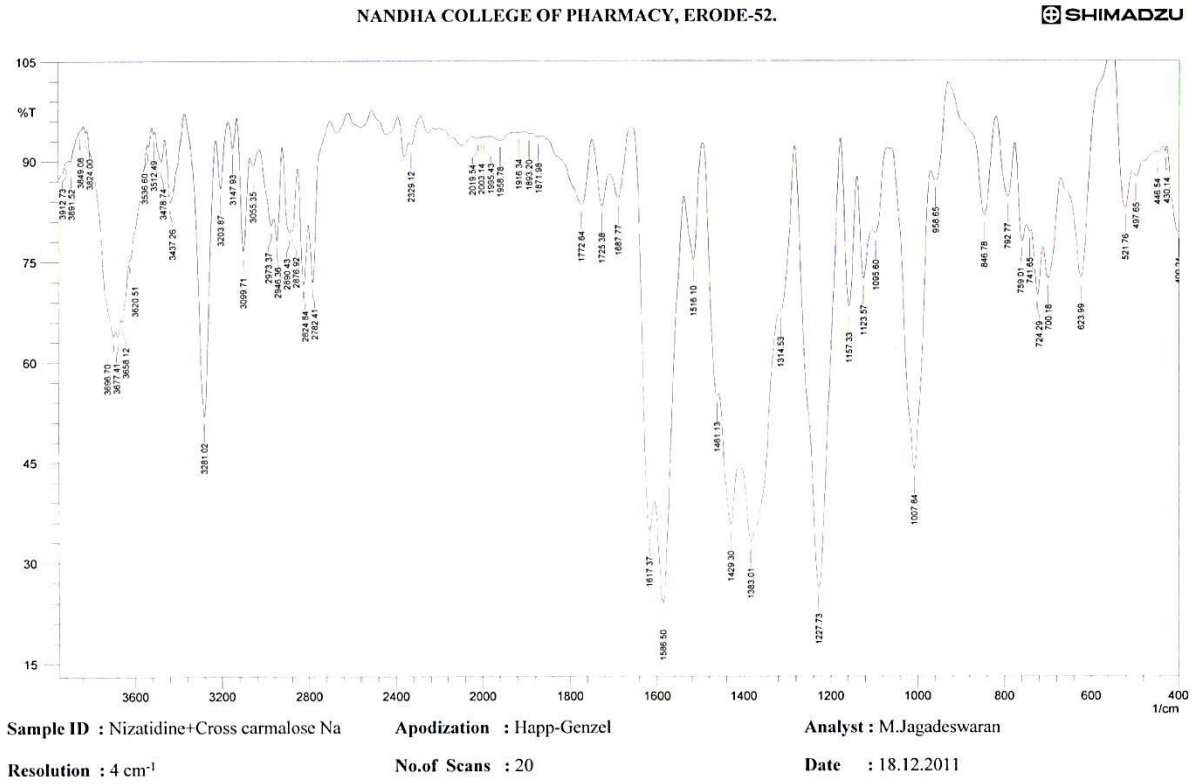
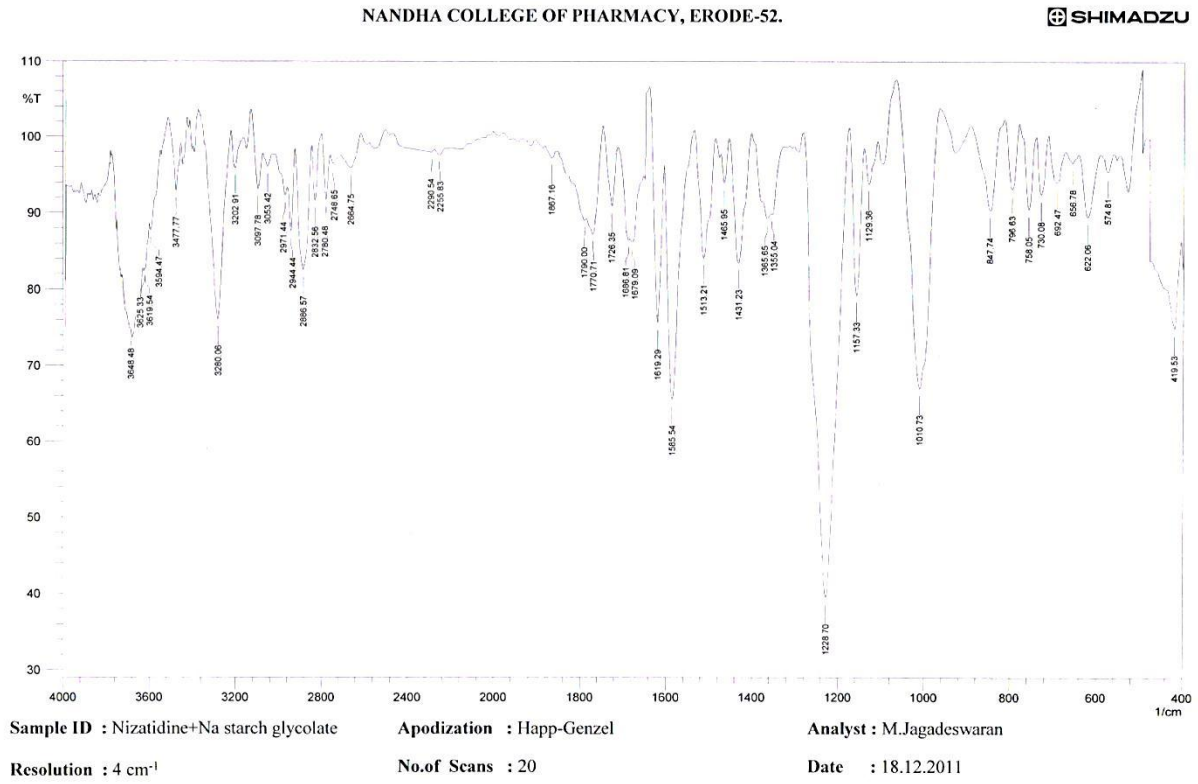


Fig No.15. Nizatidine + Sodium starch glycolate



8.1.3. CALIBRATION CURVE OF NIZATIDINE:

The absorbances of solution of Nizatidine in 0.1N HCl and in pH 6.8 buffer solution at 315 nm have been taken and it was found that the solutions show linearity in absorbance at a concentration of 0-10 µg/ml and obey beer-lamberts law. The values are illustrated in Table No.14 & Fig No.16, 17.

Table No.14 Calibration curve of Nizatidine

S.No	Concentration (µg/ml)	Absorbance at λ 315 nm (0.1N HCl)	Absorbance at 315 nm (pH 6.8 buffer solution)
1.	0	0	0
2.	2	0.193	0.165
3.	4	0.392	0.331
4.	6	0.584	0.498
5.	8	0.771	0.663
6.	10	0.940	0.827

Fig No.16. Linearity of Nizatidine calibration curve in 0.1N HCl

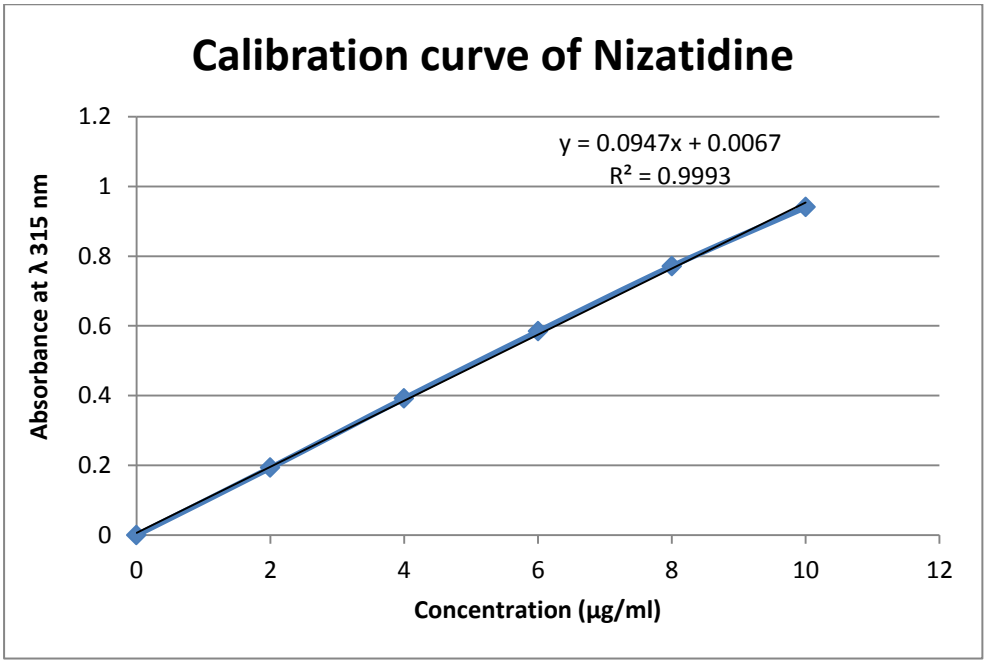
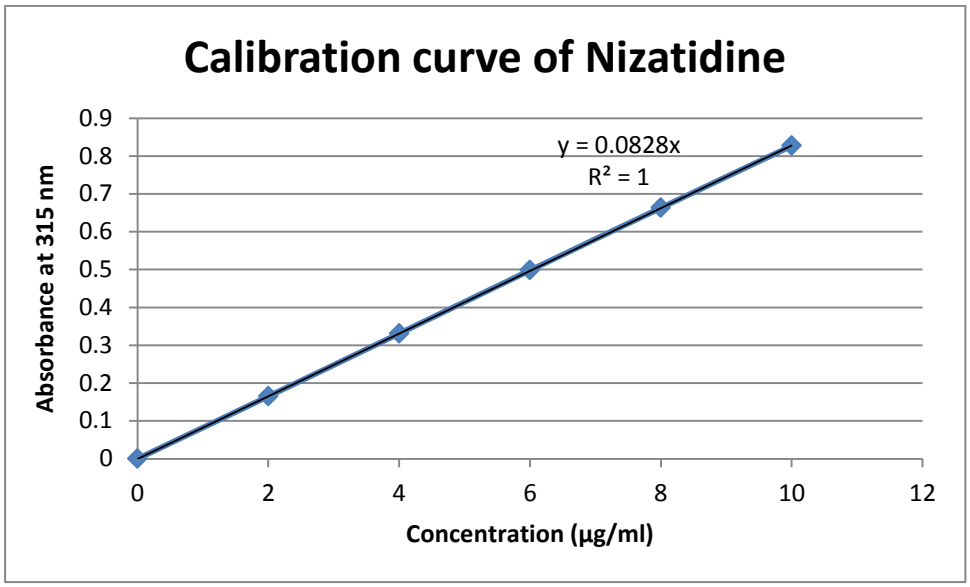


Fig No.17. Linearity of Nizatidine calibration curve in pH 6.8 buffer solution



8.1.4. Differential Scanning Colorimetry (DSC) Study of DPC:

Fig No.18. DSC thermogram of Nizatidine

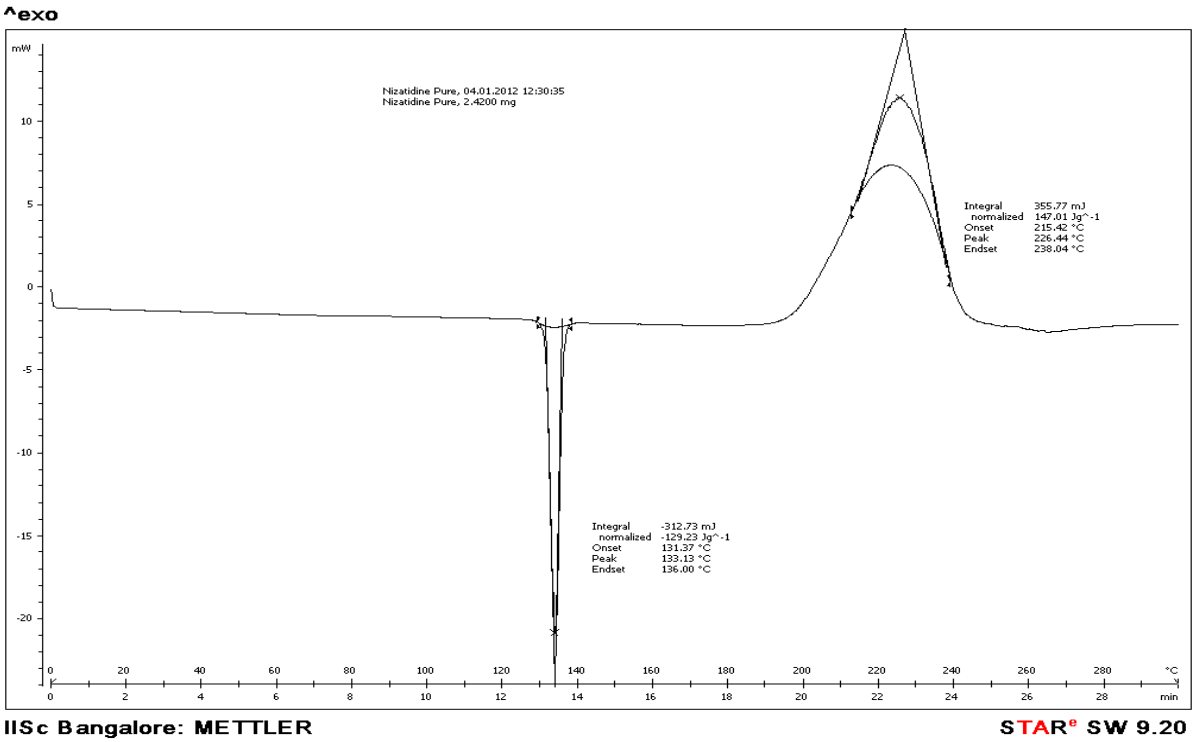


Fig No.19. DSC thermogram of Eudragit E100

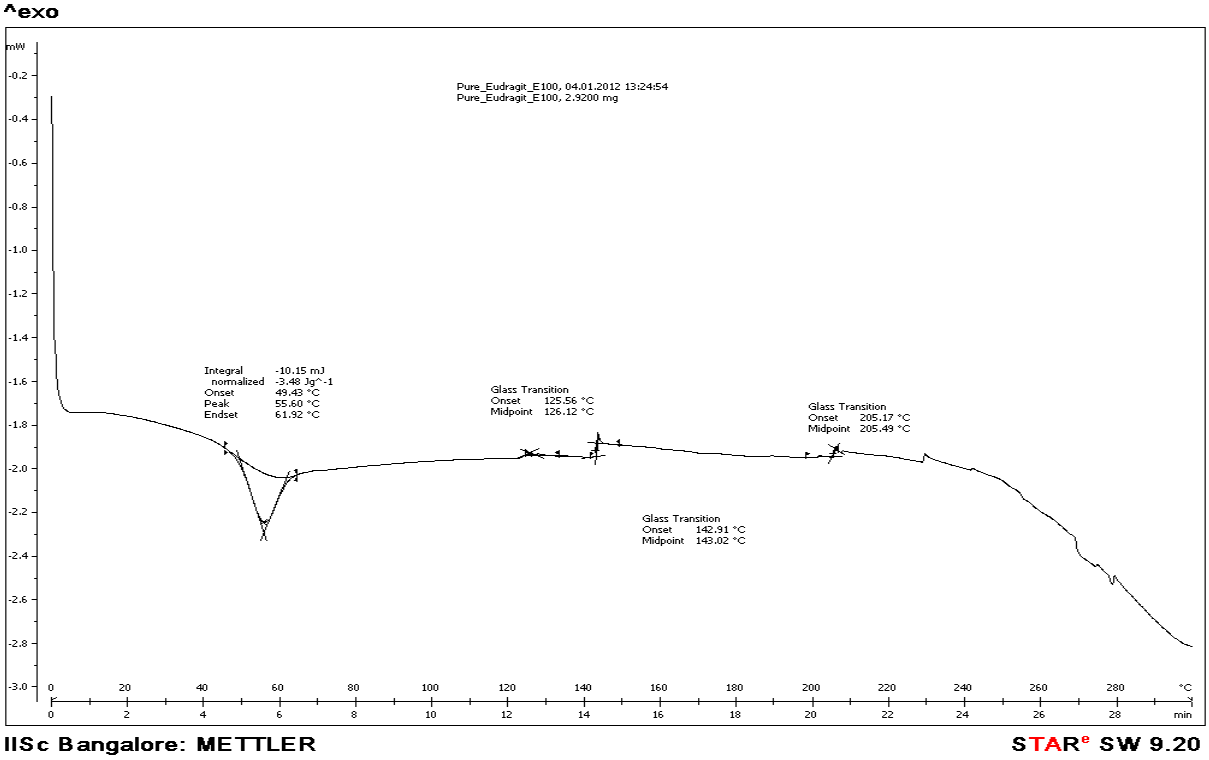
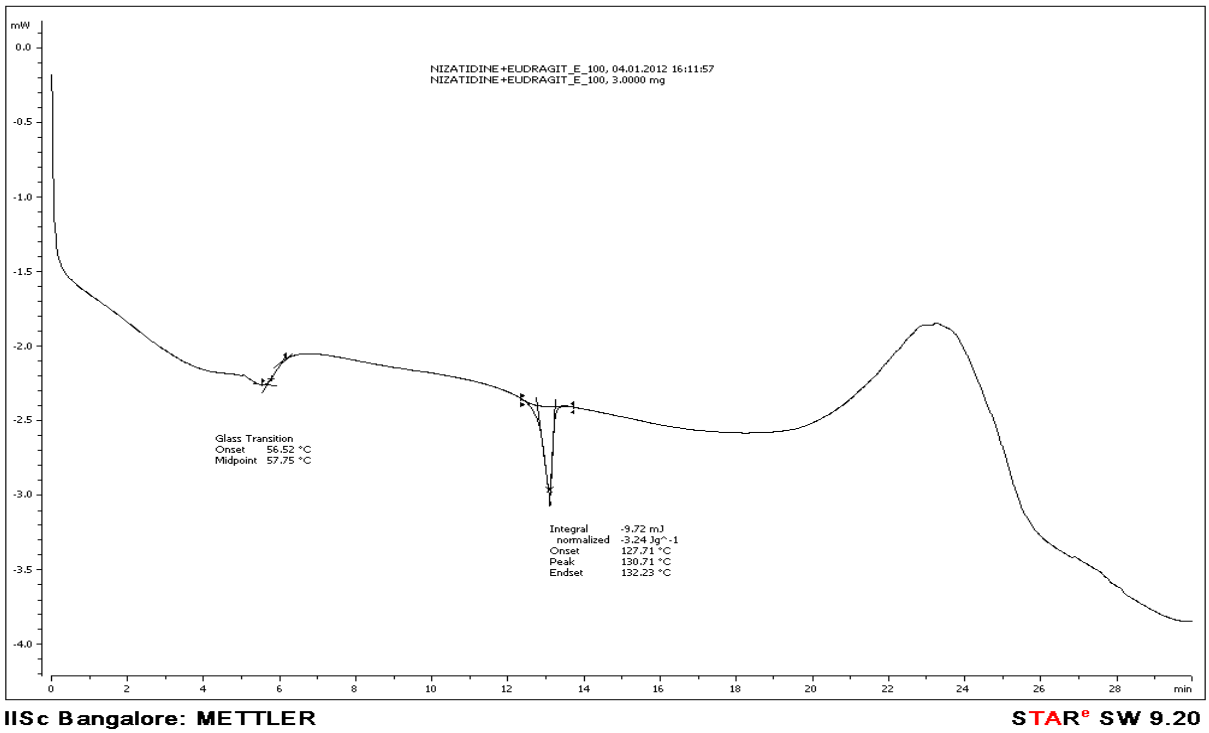


Fig No.20. DSC thermogram of Drug polymer complex



DSC analysis of Nizatidine, Eudragit E100 and DPC were carried out to check any changes in thermal properties of Nizatidine due to complexation with Eudragit E100. The DSC thermogram of Nizatidine was a single, sharp exotherm at 133.13^0C (Fig No.17). In case of DPC, the DSC thermogram was shortened exothermic peak appears at 130.71^0C (Fig No.19) which may be due to ethanol dissolution state. Thus it was showed that there were no major difference in DSC thermograms of Nizatidine and DPC, therefore the Eudragit E100 is compatible with the drug and so could be safely used to formulate ODTs.

8.2. PRE COMPRESSION STUDIES ON POWDER BLEND:

8.2.1. Bulk density:

The bulk density of the formulation mixture of drug with different superdisintegrants was measured by graduated cylinder. The bulk density was found in the range from 0.5 – 0.522 g/ml. The results are illustrated in Table No.15.

8.2.2. Tapped density:

The tapped density of the formulation mixture of drug with different superdisintegrants was measured by measuring cylinder. The tapped density was found in the range of 0.583 – 0.598 g/cm^3.The results are shown in Table No.15.

8.2.3. Compressibility index:

Compressibility index (Carr's index) indicates the flow property of the granules or the powders. Flow property plays a major role in the dosage forms especially in tablet dosage forms because improper flow of powders or granules may cause weight variation. Values of compressibility index below 15% indicate good flow whereas the values above 15% indicate poor flow property. The compressibility index of various formulation mixture of drug with different superdisintegrants was calculated by using bulk density and tapped density results and it was found in the range of 12.35 – 13.58 % which reveals that the formulations exhibit good flow property. The results are shown in the Table No.15.

8.2.4. Hausner ratio:

It is an indirect index of ease of powder flow. Lower Hausner ratio i.e., <1.25 specifies good flow property than the higher Hausner ratio i.e., >1.25. The Hausner ratio of various formulation mixture of drug with different superdisintegrants was calculated by using bulk

density and tapped density data. It was found in the range of 1.2 – 1.18 which designates that that the formulation powders having better flow properties. The results are shown in Table No.15.

8.2.5. Angle of repose (θ):

Angle of repose is direct index of the flow property. The angle of repose of various formulation blends of drug with different superdisintegrants was measured by using funnel method. The range of results is lie in between the 21.8 – 23.27^0 which indicates that the powders having good flow property. The results are illustrated in Table No.15.

Table No.15 Pre compression study of all formulations

Formulation	Bulk density* g/ml	Tapped density* g/ cm^3	Compressibility index*	Hausner ratio*	Angle of repose (θ)*
F1	0.53±0.15	0.62±0.12	12.35±0.09	1.14±0.05	22.5±0.27
F2	0.51±0.19	0.6±0.17	13.40±0.14	1.13±0.04	24.7±0.17
F3	0.57±0.21	0.65±0.21	12.48±0.08	1.06±0.08	25.9±0.21
F4	0.54±0.26	0.62±0.24	13.40±0.11	1.13±0.06	24.6±0.14
F5	0.62±0.23	0.69±0.22	12.50±0.12	1.13±0.04	23.5±0.19
F6	0.58±0.22	0.66±0.13	13.36±0.09	1.10±0.05	26.3±0.28
F7	0.54±0.14	0.61±0.19	13.46±0.07	1.16±0.07	24.2±0.22
F8	0.52±0.17	0.59±0.17	13.58±0.10	1.14±0.09	25.4±0.16
F9	0.59±0.12	0.68±0.14	13.26±0.12	1.18±0.05	26.3±0.23

*Results are the mean of 3 observations ± SD

8.3. POST COMPRESSION STUDIES:

8.3.1. Weight variation:

Prepared tablets were evaluated for the weight variation and results are depicted in Table No.16. The percentage deviation of the weight was within 5% as per monograph.

8.3.2. Hardness:

The hardness of the various formulations was depicted in Table No.16. The hardness of the tablets was found in the range of 3.13 – 3.4 Kg/cm^2 which is sufficient to withstand mechanical shocks of handling in manufacture, packing and shipping. The results have been showed that the increase in concentration of the superdisintegrants have no effect on the hardness of the tablets.

8.3.3. Thickness:

Thickness is important parameter in packing of tablets and acceptance. The thickness of the various tablet formulations was shown in Table No.16. The thickness of the tablet was found in the range of 5.13 – 5.72 mm which are sufficient for acceptance and packing.

8.3.4. Friability:

Friability value of tablets specifies resistance of the tablet to surface abrasion. The value of friability must be less than 1% for better resistance. The friability of the various tablet formulations was shown in the Table No.16. The friability of the tablet was found in the range of 0.447 – 0.493 %. The values are within the limit of official monograph i.e., <1%.

Table No.16 Post compression parameters of all formulations

Formulation	Average weight variation*	Hardness* (Kg/cm^2)	Thickness* (mm)	Friability* (%)
F1	454±0.12	3.20±0.27	5.13±0.04	0.44±0.05
F2	451±0.16	3.30±0.34	5.46±0.05	0.46±0.08
F3	449±0.16	3.30±0.38	5.72±0.02	0.44±0.04
F4	449±0.09	3.13±0.29	5.27±0.03	0.49±0.07
F5	455±0.13	3.20±0.36	5.29±0.04	0.46±0.06
F6	453±0.18	3.33±0.32	5.35±0.03	0.46±0.04
F7	452±0.09	3.26±0.28	5.58±0.02	0.47±0.09
F8	454±1.15	3.36±0.33	5.71±0.04	0.44±0.06
F9	452±1.17	3.40±0.31	5.65±0.05	0.46±0.07

*Results are the mean of 3 observations ± SD

Rapidly disintegrating property:

8.3.5. Wetting time:

The wetting time of tablets indicates the inner structure of the tablets and the hydrophilicity of the excipients which should be in the range of sec. The wetting time of the various formulations was illustrated in the Table No.17. The values were found in the range of 29 – 41.6 sec and designate that all the superdisintegrants having good hydrophilicity.

8.3.6. Modified disintegration test:

The disintegration is prior step for the dissolution of a tablet and was performed by a method which is stated under the materials and methods. The modified disintegration time of the various formulations was depicted in the Table No.17 and the values are lies in range of 34 – 43.6 sec. Among all the formulations F3 has shown lower disintegration time which contains the 5% of sodium starch glycolate. From the results obtained it has shown that with the increasing concentration of superdisintegrant the disintegration time has been decreased.

8.3.7. Water absorption ratio:

It is important criteria for understanding the capacity of disintegrants to swell in the presence of water. The water absorption ratio of the various formulations was depicted in the Table No.17. The results are lies in the range of 25.31 – 29.2. The formulations containing low concentration of superdisintegrants shows lower water absorption ratio compare to formulations containing higher concentration of superdisintegrants, which may be because of less swelling property.

8.3.8. *In Vitro* dispersion time:

The *In Vitro* dispersion time is measured by the time taken to undergo uniform dispersion. The *In Vitro* dispersion time of the various formulations was shown in the Table No.17. The results are lies in the range of 62 – 77 sec. The results showed that the crospovidone is the best superdisintegrant which may be because of showing less swelling efficiency, high water uptake capacity and spongy nature which yields porous tablet that disperse in a matter of seconds. And the results also showed that as the concentration of superdisintegrant increases the *In Vitro* dispersion time decreases. The relation between them has been shown in the below figures 20, 21, 22.

Table No.17 Rapidly disintegrating property of all formulations

Formulation	Wetting time* (sec)	In Vitro Disintegration time* (sec)	Water absorption ratio*	In Vitro dispersion time* (sec)	% Drug content*
F1	38.0±1.2	41.0±0.3	25.31±1.56	73.3±0.53	99.56±0.54
F2	34.6±1.8	40.3±0.4	26.46±1.02	70.3±0.42	99.72±0.63
F3	29.0±1.6	34.0±0.2	29.00±1.45	62.0±0.65	99.88±0.58
F4	34.6±1.4	43.6±0.5	26.18±1.12	77.0±0.73	99.16±0.51
F5	41.3±1.3	42.6±0.3	26.30±1.34	67.3±0.43	99.45±0.62
F6	33.3±1.7	37.6±0.1	27.22±1.52	64.0±0.71	99.61±0.69
F7	41.6±1.5	43.3±0.2	26.20±1.62	76.0±0.83	99.29±0.43
F8	37.0±1.6	39.6±0.6	27.01±1.89	72.0±0.59	99.48±0.58
F9	33.3±1.4	38.3±0.3	29.20±1.01	67.6±0.63	99.57±0.66

*Results are the mean of 3 observations ± SD

Fig No.21. Comparitive graph of Concentration and In Vitro Dispersion time of F1, F2, F3

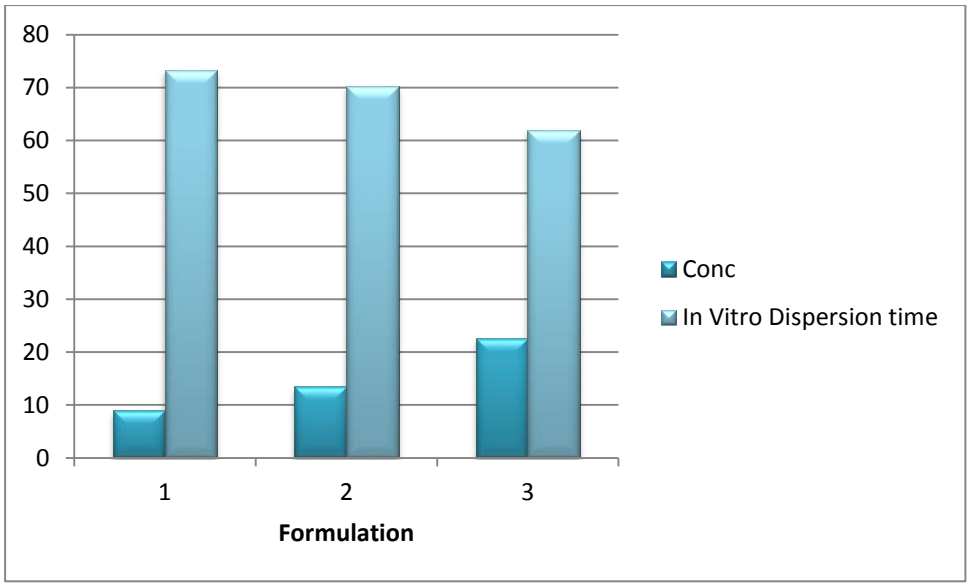


Fig No.22. Comparitive graph of Concentration and In Vitro Dispersion time of F4, F5, F6

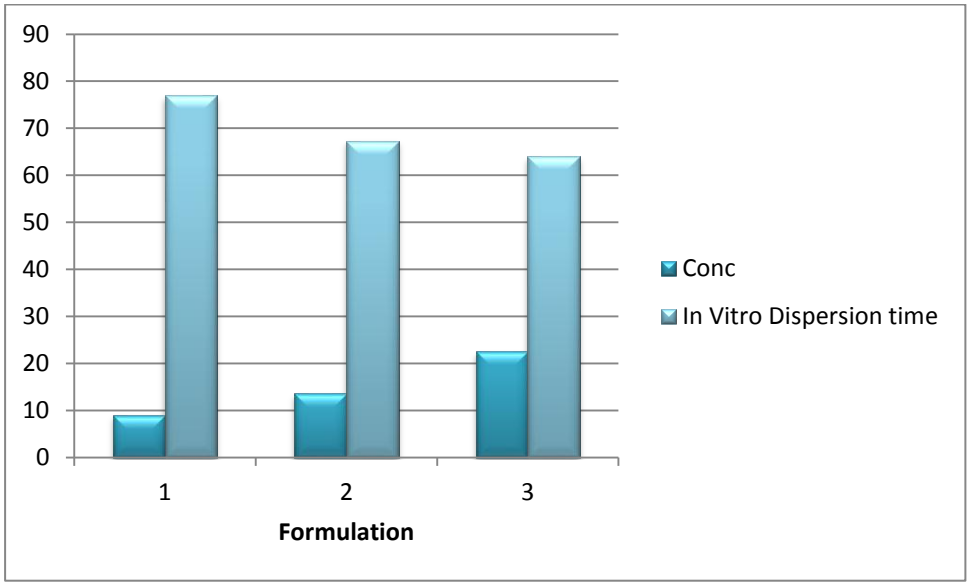
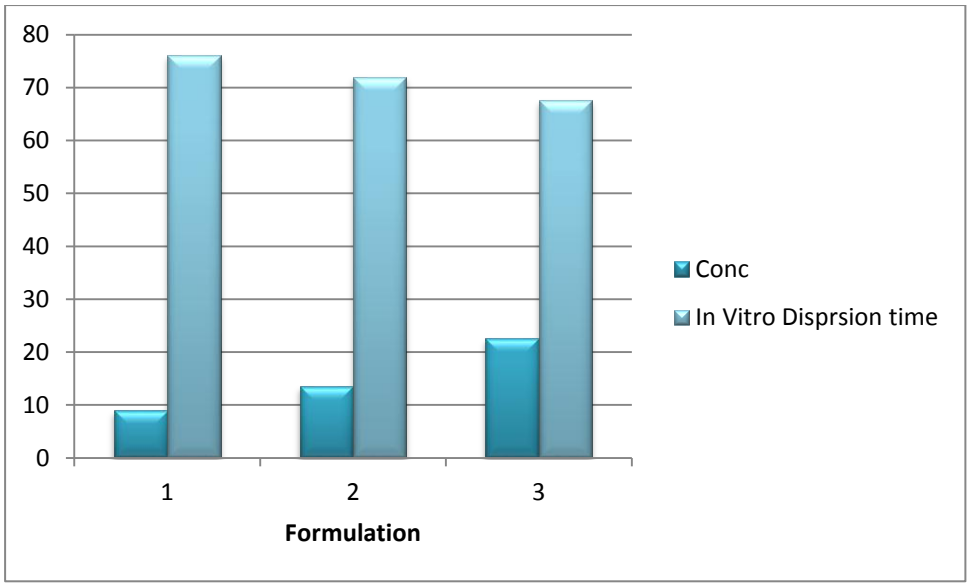


Fig No.23. Comparitive graph of Concentration and In Vitro Dispersion time of F7, F8, F9



8.3.9. *In Vitro* drug release:

In Vitro release of various formulations was studied and was shown in the Table No.18. The drug release of formulations F1 to F9 is 94.7%, 95.6%, 99.5%, 91.9%, 94.2%, 96.4%, 90.0%, 92.6%, 94.8% of Nizatidine at the end of 15 min respectively. The fast dissolution of all the formulations is might be due to quick disintegration of the tablets to fine particles and rapid absorption. Thus formulation F3 showed maximum drug release i.e., 98.5% at the end of 15 min which contains 5% of the crospovidone as superdisintegrant compared to other formulations containing sodium starch glycolate and croscarmellose sodium. It might be due to more gelling tendency and low water uptake of Croscarmellose sodium and more swelling tendency and sustained release action of sodium starch glycolate. The drug release profile of all the individual formulations have been shown from fig 23 to 31.

Table No.18 In Vitro drug release profile of all formulations

Formulation	In Vitro % drug release in different time intervals (min)				
	3	6	9	12	15
F1	64.3±0.92	71.8±0.85	80.5±0.97	87.6±1.05	94.7±0.89
F2	66.5±1.16	72.0±1.04	79.1±0.83	86.2±0.96	95.6±0.75
F3	69.6±0.91	72.0±1.12	78.3±0.86	89.4±1.08	99.5±1.15
F4	68.0±0.88	71.7±0.92	78.0±0.97	85.6±1.12	91.9±0.78
F5	69.7±1.08	73.4±1.14	79.0±0.97	87.0±0.94	94.2±0.81
F6	68.2±1.16	71.0±0.96	76.3±0.98	88.2±1.08	96.4±1.11
F7	65.1±0.95	70.1±0.89	76.4±1.03	84.5±1.13	90.0±0.91
F8	67.3±0.89	72.0±0.92	79.0±0.87	86.5±1.06	92.6±0.86
F9	68.1±1.04	74.5±1.02	79.6±0.93	88.9±1.03	94.8±0.92

Fig No.24. Dissolution profile of Formulation F1

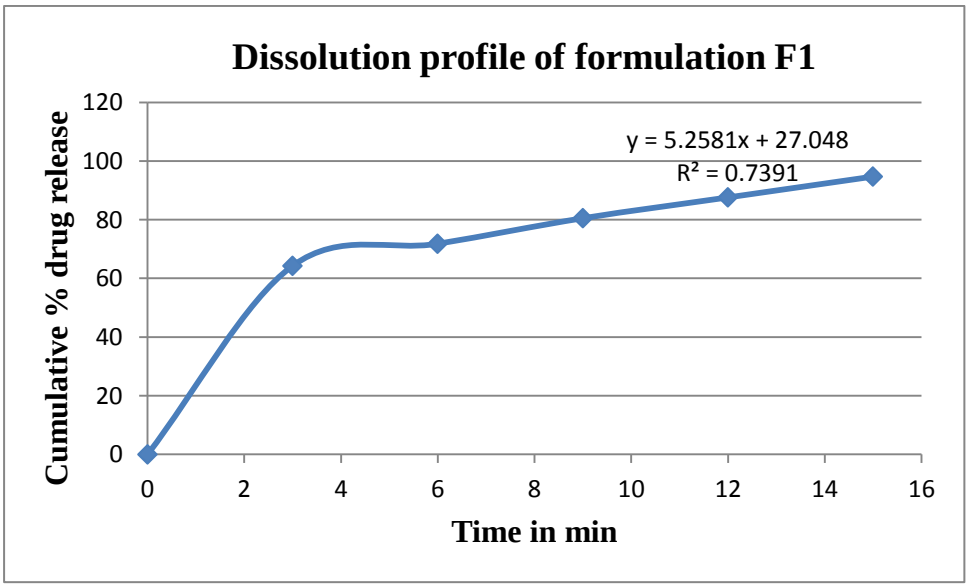


Fig No.25. Dissolution profile of Formulation F2

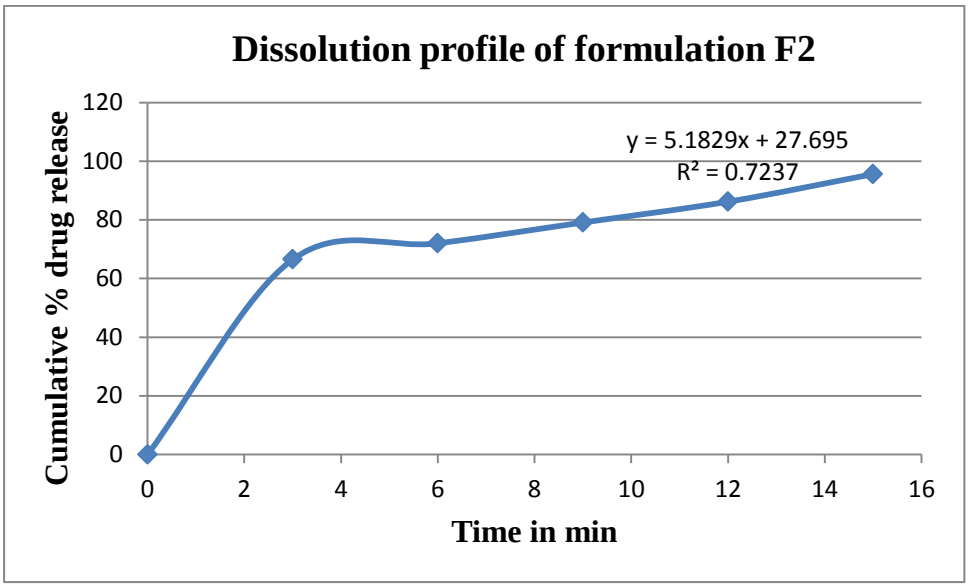


Fig No.26. Dissolution profile of Formulation F3

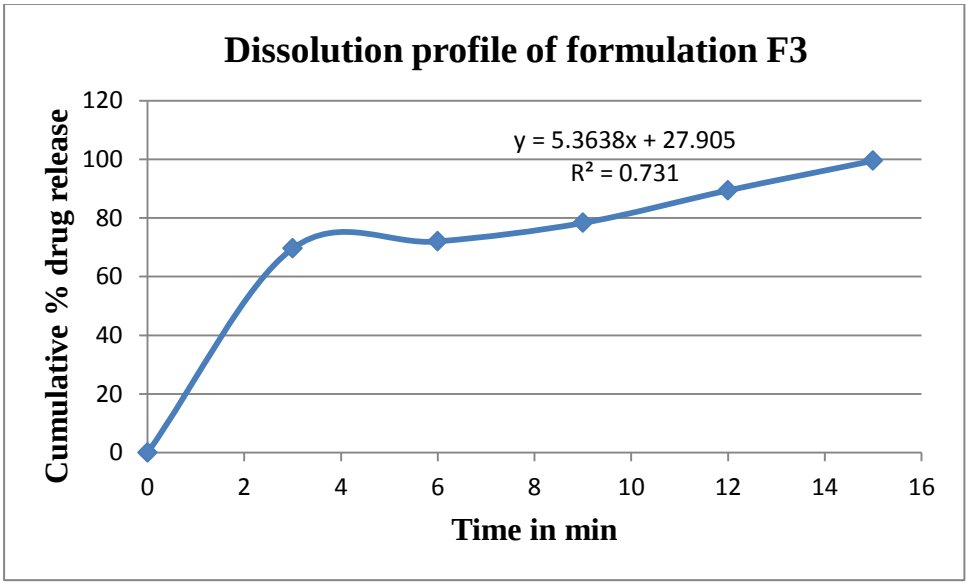


Fig No.27. Dissolution profile of Formulation F4

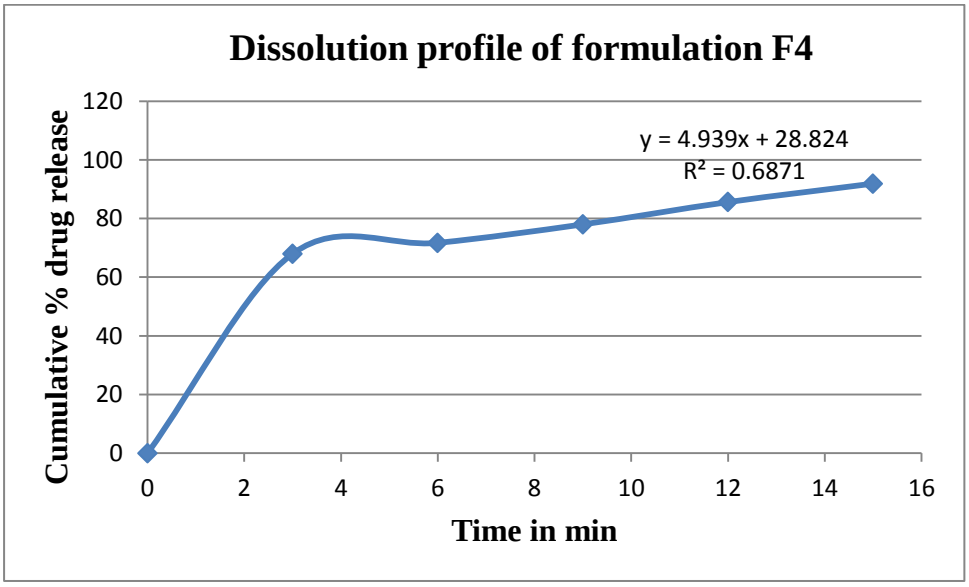


Fig No.28. Dissolution profile of Formulation F5

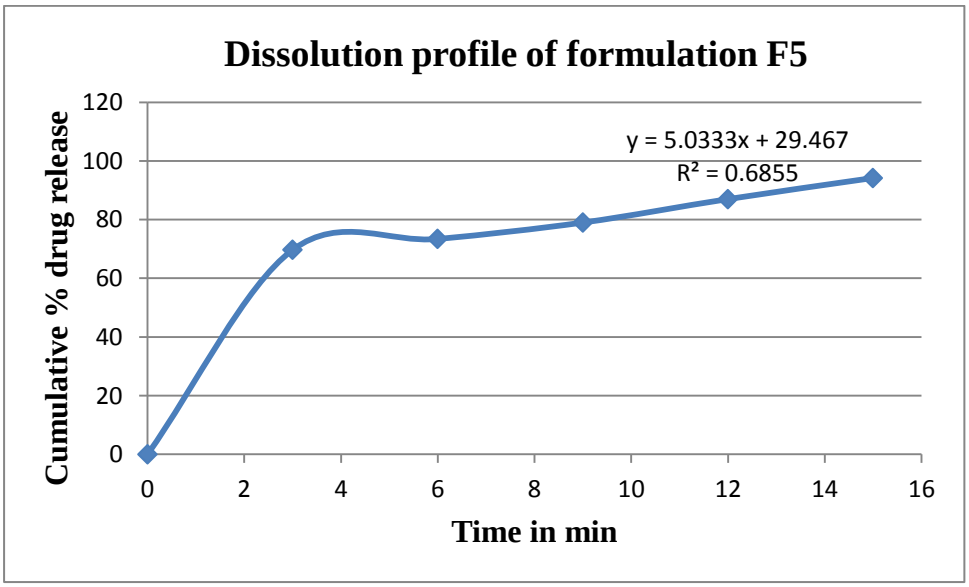


Fig No.29. Dissolution profile of Formulation F6

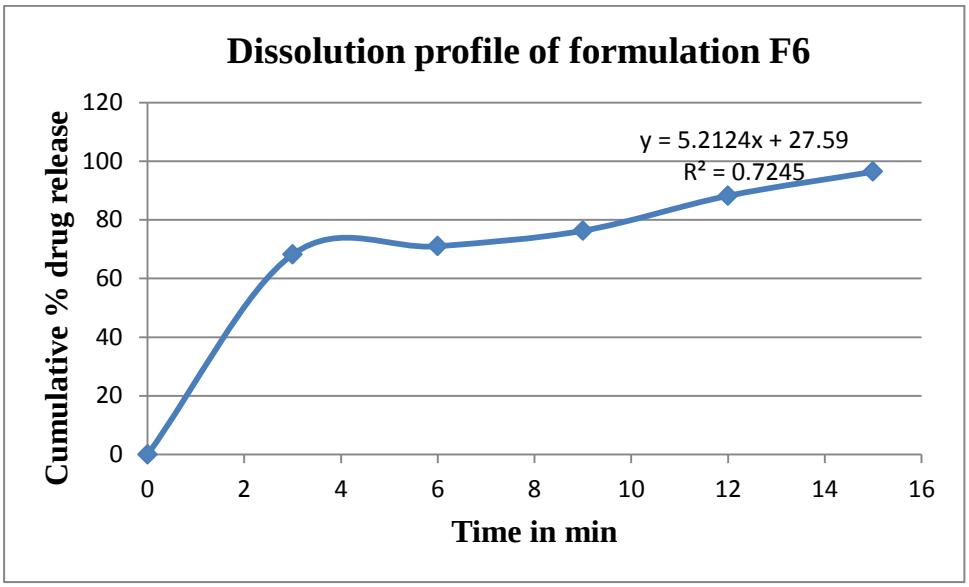


Fig No.30. Dissolution profile of Formulation F7

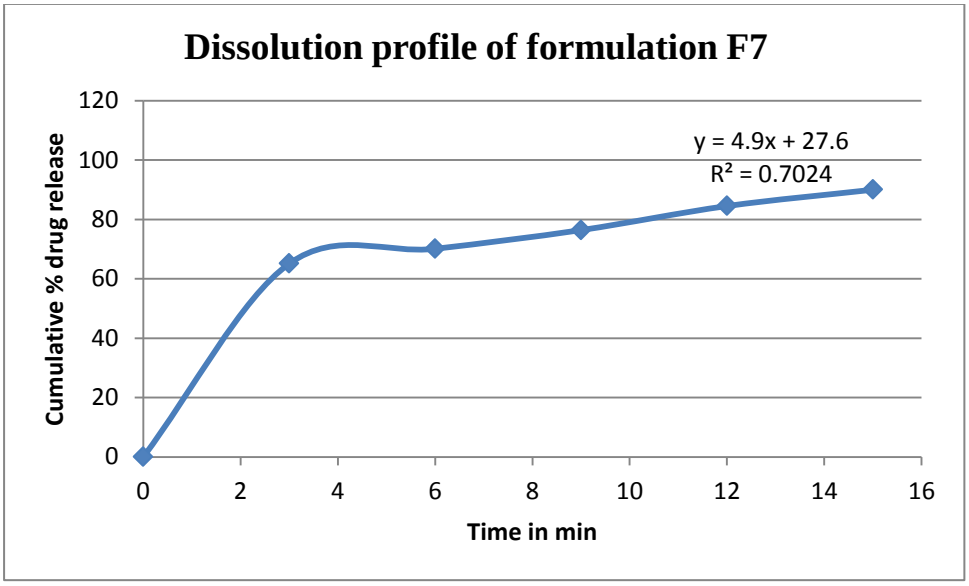


Fig No.31. Dissolution profile of Formulation F8

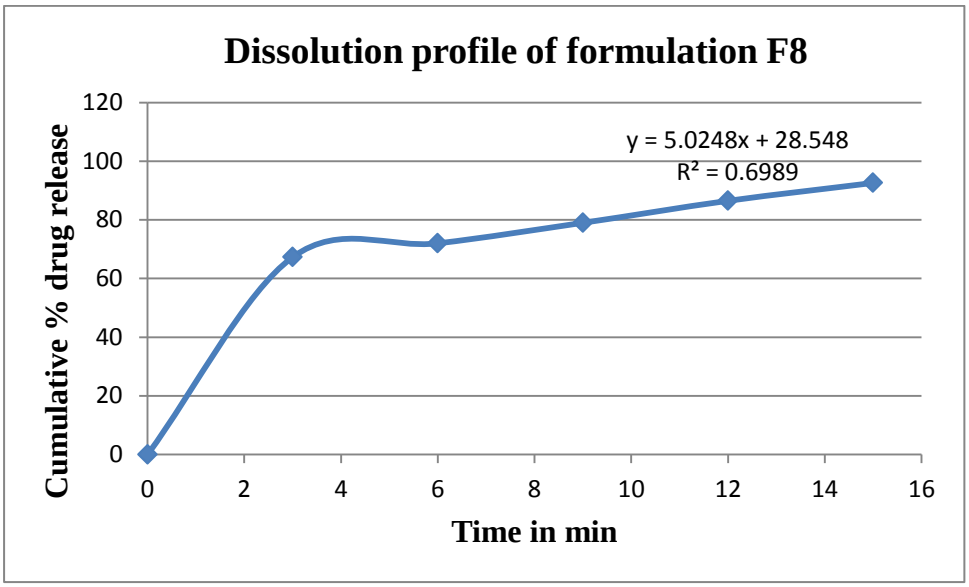


Fig No.32. Dissolution profile of Formulation F9

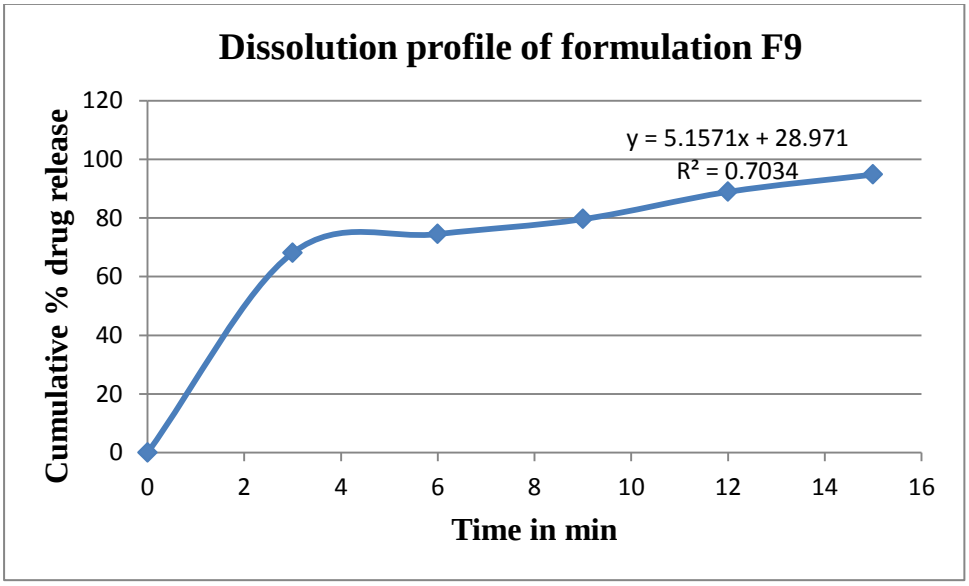


Fig No.33. Comparitive dissolution profile of F1,F2, F3

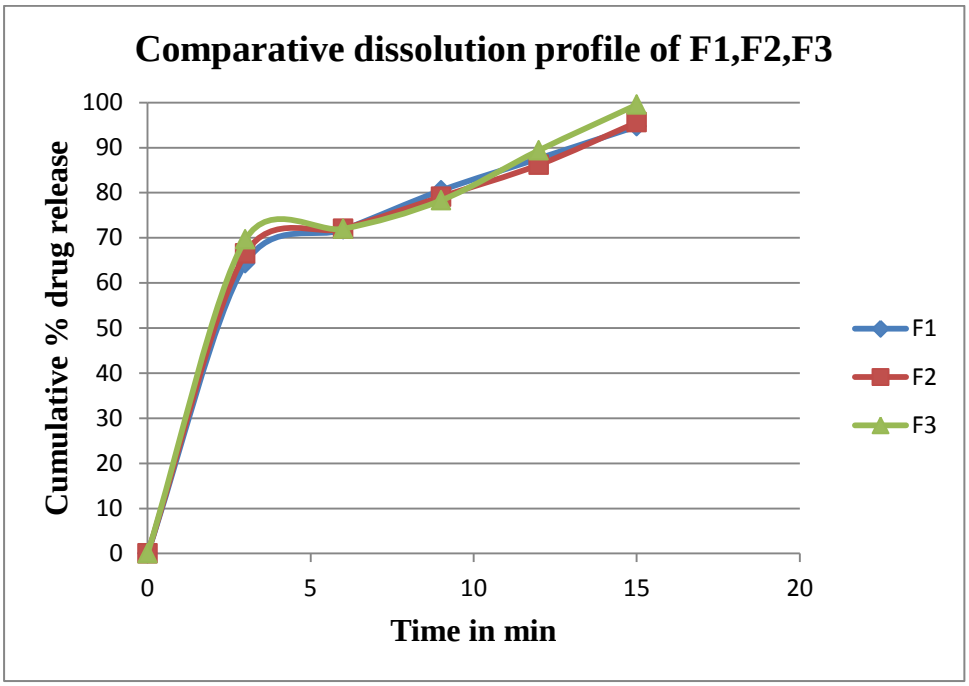


Fig No.34. Comparitive dissolution profile of F4, F5, F6

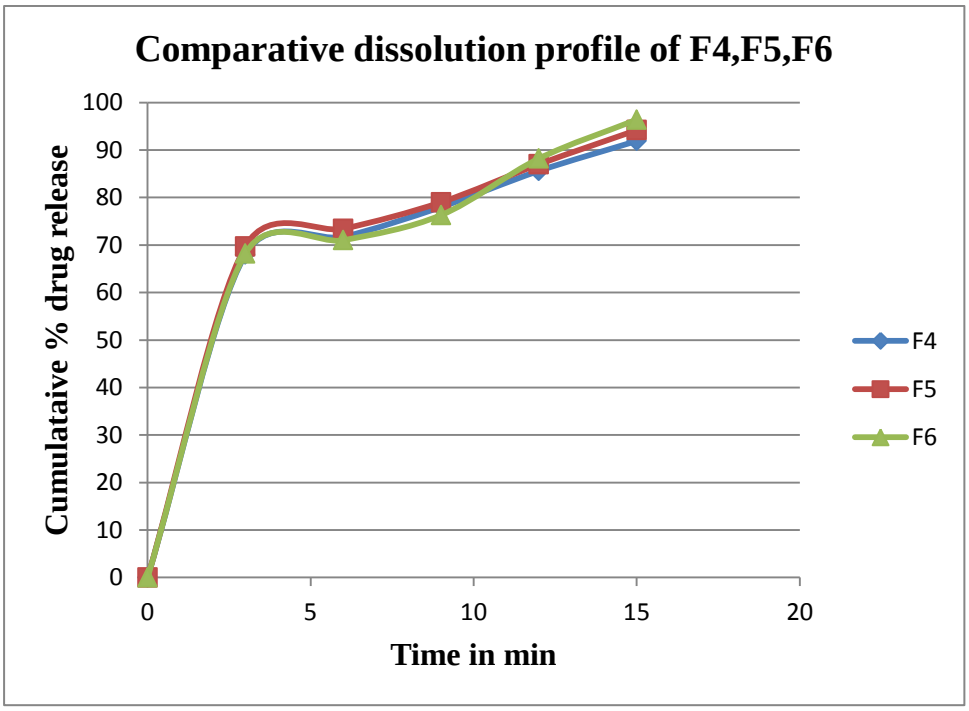


Fig No.35. Comparitive dissolution profile of F7, F8, F9

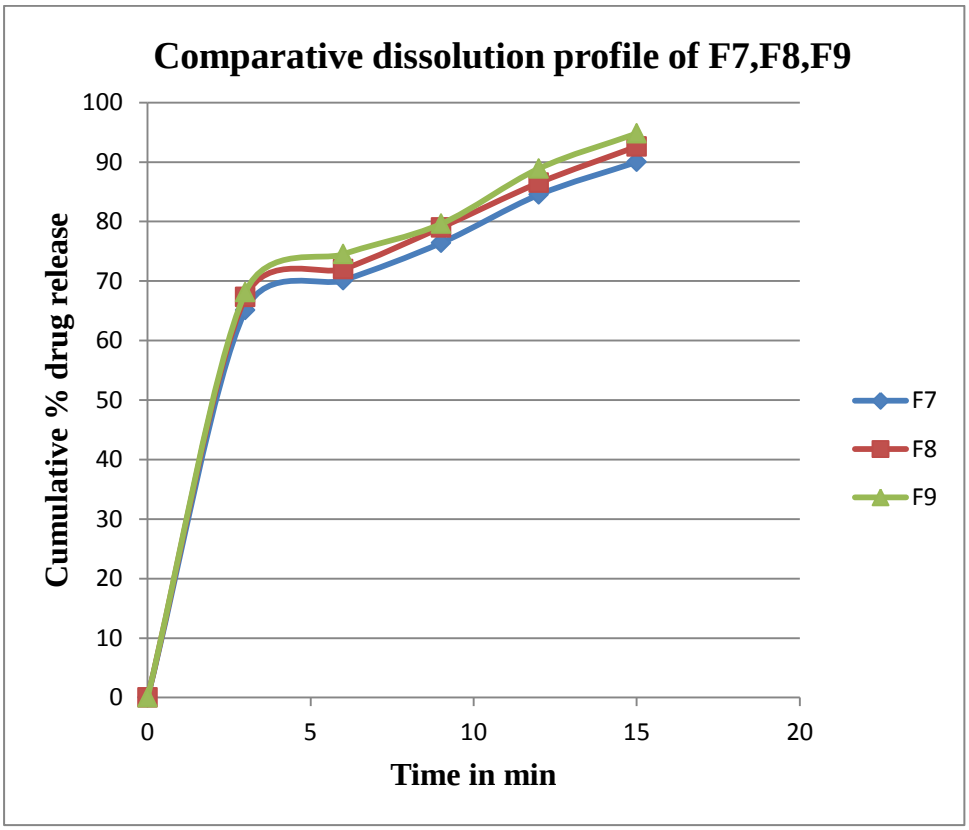
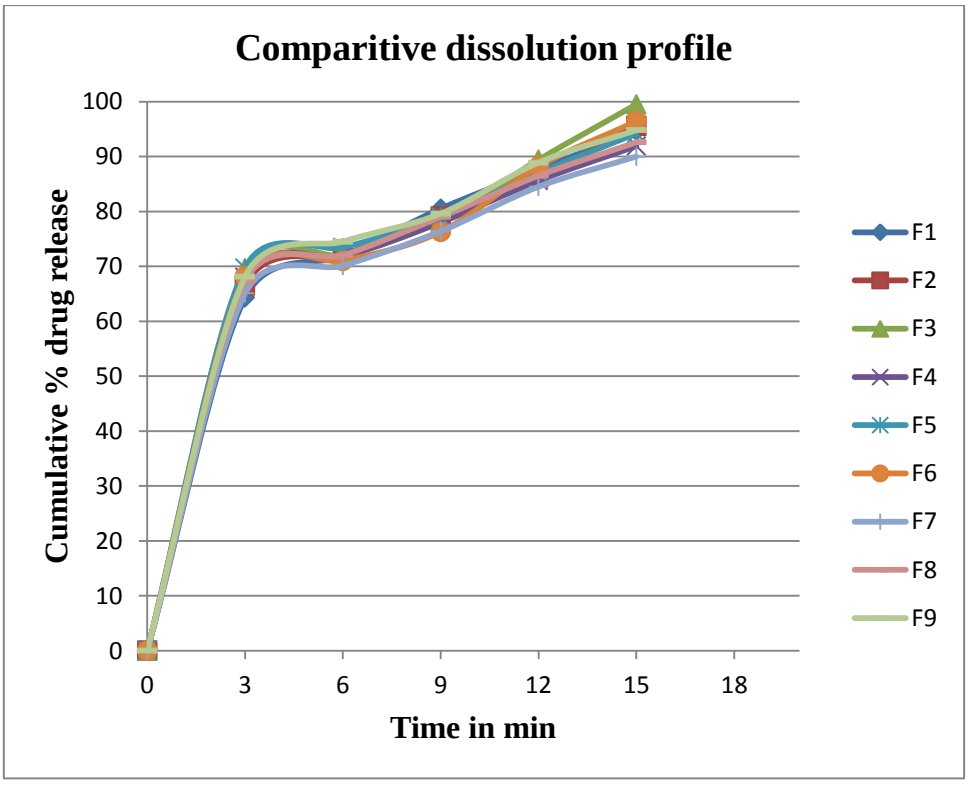


Fig No.36. Comparitive dissolution profile of all formulations



8.3.10. Drug content:

The percentage drug content of various formulations has been shown in the Table No.17 and the range of content uniformity lies between 99.16 to 99.88 %.

8.3.11. Stability study:

The formulation F3 were kept for accelerated stability study at 40±2^{0}C and 75±5% RH for one month in stability chamber. After a period of two months, the samples were observed for any change in physical parameters. It was observed, no change in colour, taste and was also noted that tablets were free of any kind of bad odour.

Results obtained from the evaluation after stability study of Nizatidine ODT are shown in Table No.19.

Table No.19 Evaluation parameters obtained after stability study of the Nizatidine ODT (2 months).

S.No	Parameters	Units	F3			
			15 Days	30 Days	45 Days	60 Days
1.	Taste	As per specifications	Not bitter	Not bitter	Not bitter	Not bitter
2.	Hardness	Kg / cm^2	3.30±0.41	3.28±0.35	3.25±0.45	3.24±0.28
3.	Friability	% w/w	0.44±0.38	0.45±0.25	0.43±0.41	0.42±0.32
4.	Disintegration time	Sec	35.0±0.4	34.6±0.2	34.1±0.5	33.4±0.2
5.	Wetting time	Sec	28.0±1.8	27.3±0.3	26.8±0.1	26.3±0.3
6.	Assay	%	99.88±0.5	99.54±0.7	99.20±0.3	98.8±0.4

SUMMARY AND CONCLUSION

ODTs are developed to avoid the choking problems which occur generally with the tablet dosage forms. The ODTs disintegrate within fraction of seconds in the mouth without need of water and shows maximum drug release within few min and shows immediate effect.

Nizatidine is an anti-histaminic drug which reversibly and competitively blocks histamine at H_2 receptors, particularly those in gastric parietal cells, antagonising the usual stimulatory effect of endogenous histamine on gastric acid production.

The present research is directed towards the development of **Formulation and evaluation of orodispersible tablets of taste masked Nizatidine** to improve the bioavailability of Nizatidine which shows 70%. As the Nizatidine is bitter in taste, taste masking has been done by using a polymer Eudragit E100 which is a cationic copolymer based on dimethylaminomethyl methacrylate, butyl methacrylate and methyl methacrylate by mass extrusion method. The drug polymer interaction was studied by DSC and the results showed no interaction between them.

The ODTs of various batches were prepared by using various concentrations of various superdisintegrants like sodium starch glycolate, crospovidone and croscarmellose sodium by direct compression method.

In the present work nine formulations were prepared using mannitol as diluent, aspertame as sweetner, and talc as glidant.

Characterization of the drug was done by performing the melting point, UV spectroscopy and IR spectroscopy. IR spectrum of the pure drug was compared with that of physical mixture of drug with all the excipients used in the study. The results showed that there was no drug-excipient interaction. The melting point was found to be 203^0C and from the UV spectral analysis of the drug solution indicated that λmax value as 315 nm.

All the prepared ODT formulations were evaluated for physical characterstics, disintegration, *In Vitro* dissolution and stability study.

The hardness of formulations (F1-F9) were in the range of 3.13 – 3.4 Kg/cm^2 indicating good mechanical strength and the thickness of formulations were in the range of 5.13 – 5.72 mm. The weight variation and the friability were found within the official limits.

The *In Vitro* dispersion time of all the formulation was done and observed that there is decrease in the *In Vitro* dispersion time with the increase in the concentration of superdisintegrant. *In Vitro* dissolution study of all the formulations was carried out for 15 min and according to results formulation F3 was found as the best formulation, which showed

99.5% drug release at the end of 15 min. The selected formulation was subjected for the short term stability study for 60 days and the hardness, taste, friability, drug content and disintegration were observed and found no significant change in the results.

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