FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF METOCLOPRAMIDE HYDROCHLORIDE

A 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

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Submitted By
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This is to certify that the work embodied in this thesis entitled, **"FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF METOCLOPRAMIDE HYDROCHLORIDE"** submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, was carried out by **Mr. NILESH CHINDHU PATIL,** Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 for the partial fulfilment for the award of degree of Master of Pharmacy in Pharmaceutics under my supervision.

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

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DECLARATION

The work presented in this thesis entitled **"FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS OF METOCLOPRAMIDE HYDROCHLORIDE"** was carried out by me in the Department of Pharmaceutics, Nandha College of Pharmacy, Erode-52 under the direct supervision of **Prof. K. RAJA M. Pharm, (Ph.D.),** Prof. Pharmaceutics, Nandha College of Pharmacy, Erode-52.

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CONTENTS

Sr.No	TITLE	Page. no
1.	INTRODUCTION	01-17
2.	REVIEW OF LITERATURE	18-26
3.	AIM AND OBJECTIVE	27-28
4.	PLAN OF WORK	29-30
5.	DRUG PROFILE	31-33
6.	EXCIPIENTS PROFILE	34-51
7.	MATERIALS AND METHODS	52-64
8.	RESULTS AND DISCUSSION	65-88
9.	SUMMARY AND CONCLUSION	89-90
10.	REFERENCES	91-94

LIST OF ABBREVIATIONS

Abbreviations	Abbreviation Terminology
ODTs	Oro-dispersible tablet
GERD	Gastro Esophageal Reflux Disease
CTZ	Chemo Receptor Trigger Zone
FTIR	Fourier Transform Infra-Red
USP	United States Pharmacopoeia
NF	National Formulary
IP	Indian Pharmacopoeia
BP	British Pharmacopoeia
IR	Infra-Red
UV	Ultraviolet
HCL	Hydrochloric acid
Ac-Di-Sol	Croscarmellose Sodium
MCC	Microcrystalline cellulose
^{0}C	Degree Celsius
%	Percentage
W/V	Weight by volume
W/W	Weight by weight
Ml	Milliliter
Cm	Centimeter
Mm	Millimeter
Nm	Nanometer
Mg	Milligram
Gm	Gram
µg	Microgram
Kg	Kilogram
T	Time
pH	Hydrogen ion concentration
Hrs	Hours
Sec	Second
Min	Minutes
SD	Standard Deviation
Rpm	Revolutions per minute
RH	Relative Humidity

1. INTRODUCTION

Oral route of drug administration is the most common and preferred method of delivery as it is the simplest and easiest way of administering drugs. The rout offers ease of drug administration in a convenient manner and patients are more familiar with this rout. So, patient compliance and thus drug treatment is typically more effective with orally given medications.[1]The tablet is most widely used dosage form existing today because of its convenience in term of self administration, compactness and ease in manufacturing. However, geriatric, paediatric and mentally ill patients experiences difficulty in swallowing conventional tablets, which is common among all age groups, especially in elderly which leads to poor patient compliance. To overcome these problem, scientists have developed innovative drug delivery system known as mouth dissolving or disintegrating tablets. This dosage forms dissolve and disintegrates in the oral cavity within minutes without need of water or chewing. This formulation is useful in administration of drug in paediatric and geriatric patients.[2]

1.1 Orodispersible Tablet

The most popular solid dosage formsare being tablets and capsules, one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage forms. Often times people experience inconvenience in swallowing conventional dosage forms such as tablet when water is not available, in the case of motion sickness (kinetosis) and sudden episodes of coughing during the common cold, allergic condition and bronchitis. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Orodispersible tablets are not only indicated for people who have swallowing difficulties, but also ideal for active people. Orodispersible tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, fast dissolving tablets, rapimelts, porous tablets, quick dissolving etc. Orodispersible tablets are those when put on tongue, disintegrates instantaneously, releasing the drug, which dissolve or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. The advantages of mouth dissolving

dosage forms are increasingly being recognized in both, industry and academics. Their growing importance was underlined recently when European pharmacopoeia adopted the term "Orodispersible tablet" as a tablet that to be placed in the mouth where it disperses rapidly before swallowing.[3]

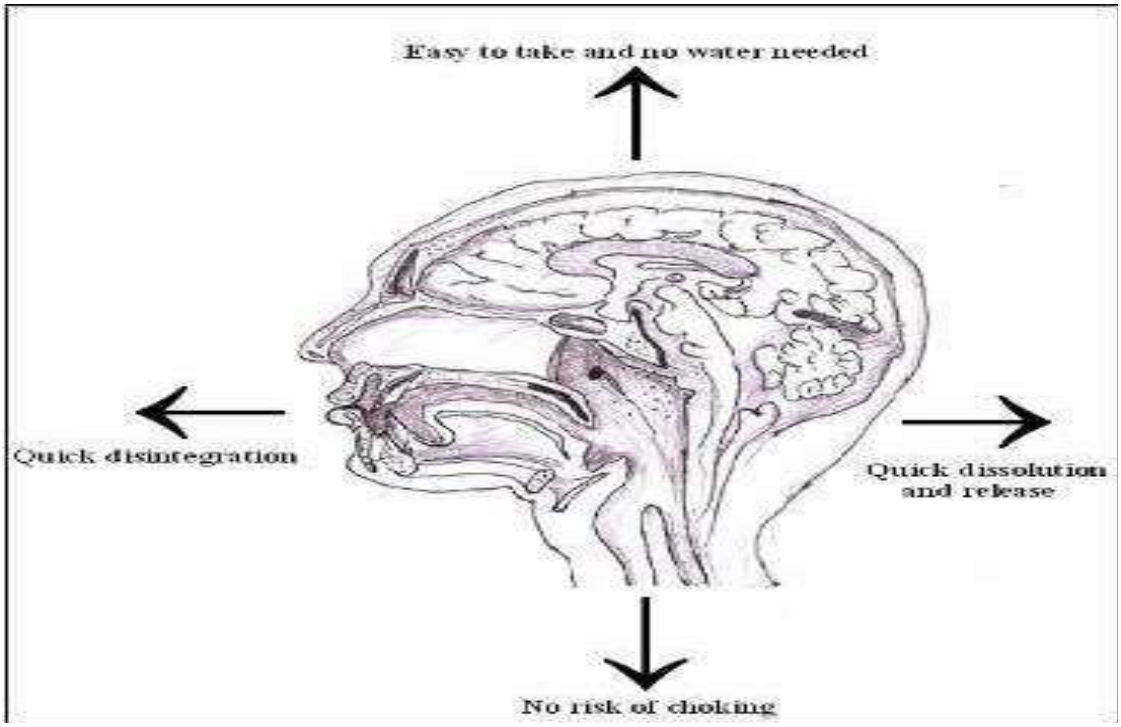


Figure 1.1: Mechanism of action of orodispersible tablet

United States Pharmacopoeia has also approved for these dosage form as orodispersible tablets. Thus, orodispersible tablets are solid unit dosage forms like conventional tablets, but are composed of super disintegrants, which help them to dissolve the tablets within a minute in the mouth in the presence of saliva without any difficulty of swallowing. It offers several advantages with respect to its stability, administration without water, accurate dosing, easy manufacturing, small packaging size, and handling. Its ease of administration in the population especially for paediatric, geriatric, or any mentally retarded persons makes it a very popular dosage form. Due to the presence of superdisintegrants, it gets dissolved quickly, resulting in rapid absorption of drug which in turn provides rapid onset of action. Since the absorption taking place directly from the mouth, so, bioavailability of the drug increases. Drugs present in orodispersible tablets are also not suffering from first pass metabolism. This type of drug delivery is becoming popular day by day due to its numerous advantages.[4]

The oral rout remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, non invasive method and ease of administration leading to high level of patient compliance. However, traditional tablets and capsules administered with a glass of water may be inconvenient or impractical for some geriatric patients because of changes in various physiological and neurological conditions associated with aging including difficulty in swallowing/dysphagia, hand tremors, deterioration in their eyesight, hearing, memory, risk of choking in addition to change intaste and smell. For these reasons, it is said that age is a convenient 'red flag' that pharmacists can use to alert themselves for patients who may have special counselling needs. Solid dosage forms also present significant administration challenges in other patient groups, such as children, mentally challenged, bed ridden and uncooperative patients. Paediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control. Moreover, patients travelling with little or no access to water, limit utility of orally administered conventional tablets or capsules. Therefore, to cater the needs of such patients, recent advancements in technology have resulted in development of viable dosage alternatives popularly known as orally disintegrating tablets (ODTs). These dosage forms are preferable alternative for oral medication in improving the quality of life and patient acceptability. ODTs are the solid unit dosage form/entities containing medicinal substances which disintegrate or dissolve rapidly in oral cavity usually within a few seconds even without the need of water or chewing. As the tablet disintegrate in mouth, this can enhance the clinical effect of drug through pregastric absorption from the mouth, pharynx and esophagus. The advantages of these dosage forms are continuously and increasingly being identified in both pharmaceutical industries as well as in academia.[5]

The most important drug delivery route is undoubtedly the oral route. It offers advantages of convenience of administration and potential manufacturing cost savings. Drugs that are administered orally, solid oral dosage forms in general and tablets in particular represent the preferred class of product. Today drug delivery companies are focusing on solid oral drug delivery systems that offer greater patient compliance and effective dosages. Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that dysphagia (difficulty in swallowing) is common among all age groups and more specific with

paediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and flavour increase the acceptability of bitter drugs by various groups of population.[6]

i) Definition

The **US Food and Drug Administration Center for Drug Evaluation and Research (CDER)** defines, in the **'Orange Book'**, an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when 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.[7]

Orodispersible tablets are those when put on tongue, disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect.[3]

ii) Need to formulate orodispersible tablets

The need for non-invasive drug delivery systems continues due to patients poor acceptance and compliance with existing delivery regimes, limited market size for drug companies and drug uses coupled with high cost of disease management. ODT is one such dosage form which is useful for geriatric patients mainly suffering from conditions like hand tremors and dysphasia.

- Paediatric patients who are unable to swallow easily because their central nervous system and internal muscle are not developed completely.
- Travelling patients suffering from motion sickness and diarrhoea that do not have easy access to water.
- Especially for patients with persistent nausea for a long period of time are unable to swallow.
- Mentally challenged patients, bedridden patients, and psychiatric patients.

iii) Limitation of ODTs

- Drugs with relatively larger doses are difficult to formulate into ODTs e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500mg of the drug.
- Patients who concurrently take anticholinergic medications may not be the best candidates for ODTs.

- Patients with sjogrens syndrome or dryness of mouth due to decreased saliva production may not be good candidates for these tablet formulations.[6,7]

iv) Criteria for Orodispersible Drug Delivery System

The tablets should :

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental conditions as humidity and temperature.
- Allow the manufacture of tablet using conventional processing and packaging equipments at low cost.[3]

v) Salient Features of Orodispersible Drug Delivery System

- Ease of administration to patient who refuses to swallow a tablet, such as paediatric geriatric patients and psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have immediate access to water.
- Rapid dissolution and absorption of drug, which will produce quick onset of action.
- Some drugs are absorbed from mouth, pharynx and oesophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs increased.[3]

vi) Advantages of ODTs

- Rapid onset of action and may offer an improved bioavailability.
- Improved patient compliance.
- Useful for paediatric, geriatric and psychiatric patients.
- Suitable during travelling where water may not be available.
- No specific packaging required, can be packaged in push through blisters.
- Smooth mouth feel and pleasant taste.
- Conventional manufacturing equipment.

- Cost effective.
- Good chemical stability as conventional oral solid dosage form.
- Convenience of administration and accurate dosing as compared to liquid formulations.
- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action.
- Pre-gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
- Beneficial in case such as motion sickness, suede-episodes of allergic attack (or) coughing, where an ultra rapid onset of action required.
- Portable without fragility concern.
- Advantageous over liquid medication in terms of administration as well as.
- First pass metabolism is reduced, thus offering improved bioavailability and thus reduced dose and side effects.
- Offering improved safety.[8]

vii) Disadvantages of ODTs

- Orodispersible tablet is hygroscopic in nature so must be keep in dry place.
- Some time it possesses mouth feeling.
- ODT require special packaging for properly stabilization and safety of stable product.[9]

1.2 Superdisintegrants

Disintegrating agents are substances routinely included in the tablet formulations to aid in the break-up of the compacted mass into the primary particles to facilitate the dissolution or release of the active ingredients when it is put into a fluid environment. They endorse moisture penetration and dispersion of the tablet matrix. The major function of disintegrants is to oppose the efficiency of the tablet binder and physical forces that act under compression to structure the tablet. Recently new material termed as “superdisintegrants” have been developed to improve the disintegration processes.

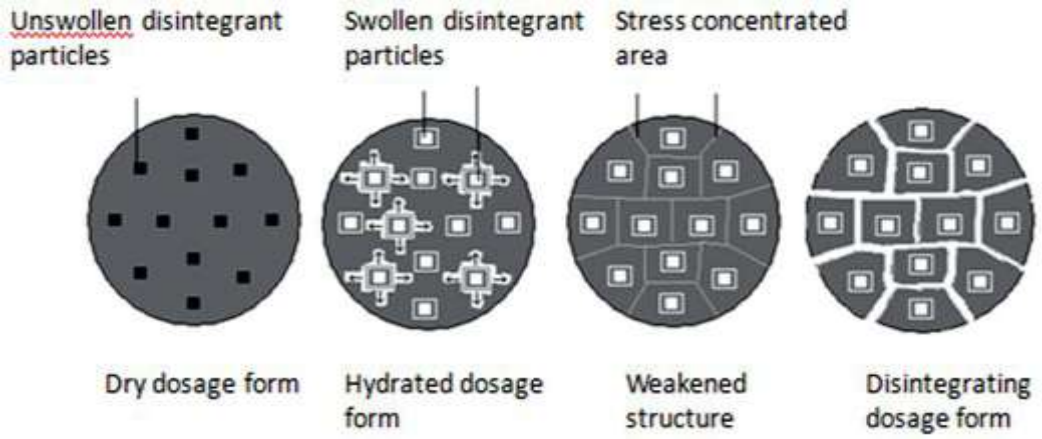


Figure 1.2 : Disintegration mechanism of superdisintegrant materials.

1.2.1 Selection of Superdisintegrants :-

Since supredisintegrant is used as an excipient in the tablet formulation, it has to meet certain criteria other than its swelling properties. The requirement placed on the tablet disintegrant should be clearly defined. The ideal disintegrant should have-

1) Poor solubility.
2) Poor gel formation.
3) Good hydration capacity.
4) Good moulding and flow properties.
5) No tendancy to form complexes with the drugs.
6) Good mouth feel.
7) It should also be compatible with the other excipients and have desirable tableting properties.

1.2.2 Advantages of Superdisintegrants

1) Effective in lower concentrations than starch.
2) Less effect on compressibility and flow ability.
3) More effective intragranularly.

1.2.3 Mechanism of Superdisintegrants

Superdisintegrants are used to improve the efficacy of solid dosage forms. This is achieved by various mechanisms. The mechanism by which the tablets are broken into small pieces and then produces a homogeneous suspension is based on :

1) Swelling

2) Porosity and capillary action (wicking)
3) Heat of wetting
4) Chemical reaction (Acid-Base reaction)
5) Particle repulsive forces
6) Deformation recovery
7) Enzymatic reaction

1) Swelling

Swelling is probably the most widely accepted mechanism of action for tablet disintegrants. Particles of disintegrant swell on coming in contact with suitable medium and a swelling force develop which leads to break-up of the matrix. 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.

2) Porosity and capillary action (Wicking)

Effective disintegrants that do not swell are believed to impart their disintegrating action through porosity and capillary action. Tablet porosity provides pathways for penetration of fluid into tablets. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replace the air adsorbed on the particles, which weakens the inter molecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug / excipient and on tableting conditions. For these type of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

Figure 1.3 :Disintegration of tablets by swelling and wicking mechanism.

3) Heat of wetting

When disintegrants with exothermic properties get wetted, localised stess is created due to capillary air expansion which aids in disintegration of tablet. This explanation, however, is

limited to only a few types of disintegrants and can not describe the action of most modern disintegrating agents.

4) Chemical reaction (Acid-Base Reaction)

The tablet is quickly broken apart by internal liberation of co_2 in water due to interaction between tartaric acid and citric acid (acids) with alkali metal carbonates or bicarbonates (bases) in presence of water. The tablet disintegrates due to generation of pressure within the tablet. Due to lberation of co_2 gas, the dissolution of active pharmaceutical ingredients in water as well as taste masking effect is enhanced. As these disintegrants are highly sensitive to small changes in humidity level and temprature, strict control of environment is requiredduring preparation of the tablets. The effervescent blend is either added immediately prior to compression or can be added in two separate fraction of formulation.

5) Particle repulsive forces

This is another mechanism of disintegration that attempts to explain the swelling of tablet made with non-swellable disintegrants. According to Guyot-Hermann's particle-particle repulsion theory, water penetrates into tablet through hydrophilic pores and a contineous starch network is created that can convey water from one particle to the next, imparting a significant hydrostatic pressure. The water then penetrates between starch grains because of its affinity for starch surface, there by breaking hydrogen bonds and other forces holding the tablet together. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it.

6) Deformation recovery

Deformation recovery theory implies that the shape of disintegrant particles is distorted during compression and the particles return to their pre-compression shape upon wetting, there by this increase in size of the deformed particles causing the tablet to break apart. Such a phenomenon may be an important aspect of the mechanism of actio of disintegrants such as corspovidone and starch that exhibit little or no swelling.

Water is drawn into the pores particles repel each other the resulting electrical force.

Particles swells to pre-compression size and break up the matrix of the becaues of tablet.

Figure 1.4 : Disintegration of tablets by repulsion and deformation mechanism.

7) By enzymatic reaction

Enzymes present in the body also act as disintegrants. These enzymes dearth the binding action of binder and helps in disintegration. Due to swelling, pressure is exerted in the outer direction that causes the tablet to burst or the accelerated absorption of water leads to an enormous increase in the volume of granules to promote disintegration.

Table No. 1.1 : Disintegrating Enzymes

Enzyme	Binder
Amylase	Starch
Protease	Gelatin
Cellulase	Cellulose and its derivatives
Invertase	Sucrose

1.3 Various technologies used in the manufacture of ODT

The performance of ODT depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approches to develop ODT include maximising the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water soluble exipients in the formulation. Following technologies have been used to prepare ODT-

1. Freeze-Drying or Lyophilization.
2. Tablet Moulding.
3. Spray Drying.
4. Sublimation.
5. Direct Compression.
6. Mass-Extrusion.

1) Freeze-Drying or Lyophilization

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solusion of a carrier/polymer. The mixture is dosed by weight and poured in the wells of the preformed blister packs. The trays holding the blister packs are passed through the liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in the refrigerated cabinets to continue freeze drying. After freeze drying the aluminium foil backing is applied on a blister sealing machine. Finally the blisters are packged and shipped. The major disadvantages of lyophilization technique are that it is expensive and time consuming; fragility makes conventional packgaing unsuitable for these products and poor stability under stressed conditions.

2) Tablet Moulding

The preparation of ODT using moulding technology employs water soluble ingredients so that the tablet dissolves completely and rapidly. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. Moulding process is of two type's i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydroalcoholic solcent follwoed by compression at low pressures in moulded plates to form a wetted mass (compression moulding). The solvent is than removed by air drying. The tablets manufactured in this manner are iess compact than compressed tablets and posses a porous structure that hastens dissolution. The heat moulding process involves preparation of a suspension that contains a drug, agar and sugar (e.g.mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temprature to form a jelly and drying at 30^0 under vaccum. The mechanical strength of molded tablets is a matter of great concern.Binding agents, which increase the mechanical strength of the tablets, need to be

incorporated. Taste masking is an added problem to this technology. To overcome this, Van Scoik incorporated taste masked drug particles. The taste masked drug particles were prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophilization technique, talets produced the by molding technique are easier to scale up for industrial manufacture. Masaki uses an agar solution as a binding agent and a blister packaging as well as a mold to prepare an intra buccally fast disintegrating tablet.

3) Spray Drying

Spray drying is used in pharmaceutical industries to produce highly porous powdres. The pocessing solvents is evaporated rapidly by spray drying, which renders the product highly porous and thus can be used in manufacturing ODT. In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or cross carmellose or crospovidone are used as superdisintegrants. Tablets manufactured form the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. Allen and wang have reported this technique for preparing fast dissolving tablets. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like sodium starch glycolate and crosscarmellose sodium and acidic ingredients (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

4) Sublimation

This technique is based on the use of volatile ingredients (e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane etc.) to other tablet excipients and the mixture is then compressed into tablets. Entrapped volatile material is then removed via sublimation, which leads to formation of a porous structure. These compressed tablets which have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva. Several solvents like cyclohexane, benzene etc. can also be used as pore forming agents. Orodispersible tablets with highly porous structure and good mechanical strength have been developed by this method.

Koizumi et al. prepared highly porous compressed tablets. They used mannitol as a tablet matrix material while camphor as subliming agent. Camphor was removed by subliming in vaccume at 80^0C for 30 minutes to develop pores in the tablets.

Makino et al. described a method of producing a fast dissolving tablet using water as a pore forming material. They used a mixture containing active ingredient and carbohydrates (glucose, mannitol, xylitol etc) which then moistened with water (1-3%w/w) and compressed into tablets. Then water was removed, yielding highly porous tablet.

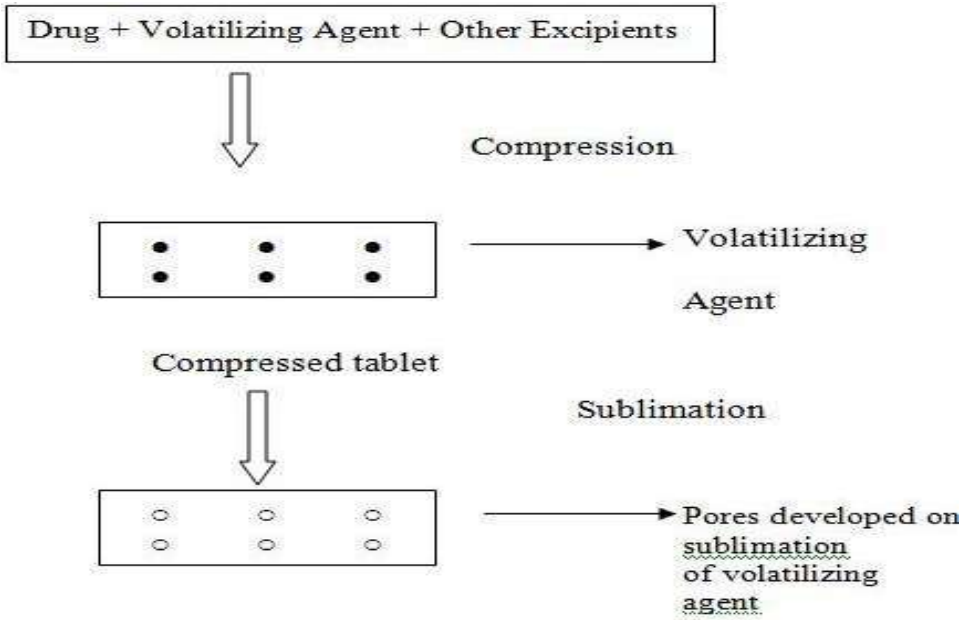


Figure 1.5 : Steps involved in sublimation technique

5) Direct Compression

It is the easiest way to manufacture tablets. Conventional equipments, commonly available excipients and limitated 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 method. This technique can now be applied to fast dissoliving tablets because of the availability of improved tablet excipients, especially tablet disintegrants and sugar based excipients. Addition of disintegrants in fast dissolving tablets, leads to quick disintegration of tablets and hence improves dissolution. In many fast dissolving tablet technologies based on direct compression, the disintegrants principally affect the rate of disintegration and hence the dissolution. The introduction superdisintegrants and a better understanding of their properties have increased the popularity of this technology. Tablet disintegration time can be optimised by concentrating the disintegrants. Below critical concentration, tablet disintegration time is inversly proportional to disintegrants concentration. Above the critical concentration level, however, disintegration time remains approximately constant or even increases.

Microcristalline cellulose, cross linked carboxymethyl cellulose sodium, cross linked polyvinyl pyrrolidone and partially substituted hydroxypropyl cellulose, through water insoluble, absorb water and swell due to capillary action and are considered as effective disintegrants in the preparation of fast dissolving tablets. Bi et al. and Watanbe et al. used microcristalline cellulose (MCC) and low substituted hydroxypropyl cellulose (HPC) to manufacture rpidly disintegrating tablets. The ratios of MCC to HPC varied from 8:2 to 9:1. Ito and sugihan investigated applying agar powder as a disintegrants because the powder absorbs water and swell considerably with forming a gel at physiological tempratures

Fast disintegration of tablets can also be achived by incarporating effervescent disintegrating agents, which generates carbon dioxide. This phenomenon also resulted in partial taste masking of unacceptable taste of the drug. The major drawback of effervescent excipients is their hygroscopicity (i.e. the ability to absorb atmospheric moisture). Hence, their manufacture requires control of humidity conditions and protection of the final product. This is reflected by the overall cost of the product.

Another approach to fast dissolving tablets or orodispersible tablets by direct compression is the use of sugar based excipients (e.g. dextrose, fructose, isomalt, maltitok, maltose, mannitol, sorbitol, starch hydrolyse, polydextrose and xylitol), which display high aqueous solubility and sweetness, and hence, impart taste masking and pleasing mouthfeel.

Figure 1.6 : steps involved in direct compression technique

6) Mass Extrusion

In this technique, a blend of active drug and other ingredients is softened using solvent mixture of water soluble polyethylene glycol, using methanol and then softened mass is extruded through the extruder or syringe to get a cylinder of product, which is finally cut into even segments with the help of heated blades to get tablets. The dried cylinder can be used to coat the granules of bitter tasting drugs and thereby masked their bitter taste.

1.4 Patented technologies for oral dispersible tablets

The various technologies are developed for the preparation of orodispersible drug delivery system that are –

1. Zydis technology.
2. Durasolv technology.
3. Orasolv technology.
4. Flash dose technology.
5. Wowtab technology.
6. Flashtab technology.
7. Oraquick technology.

1) Zydis technology

Zydis, the best known of the fast dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. A zydis tablet is produced by lyophilizing or freeze drying the drug in a matrix usually consisting of gelatin (Gregory et al, 1981 and Mizumoto et al, 1996). The product tablet is very lightweight and fragile and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The zydis product is made to dissolve on the tongue in 2 to 3 seconds. The zydis formulation is also self preserving because the final water concentration in a freeze dried product is too low to allow for microbial growth. A major claim of zydis product is increased bioavailability compared to traditional tablets. Because of its dispersion and dissolution in saliva while still in the oral cavity, there can be a substantial amount of pregastric absorption from this formulation.

2) Durasolv technology

Durasolv is cima's second generation fast dissolving / disintegrating tablet formulation. Produced in a fashion similar to orasolv, durasolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. Durasolv tablets are prepared by using conventional tableting equipment and have good rigidity. The durasolv product is thus produced in a faster and more cost effective manner. Durasolv is so durable that it can be packaged in traditional blister packing, pouches or vials. (Mizumoto et al, 1996 and Mizumoto et al, 2003). One disadvantages of durasolv is that the technology is not compatible

with larger doses of active ingredients, because the formulation is subjected to such high pressure on compaction.

3) Orasolv technology

Orasolv was cima's first dissolving dosage form. The orasolv technology unlike zydis dispers in saliva with the aid of almost imperceptile effervescence. The orasolv technology is best described as a fast dissolving tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste masking associated with the orasolv formulation is twofold. The unpleasant flavour of a drug is not merely counteracted by sweetners or flavour; both coating the drug powder and effervescence are means of taste masking in orasolv. This technology is frequently used to develop over the counter formulation, (wehling et al, 1996 and 1993).

4) Flash dose technology

A fuize technology has three oral drug delivery systems that are related to fast disslution. The first two generation of quick dissolving tablets, soft chew and ez chew, require some chewing. However, these paved the way for fuize's most recent development, flash dose technology. The flash dose technology utilizes a unique spinning mechanism to produce floss- like crystalline structure; much like cotton candy. This crystalline sugar can then incorporate the active and be compressed into the tablet. This procedure has been patented by fuize and is known as shearform. The final product has a very high surface area for dissolution. It disperses and dissolves quickly once placed onto the tongue.

5) Wowtab technology

The wowtab technology has been on the japanese market for a number of years. Wowtab technology is patented by Yamanouchi pharmaceutical co. The wow in wowtab signifies the tablet is to be given "with out water". It has just recently been introduced into the US. The wowtab technology utilizes sugar and sugar – like (e.g. mannitol) excipients. This process uses a combination of low mouldability saccharides (rapid dissolution) and hihg mouldability saccharides (good binding property) the two type of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate due to its significants hardness, the wowtab formulation is a bit more stable to the environment than the zydis and orasolv (Mizumoto et al, 1996 and 2003).

6) Flashtab technology

Prographarm laboratories have patented the flashtab technology. This technology involves the preparation of rapidly disintegrating tablet which consists of an active ingredient in the form of microcrystal. Drug microgranules may be prepared by using the conventional techniques like coacervation, extrusion- spheronization, simple pan coatin methods and microencapsulation (cousin et al, 1995). The microcrystals of micogranules of the active ingredient are added to the granulated mixture of excipients prepared by wet or dry granulation and compressed into tablets.

7) Oraquick technology

The oraquick fast dissolving / disintegrating tablet formulation utilizes a patented taste masking technology. Kv pharmaceutical claims its microsphere technology, known as micromask, has a superior mouthful 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 / disintegrating technologies makes oraquick appropriate for heat sensitive sterilization.

Patented technology	**Basis of technology**	**Technology developed by company**	**Active ingredient**
Zydis	Lyophilization	R.p scherer , inc	Loratidine
Durasolv	Direct compression	Cima lab, inc	Zolmitriptan
Orasolv	Direct compression	Cima lab, inc	Zolmitriptan
Flashdose	Cotton candy processs	Fuize technology ltd.	Tramadol
Flashtab	Direct compression	Ethypharm	Ibuprofen
Wowtab	Direct compression	Yamanouchi pharma yech. Inc.	Famotidine
Oraquick	Micromask taste masking	Kv pharm Co. inc.	Hyoscyamine sulphate mdt

Table no. 1.2 : Patented technologies based branded products

2. REVIEW OF LITERATURE

Nitin Mohire *et al*., (2009) Metronidazole orodispersible tablets have been prepared by three different techniques of taste masking and three different disintegrating agents' viz. sodium starch glycolate (SSG), Bamboomanna (BB), Chitosan (CHN) and combination thereof. Metronidazole is a choice of drug in most of the oro-dental problems. The metallic taste and large dose size limits its use in dentistry. Pleasantly flavored and taste masked orodispersible metronidazole in tablet form helps to overcome these drawbacks and thereby increases patient compliance. The combination of SSG:BB and SSG:CHN in the proportion of 1:1 and have been found most effective in disintegrant property. Bamboomanna used alone did not show superdisintegrant property. However it when it was in combination with other established superdisintegrants, showed significant increase in disintegrant property. Complex formation of drug with glycerrhiza glabra extract showed good result of taste masking.

B. G. Shiyani *et al*., (2009) Compare the disintegrants efficiency of the three superdisintegrants (Ac-De-Sol, Polyplasdone XL and Explotab) and also to compare the disintegrant properties and disintegrant efficiency of agar (AG) and gellan gum (GG) with treated agar (TAG) and treated gellan gum (TGG) by formulating Metoclopramide HCL immediate release tablets by direct compression method. Disintegration efficiency of powder disintegrants compared by swelling and hydration capacity of disintegrants. While efficiency of disintegrants in tablets compared by various test like disintegration time, dissolution test, wetting time and maximal water uptake study of metoclopramide HCL immediate release tablets. The rapid disintegration observed for the TAG and TGG containing tablets due to high porous structure of treated form of disintegrants which confirmed by photomicroscope study.

Bhunia Biswajit *et al*., (2011) Have prepared orodispersible tablets of Amlodipine Besilate by using three different disintegrants like cross povidone (Polyplasdone XL 10), Sodium starch glycolate (SSG), Cross carmellose sodium (Ac-De-Sol). Two method of preparation are used to formulate the orodispersible tablet of amlodipine besilate like direct compression and sublimation method. And compare the dissolution profile of drug in two techniques. Comparison of two methods by using different superdisintegrants formulate the orodispersible tablet. Sublimation method showed good result as compare to direct compression.

Sutradhar *et al*., (2012) Prepared taste masked oral dispersible tablets of Domperidone by sublimation method and investigate the effects of superdisintegrants (Kollidone CL) on the disintegration time as well as the percent release of a model drug from Kollidone 30, Ispaghula husk, and Guar Gum based formulation. Domperidone, an anti-emetic drug was taken as the model drug for the study. A high porosity was achieved using camphor as volatilizing agent which allowed easy penetration of dissolution media followed by rapid release of the drug. The granules and tablets were evaluated and found to be acceptable according to standard limits. In-vitro release studies were performed using USP apparatus –II (paddle method) in 900 ml of 0.1N HCL (pH 1.2) at 50 rpm. The release mechanisms were explored and explained with different kinetic model.

Honey Goel *et al*., (2008) Formulate fast disintegrating tablets (FDTs) for nausea and vomiting using aminoacetic acid, carmellose, and sodium alginate with enough mechanical strength. Ondansteron HCL (water soluble) or domperidone (water insoluble) drug were added to FDTs and their disintegration behaviour was evaluated. Placket Burman Screening Design was used to screen the dependent and independent variables for the drugs. Ondansteron HCL is soluble in water (1g in 3 ml) whereas dompridone is insoluble in water. Therefore, Ondansteron HCL and domperidone with different solubility profiles were selected for formulating FDTs containing aminoacetic acid, carmellose and sodium alginate. Thus, FDTs of these drugs will be helpful in rapid drug delivery, even without the intake of water, thereby alleviating nausea and vomiting sensation at an early stage.

Anilkumar J. Shinde *et al*., (2009) Developed fast dissolving tablet of Cephalexin. A combination of superdisintegrants i. e. Sodium starch glycolate(SSG) and cross carmellose sodium (CS) were used along with camphor as a subliming material. An optimized concentration of camphor was added to aid the porosity of the tablet. The addition of flavor and sweetener impacts pleasant taste to the formulation. Full factorial design was applied to investigate the combined effect of two formulation variables amounts of SSG and CS. Infrared (IR) spectroscopy was performed to identify the physicochemical interaction between drug and polymer. IR spectroscopy showed that there is no interaction of drug with polymer. Alcoholic solution of polyvinyl pyrrolidone k-30 (PVP) was used to preparation of granules of physical mixture of drug, excipients and camphor. The granules were compressed into tablet using flat face single punch tablet machine. Camphor was sublimed from the tablet by exposing the tablet

to vacuum drier at 60^0 for 12 hrs. all the formulations were evaluated for their characteristics such as average weight, hardness, wetting time, friability, content uniformity, disintegration time and dissolution rate.

Bhupendra G. Prajapati *et al.*, (2010) Developed fast dissolving tablets of Domperidone by wet granulation method. Sodium Starch Glycolate, was taken as superdisintegrant and starch paste as a binder for the study. The domperidone (anti-emetic) is taken as the model drug for the study an wet granulation as a method of preparation of the fast dissolving tablet. The disintegrant may be incorporated during the wet granulation process as extra granular incorporation. Full factorial design was applied to investigate the combine effect of 2 formulation variables : Sperdisintegrants and starch paste. The concentration of superdisintegrants and concentration of starch paste were taken as independent variables, X_1 and X_2 respectively. And there effect of Disintegration time, wetting time Q_{30} and friability were investigated which are taken as dependent parameters. And also studied the efficiency of different sperdisintegrant for the wet granulation.

Kulkarni *et al.*, (2010) Developed fast dissolving tablets of Meloxicam by employing vacuum drying technique utilizing single and multi-volatile components. Analysis revealed that, formulation containing camphor and menthol as subliming agents yielded the best result in term of dissolution rate (M7). Result also revealed that, all the formulations had enough mechanical strength, good mouth feel and lesser wetting and disintegration time. Stability study indicates that upon storage disintegration and wetting time of tablets decreased significantly without losing their mechanical strength.

Basawaraj S. Patil *et al.*, (2011) Prepared fast dissolving tablets (FDTs) of Granisteron HCL by sublimation technique. Granisteron HCL is a selective 5-HT_3 receptar antagonist, which may have beneficial therapeutic effects in the treatment of vomiting and nausea resulting from cancer therapy. The prepared formulation were evaluated for pre-compressional and post-compressional parameters. The compatibility of drug with other ingredients was checked by FTIR studies , the result revealed that there was no interaction between drug and other excipients. The disintegration time of the tablets decreased significantly with increase in the concentration of subliming agent.

Reeta *et al.*, (2012) Review onrecent advancement in orally disintegrating preparations. Oral route is the most convenient route for the drug administration due to the highest component

of compliance mainly the pediatrics and geriatrics. It is regarded as the most economical and safest method of drug delivery. Formulation of a orally disintegrating dosage form is beneficial for patients suffering from motion sickness, repeated emesis, mental disorder and dysphasia because they cannot swallow large quantity of water and it is easy to administer. The unique property of orally disintegrating dosage form is that they are readily disintegrating and dissolve in saliva and avoids requirement of water which is the major benefit over conventional dosage form.

Rakesh Pahwa *et al*., (2010) studies of Orally Disintegrating Tablets - Friendly to Pediatrics and Geriatrics to obviate the problem of dysphagia and to improve patient compliance, ODTs have gained considerable attention as preferred alternatives to conventional tablet and capsule formulations these techniques render the disintegration of tablet rapidly and dissolve in mouth without chewing or additional water intake.

Ashok Kumar *et al*., (2009) Developed orally disintegrating tablet of Terbutaline Sulphate for asthma by wet granulation technique. Asthma is defined simply as reversible airway obstruction characterized by attacks of breathlessness, tight chest, wheezing and coughing. Granules containing drug, diluent, subliming agents, aspartame were prepared by wet granulation technique using alcoholic solution of polyvinyl pyrrolidone K25 (10% w/v) as a binder. The dried granules were then mixed with lubricant magnesium stearate and glidant talc and compressed into tablets. Subliming agents was sublimed from the tablet by exposing it to drying at 60 ^{0}C. the tablets were evaluated for percentage friability, hardness, weight variation, disintegration time and percentage drug content. Menthol containing tablets resulted in rapid disintegration as compared with tablets containing ammonium bicarbonate and camphor.

Pooja *et al*., (2010) Prepared and evaluate orodispersible tablets of Levocetrizine HCL to disintegrate in mouth (without the aid of water), to enhance the clinical effects and bioavailability through pre-gastric absorption. Orodispersible tablets were formulated using two technique, that is direct compression (containing superdisintegrant) and effervescent technique. Various formulation batches B_1-B_9 were prepared; all ingredients were passed through sieve no 60, mixed and compressed. The compression of orodispersible tablets by direct compression using suuperdisintegrant, as compared to effervescent technique significantly affects the drug release rate and disintegration time.

Avani R. Gosai *et al.*, (2008) Developed orodispersible tablets of Ondansetron HCL, because of its application in emesis condition, fast onset of action and avoidance of water is highly desirable. Tablets were prepared by direct compression using sodium starch glycolate and croscarmellose as superdisintegrants, as the combination of these two agents gives better disintegration of the tablet. Microcrystalline cellulose was used as diluent and mannitol, mint flavor, sodium saccharine to enhance the organoleptic properties of tablets. The tablets were evaluated for weight variation, mechanical strength, in-vitro disintegration time, in-vivo disintegration time, wetting time and drug release characteristics. Hardness and friability data indicated good mechanical strength of tablets. Dissolution study revealed faster release rate of Ondansetron HCL from the tablets as compared to pure drug and marketed conventional tablet formulation of Ondansetron hydrochloride.

Radke R.S. *et al.*, (2009) Have been prepared Orodispersible tablets of baclofen using various concentrations of superdisintegrant agents like Ac-Di-Sol, crospovidone, sodium starch glycolate by direct compression method. Nine formulations having superdisintegrants at different concentration levels were prepared. These tablets were evaluated for drug content, weight variation, friability, hardness, wetting time and in-vitro disintegration time. The superdisintegrants addition technique is a useful method for preparing orodispersible tablets by direct compression method.

M. Kruthi *et al.*, (2012) Developed taste masked orodispersible tablets of Drotaverine HCL. Taste masking is means of masking the bitter taste of drug for the improvement of palatability of the drug. Drotaverine HCL drug is a highly potent spasmolytic agent. These drug is capable for relieving the spasms of various organs, but it is a very bitter drug and slightly soluble in water. Formulate and evaluate orodispersible tablets of Drotaverine HCL, highly bitter drug, in which its bitter taste can be masked. Solid dispersion technique such as melt granulation and kneading method are used to mask the taste of the drug. The carriers like Glyceryl Behenate (Compritol 888 ATO), Glyceryl pamito sterate (precirol ATO 5) and sucrose fatty acid ester (D 1811) are used to mask the bitterness of the drug by solid dispersion technique and these dispersion will be formulated further using super disintegrates.

Sharma Deepak *et al.*, (2012) Review on taste masking technologies for the drug. Acceptability of any dosage form are mainly depends over its taste i.e. mouth feel. Drug molecule interacts with taste receptor on the tongue to give bitter, sweet or salty taste sensation,

when they dissolve in saliva. In market, there are numbers of pharmaceutical preparations available in which actives in bitter taste. The improved palatability in these products has prompted the development of numerous forfulations, which improved performance and acceptability. These techniques are not only mask the bitter taste of drug but also enhance the bioavailability and performance of drug dosage form. It includes adding sugars, flavors, sweeteners, use of lipoproteins, numbing taste buds, granulation, use of adsorbates, coating of drug, microencapsulation, multiple emulsion, viscosity modifier, vesicles and liposomes, prodrug and salt formation, inclusion and molecular complex, solid dispersion and Ion Exchange Resins (IERs) which have been tried by the formulators to mask the unpleasant taste of the bitter drugs.

Tejash Serasiya *et al.*, (2009) Design and optimization of orodispersible tablets of Pheniramine maleate were prepared by direct compression method using various superdisintegrants like crospovidone, croscarmellose, sodium starch glycolate, low substituted hydroxypropyl cellulose, pregelatinized starch. The prepared tablets were evaluated for uniformity of weight, hardness, friability, wetting time in-vitro disintegration time, in-vitro dispersion time and drug release study. The concentration of superdisintegrants had an effect on disintegration time and in-vitro drug dissolution whereas hardness and friability of resulting tablets were founds to be independent of disintegrant concentration. The two formulations, one containing 10% of crospovidone and second containing 10% of croscarmellose sodium were found to give the best result.

P.V. Swamy *et al.*, (2010) Designed cost effective orodispersible tablets of Diethylcarbamazine Citrate. The Diethylcarbamazine Citrate an anthelmintic for improving patients compliance, especially, those of pediatric and geriatric categories with difficulty in swallowing, with the prime objective of arriving at cost effective product by effervescent method. In the effervescent method mixture of sodium bicarbonate and tartaric acid along with treated agar were used as disintegrants.

Ramesh veeraveni *et al.*, (2011) Developed orodispersible tablets of Valdecoxib, to disintegrate rapidly in the oral cavity upon contact with saliva by formation of easy to swallow suspension without the aid of water were prepared. Mass extrusion technique and sublimation methods were employed in designing of orodispersible formulations. In the study, bitter taste of valdecoxib was masked by using previously optimized ratio of Valdecoxib : Eudragit E-100. Orodispersible tablets were developed using the prepared taste masking granules and a mixture

of excipients consisting of MCC and L-HPC by mass extrusion technique. Sublimation method also employed to formulate orodispersible tablets using camphor as subliming material and water soluble materials like mannitol.

Paramita Dey *et al.*, (2012) Review on orodispersible tablets, a new trend in drug delivery. The most common and preferred route of drug administration is through the oral route. Orodispersible tablets are gaining importance among novel oral drug delivery system as they have improved patients compliance and have some additional advantages compared to other oral formulation. They are also solid unit dosage forms, which disintegrate in the mouth within a minute in the presence of saliva due to super disintegrants in the formulation. Thus this type drug delivery helps a proper peroral administration in pediatric and geriatric population where swallowing is a matter of trouble.

Monica R P Rao *et al.*, (2010) Designed and developed immediate release tablets of Metoclopramide HCL using simplex centroid mixture design. Metoclopramide HCL is mainly used as an anti-emetic agent in the cancer chemotherapy. Immediate release tablet formulations is based on the use of super disintegrants separately or in combination. Seven formulations were prepared by using simplex centroid mixture design where sodium starch glycolate (X_1), cross carmellose sodium (X_2), pregelatinised starch (X_3) were selected as independent variables and dependent variables were disintegration time (Y_1), and release at 15 minutes (Y_2). Optimum formulation were selected by grid search method. X_1, X_2 andX_3 when used individually gave satisfactory results but when used in combination gave better results. The results showed a good relationship between the experimental and predicted values.

Rajesh Roshan Rai *et al.*, (2012) Fast dissolving tablets a novel approach to drug delivery. Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as thesafest, most convenient and most economical method of the drug delivery having the highest patient compliance. Yet, dysphagia is a common problem encountered in all age groups in concern to solid dosage forms. To overcome such problems, certain innovative drug delivery systems, like fast dissolving tablets (FDT) have been developed. Fast dissolving tablets have received ever- increasing demand during the last decade and the field has become a rapidly growing area in the pharmaceutical industry.

Supriya Shidhaye *et al.*, (2009) Developed novel melt granulation using sugars for Metoclopramide HCL orally disintegrating tablet. The taste masking of Metoclopramide HCL

was carried out by forming complex with indion 244 using batch process. Further this complex was formulated into ODT using melt granulation technique. A blend of low melting and high melting sugar was used in this technique.

Mathew Ebin P Sovichan *et al.*, (2012) Developed Amoxicillin Trihydrate dispersible tablets in a low production value, using cheap amoxicillin trihydrate raw materials available in the market, with direct compression or wet granulation. Amoxicillin trihydrate is a semisynthetic antibiotic, an analogue of ampicillin with a broad spectrum of bactericidal activity against gram positive and gram negative organism. Amoxicillin trihydrate dispersible tablets was manufactured with the different disintegrants such as maize starch, crospovidone, croscarmellose, sodium starch glycolate. And then tablets are evaluate, the wet granulation was excluded from the formulation due to its high cost of production, direct compression was selected due to its low cost and easy of production.

Amrutkar *et al.*, (2010) Designed chewable dispersible tablet of Lamotrigine by melt granulation. Lamotrigine, an antiepileptic drug (AED) of the phenyltriazine class, is chemically unrelated to existing antiepileptic drugs. But it is a bitter drug and slightly soluble in water. Thus, in the work under taken, an attempt was made to mask the taste and to formulate into a chewable dispersible tablet by complexation with precirol ATO-05 ratio of 1:2, 1:1.5, 1:1, 1:0.5. the prepared tablets were then evaluated for general appearance, content uniformity, hardness, friability, taste evaluation, mouth feel, in-vitro disintegration time and in-vitro dissolution studies. Tablets with preciol ATO-05 have shown good disintegrating features, also, the dispersion not showing any bitter taste.

Srinivasa Rao *et al.*, (2011) Developed fast dissolving tablets of taste masked Ondansetron HCL. The Ondansetron HCL is a selective inhibitor of type-3 serotonium (5-HT 3) receptor, is an antiemetic. It is an intensely bitter in taste. In this investigation an attempt has been made to prepare bitter less fast dissolving tablet of Ondansetron HCL using Eudragit E 100 as a taste masking agent. Mass extrusion was the technique used for preparing the taste masked granules. Drug polymer complexes were tested for drug content, in-vitro taste evaluation in simulated salivery fluid (SSF) of pH 6.2 and drug excipient interaction (IR Spectroscopy). Complex that did not release drug in SSF was considered taste masked and selected for formulation of fast dissolving tablets.

Adel M. Aly *et al.*, (2011) Prepared and evaluate rapidly disintegrating tablets of Glimepiride by direct compression, and also evaluate Pharmaburst as a newly introduced diluent for this type of tablets, either alone or in combination with other well-known tablet excipients. Orange flavor was the most preferred flavor for the prepared rapidly disintegrating tablets containing pharmaburst as a single diluent. The prepared Glimepiride RDT were found to have faster onset of action than the conventional Glimepiride tablets.

Rajesh M. *et al.*, (2012) Developed taste masked Cefuroxime Axetil tablet by direct compression method. This study was aimed to formulate dispersible tablets in pediatric strength and to overcome the drawbacks of conventional Cefuroxime Axetil tablets such as swallowing difficulty and bitter taste. Taste masking was done by adopting four taste masking methods including Addition of flavors and sweetener, Granulation with stearic acid by slugging process, polymer coating method and inclusion complexation with β-cyclodextrin. Seven formulations were prepared by above four taste masking methods and various pre-compression parameters like angle of repose, bulk density, tapped density, compressibility index, hausners ratio and post compression parameters like appearance, thickness, hardness, weight variation, friability, disintegration time, drug content, wetting time, water absorption ratio, fineness of dispersion, in-vitro drug release and taste evaluation were studied. The formulation prepared by using inclusion complexation taste masking method was considered as optimized formulation.

3. AIM AND OBJECTIVE

NEED AND SCOPE OF THE STUDY:

Tablets and capsules are most papular solid dosage forms. However, many people face difficulty in swallowing tablets and hard gelatin capsules. This difficulty in swallowing is called as dysphasia. This problem has been encountered in all groups of patients, but especially with pediatric and geriatric populations. Thus, these conventional dosage forms result in high incidence of noncompliance and ineffective therapy with respect to swallowing specially in the case of pediatric, geriatric, or any mentally retarded persons. An Orodispersible tablet of metoclopramide hydrochloride is developed by direct compression techniques which disintegrate in oral cavity without the need of water within a matter of seconds when placed upon the tongue. "Orodispersible tablet are not only indicated for people who have swallowing difficulties, but also ideal for active people." Hence, to resolve these problems the present work is aimed to develop and evaluate orodispersible tablets of metoclopramide hydrochloride using different superdisintegrants.

The aim of study is to develop and evaluate the orodispersible tablets of metoclopramide Hcl.

- To improve patient compliance.
- To develop cost effective product.
- To enhanced the onset of action of metoclopramide Hcl.
- To enhance the safety and efficacy of metoclopramide Hcl.

The main aim of the present study is to develop orodispersible tablets of metoclopramide hydrochloride (an antiemetic) for improving patient compliance, especially those of pediatric and geriatric categories with difficulty in swallowing, nausea and vomiting with prime objective of arriving at cost effective product, by direct compression techniques.

The objective is to increase the release rate of dissolution by increase the release rate of drug from the solid oral dosage form by using different superdisintegrants.

In the present work, metoclopramide hydrochloride is chosen as a model drug. Metoclopramide hydrochloride is a prokinetic drugs. It is chemically 4 - amino - 5 - chloro - N - (2 - (diethylamino) ethyl) - 2 - methoxy benzamide monohydrochloride monohydrate. It is an

effective antiemetic. Metoclopramide hydrochloride is rapidly absorbed from orally its oral bioavailability is 80% and half-life is 5-6 hrs. Metoclopramide hydrochloride is a dopamine antagonist, it blocks D_2 receptors in the CTZ. And shows the antiemetic action. On high dose it shows a 5-HT_3 receptor antagonist. It is also used to treat gastroesophageal reflux disease (GERD). The dose of metoclopramide hydrochloride is 5 to 10mg for adults and 0.25 to 0.5mg for childrens t.i.d. orally.

The objective of present work is to mask the taste of metoclopramide hydrochloride by using flavours and sweetners. And to develop the orodispersible tablets by simple and cost effective methods. The scope of this orodispersible drug delivery system is suitable for patients who suffering from dysphasia, nausea and vomiting, bedridden. And in the present work we have find out the comparative dissolution and disintegration study between our tablet formulation of metoclopramide hydrochloride orodispersible tablet.

OBJECTIVES OF THE STUDY:

1. To prepare ODT of metoclopramide Hcl. by direct compression using different concentration of superdisintegrants like crospovidone (polyplasdone), croscarmellose sodium (Ac-Di-Sol), and sodium starch glycolate (explotab).
2. To evaluate the formulated tablets for various parameters, including stability study.
3. To develop a dosage form which gives more rapid onset of action compared to oral conventional dosage form to improve patient compliance.

4. PLAN OF WORK

1. Literature survey.

2. Procurement of drug,polymer and excipients.

3. Preformulation studies.

I) Identification and characterization of Metoclopramide Hcl.

- Melting point.
- Infrared absorption spectrophotometer.
- Ultra visible spectrophotometer.
- Identification test.
- Solubility.

II) Drug Excipient Interaction study by FTIR.

III) Development of standard calibration curve of Metoclopramide Hcl.

4. Formulation Design.

- Development of oro-dispersible tablet formulation using three different Superdisintegrating agent.
- Preparation of powder blend of drug and excipients.

5. Pre-compression assessment of powder blend.

- Angle of repose.
- Bulk density.
- Tapped density.
- Compressibility index.
- Hausner ratio.

6.Compression of powder blend into tablet by direct compression method.

7. Post compression assessment of oro-dispersible tablet.

- Hardness.
- Friability.
- Thickness.
- Weight variation.
- In-vitro dispersion time.
- Wetting time.
- Water absorption ratio.
- Disintegration time.
- Drug content.
- In-vitro dissolution.

8. Stability study.

9. Comparison of Best Formulation with all batches.

10. Result and discussion.

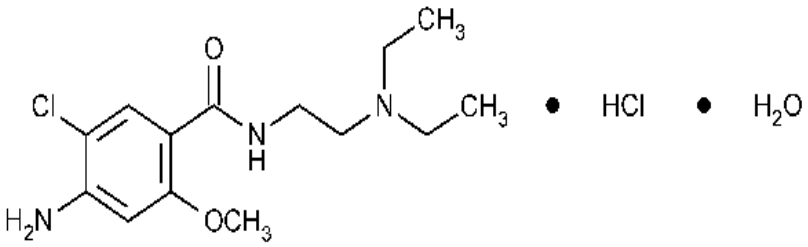
11. Summary and conclusion.

5. DRUG PROFILE

METOCLOPRAMIDE HYDROCHLORIDE

Molecular Formula :$C_{14}H_{22}ClN_3O_2.HCl.H_2O$

Chemical Structure :



IUPAC Name : 4-amino-5-chloro-N-[2-(diethylamino) ethyl]-2methoxybenzamide hydrochloride monohydrate.

Brand Name : Emetid, Imperan, Maxolon, Reclomide, Reglan.

Drug Category : Antiemetics,Dopamine Antagonists,Prokinetic Agents.

Molecular Weight : 354.3

State : solid

Melting Point : 182.5-184 ^{0}C

Description : A white or almost white, crystalline powder or crystals.

Solubility : Very soluble in water, freely soluble in alcohol, sparingly soluble in methylene chloride.

Indication : For the treatment of nausea and vomiting.

Dose : In adults 5-10 mg, in children 0.25-0.5 mg/kg tid. Orally.

Bioavailability : 80±15% (oral)

Protein Binding : 30%

Half Life : 5-6 hr

Absorption : Rapidly and well absorbed from orally

Biotransformation : Hepatic

Excretion : 70-85% renal, 2% faecal

Pharmacology :

Metoclopramide hydrochloride, although chemically related to procainamide, does not possess local anesthetic or antiarrhythmic properties. Metoclopramide hydrochloride is used to enhance GI motility, to treat diabetic gastroparesis, as an antinauseant, and to facilitate intubation of the small bowel during radiologic examination. Metoclopramide hydrochloride may be used to treat chemotherapy induced emesis.

Mechanism of Action :

Metoclopramide hydrochloride inhibits gastric smooth muscle relaxation produced by dopamine, therefore increasing cholinergic response of the gastrointestinal smooth muscle. It appears to bind to dopamine D_2 receptors where it is a receptor antagonist. The antiemetic action of metoclopramide hydrochloride is due to its antagonist activity at D_2 receptors in the chemoreceptor trigger zone (CTZ) in the central nervous system this action prevents nausea and vomiting triggered by most stimuli. It accelerates intestinal transit and gastric emptying by preventing relaxation of gastric body and increasing the phasic activity of antrum. Simultaneously, this action is accompanied by relaxation of the upper small intestine, resulting in an improved coordination between the body and antrum of the stomach and upper small intestine. Metoclopramide hydrochloride also decreases reflux into the esophagus by increasing the resting pressure of the lower esophageal sphincter.

Therapeutic Uses :

Therapeutic indication are used to treat nausea and vomiting, it is effective and popular drug for many types of vomiting. Gastrokinetic: to accelerate gastric emptying, Dyspepsia, Gastroesophageal reflux disease (GERD).

Adverse Effects :

Common adverse drug reactions arerestlessness, drowsiness, dizziness, fatigue, and focal dystonia. Rare but serious adverse drug reactions are agranulocytosis, tardive dyskinesia.

Contraindications :

Metoclopramide hydrochloride is contraindicated in phaeochromocytoma, It should be used with caution in parkinson's disease.

Drug Ineraction :

Drug	**Interaction**
Cyclosporine	Metoclopramide hydrochloride increases serum levels of cyclosporine.
Levodopa	Levodopa decreases the effect of metoclopramide hydrochloride.
Paliperidone	Metoclopramide hydrochloride may increase the risk of extrapyramidal side effects of paliperidone.
Tacrolimus	Metoclopramide hydrochloride may incerase the concentration of taccrolimus in the blood.
Venlafaxine	Possible serotoninergic syndrome with this combination.

Food Interaction : Food reduces availability, take 30 minutes before meals. Avoid alcohol.

Storage : Store protected from light and moisture.

6. EXCIPIENTS PROFILE

A) Croscarmellose sodium

Nonproprietary Name **:** USP-NF :Croscarmellose sodium.

Synonyms **:** Ac-Di-Sol, cross-linked carboxymethyl cellulose sodium,

Chemical Name **:** Cellulose, carboxymethyl ether, sodium salt, crosslinked.

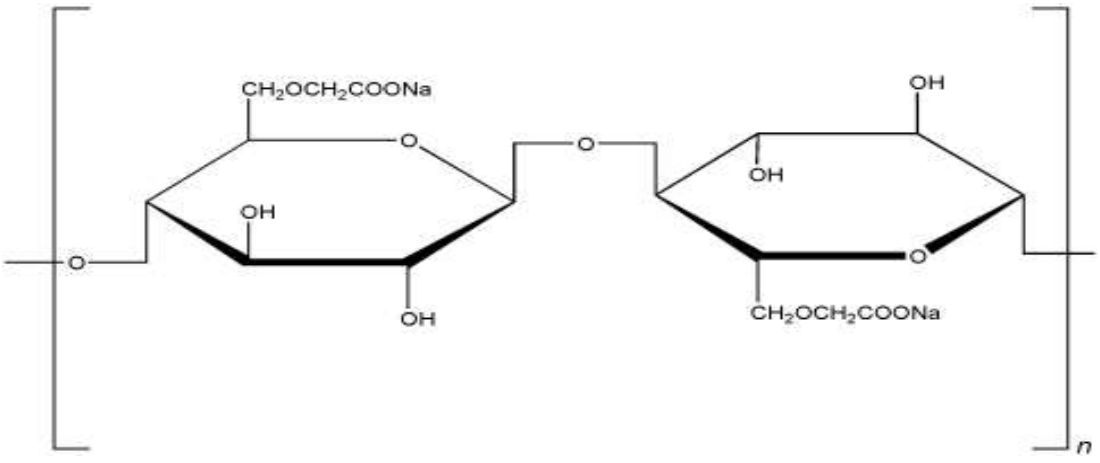
CAS RegestryNumber **:** 74811-65-7.

Molecular Weight **:** 90000-700000.

Functional Category **:** Tablet and capsule disintegrant.

Description : Croscarmellose sodium occurs as an odorless, white or grayis white powder.

Structural formula :



pH **:** 5.0-7.0 in aqueous dispersion.

Specific Surface Area : 0.81-0.83 m^2/g.

Solubility : Insoluble in water. Although croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. Practically insoluble in acetone and ethanol.

Application:

Croscarmellose sodium is used in oral pharmaceutical formulation as a disintegrant for capsules, tablets and granules.In tablet formulation, croscarmellose sodium may be used in both direct compression and wet granulation processes.Whenused in wet granulations, the croscarmellose sodium should beadded in both the wet and dry stages of the processes (intra and exatra granulary) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium atconcentrations up to 5% w/w may be used as tablet disintegrant, although normally 2% w/w is used in tablet prepared by direct compression and 3% w/w in tablet prepared by a wet granulation process.

Stability And Storage Condition:

Croscarmellos sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression,with croscarmellose sodium as a disintegrant, showed no significant difference in drug dissolution after storage at 30^0c for 14 months. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet granulation or direct compression process that contain hygroscopic excipients such as sorbitol.

Saftey:

Croscarmellose sodium is mainly used as a disintegrant in oral pharmaceutical formulation and is generally regarded as an essentially nontoxic and nonirritant material. However, oral consumption of large amounts of croscarmellose sodium may have a laxative effect, although the quantities used in solid dosage formulations are unlikely to cause such problems.

B) Crospovidone

Nonproprietary Name : BP : Crospovidone.

PhEur : Crospovidonum.

USPNF : Crospovidone.

Synonyms : Croslinked povidone, kollidon CL, polyplasdone XL, PVPP, polyvinyl polypyrrolidone.

Chemical name : 1-Ethenyl-2-polypyrrolidinone homopolymer.

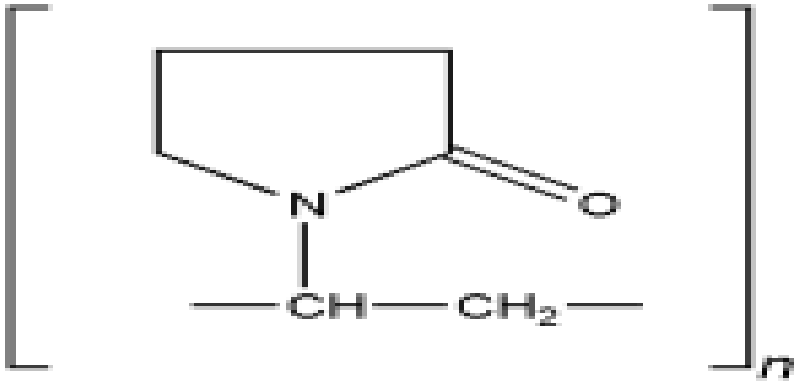
CAS Regestry Number : 9003-39-8.

Molecular Weight : >1 000 000.

Functionly Category : Tablet disintegrant.

Description : Crospovidone is a white to creamy white, finely divided,free flowing, practically tasteless, odorlessor nearly odorless, hygroscopic powder.

Structural Formula :



pH **:** 5.0-8.0 (1% w/v aqueous slurry).

Density **:** 1.22 g/cm^3.

Solubility **:** Practically insoluble in water and most common organic Solvents.

Moisture Content **:** Maximum miosture sorption is approximately 60%.

Application :

Crospovidone is a water insoluble tablet disintegrants and dissolution agent used at 2-5% concentration in tablet 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. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particle provides afaster disintegration than smaller particles. 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. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

Stability And Storage Condition :

Since crospovidone is hygroscopic, it should be stored in air tight container in a cool and dry place.

Incompatibilities :

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials.

Safety :

Crospovidone is used in oral pharmaceutical formulations and is generally regarded as a nontoxic and nonirritant material. Short-term animal toxicity studies have shown no adverse effects associated with crospovidone.

C) Sodium Starch Glycolate

Nnonproprietary Name : BP : Sodium starch glycollate.

PhEur : Carboxymethylamylum natricum.

USPNF : Sodium starch glycolate.

Synonyms **:** Carboxymethyl starch, Sodium salt, Explotab, Primojel.

Chemical Name **:** Sodium carboxymethyl starch.

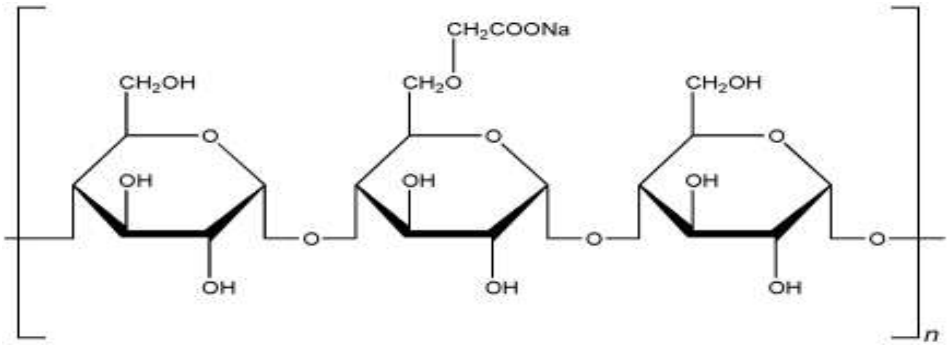
CAS Regestry Number : 9063-38-1.

Molecular Weight **:** 5×10^5-1×10^6.

Functional Category **:** Tablet and capsule disintegrant.

Description **:** Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. It consist of oval or spherical granules 30-100µm in diameter.

Structural Formula :



pH **:** 3.0-5.0.

Melting Point **:** Does not melt, but chars at approximately 200^0C.

Specific Surface Area **:** 0.24 m^2/g.

Solubility **:**Sparingly soluble in ethanol (95%), practically insoluble in water.

Swelling Capacity **:** In water, sodium starch glycolate swells to up to 300 time its volume.

Application :

Sodium starch glycolate is widely used in oral pharmaceuticale 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 swelleing.

Stability And Storage Condition :

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

Incompatibilities :

Sodium starch glycolate is incompatible with ascorbic acid.

Safety :

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

D) Microcrystalline Cellulose (MCC)

Nonproprietary Name : BP : Microcrystalline cellulose.

PhEur : Cellulosum microcrystallinum.

USPNF : Microcrystalline cellulose.

Synonyms **:** Avicel PH, cellulose gel, emcocel, fibrocel, tabulose.

Chemical Name **:** Cellulose.

CAS Regestry Number : 9004-34-6.

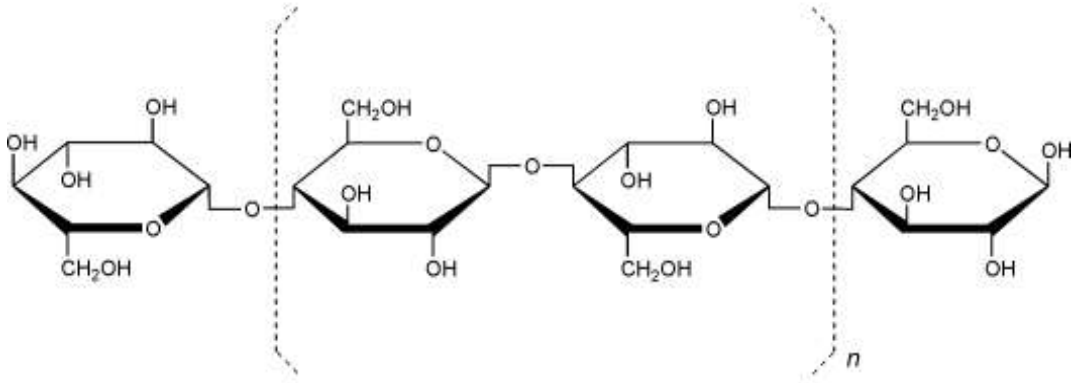
Molecular Weight **:** 36,000.

Functional Category **:** Adsorbent, suspending agent, tablet and capsule diluent, tablet disintegrant.

Description **:**

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

Structural Formula :



Uses of microcrystalline cellulose :

Use	**Cconcentration (%)**
Adorbent	20-90
Antiadherent	5-20
Capsule binder /diluent	20-90
Tablet disintegrant	5-15
Tablet binder /diluent	20-90

Melting point **:** Chars at 260-270^{0}C.

Moisture Content **:** Less than 5% w/w.

Specific Surface Area : 1.21-1.30 m^2/g.

Solubility **:** Slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water.

Application :

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

Stability And Storage Condition :

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

Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

E) Aspartame

Nonproprietary Name : BP : Aspartame.

PhEur : Aspartamum.

USPNF : Aspartame.

Synonyms **:**Canderel, equal, nutrasweet, pal sweet tri-sweet.

Chemical Name **:**N-α-L-Aspartyl-L-phenylalanine 1-methyl ester.

CAS Regestry Number : 22839-47-0.

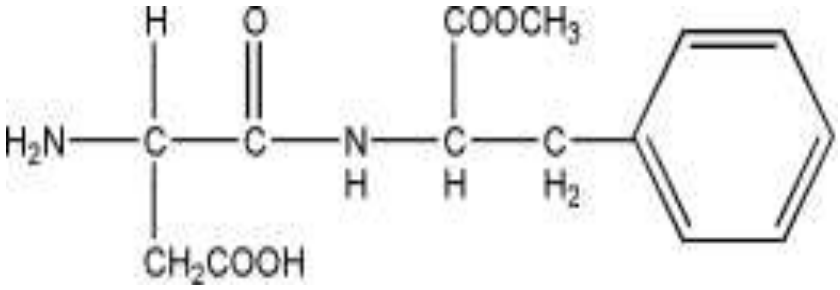
Moleculer Weight **:** 294.31.

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

Functional Category **:**Sweetening agent.

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

Structural Formula :



pH **:** 4.5-6.0 (0.8% w/v in aqueous solution).

Melting Point **:** 246-247^{0}C.

Solubility **:** Slightly slouble in ethanol (95%), sparingly slouble in water.

Application :

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweetners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics, the approximate sweetening power is 180-200 times that of sucrose. Aspartame is metabolized in the body and consequently has some nutritive value: 1g provides approximately 4 kcal. Therapeutically, aspartame has also been used in the treatment of sickle cell anemia.

Stability And Storage Condition :

Aspartame is stable in dry conditions. The bulk material should be stored in a well-closed container in a cool, dry place.

Safety :

Aspartame is widely used in oral pharmaceutical formulations, beverages, and food products as an intense sweetner and is generally regarded as a nontoxic material. The WHO has set an acceptable daily intake for aspartame at upto 40mg/kg body weight.

F) Magnesium Stearate

Nnonproprietary Name : BP : Magnesium Stearate.

PhEur : Magnesii stearas.

USPNF : Magnesium stearate.

Synonyms : Magnesium octadecanoate, octadecanoic acid, magnesium salt.

Chemical Name : Octadecanoic acid magnesium salt.

CAS Regestry Number : 557-04-0.

Empirical Formula : $C_{36}H_{70}MgO_4$.

Molecular Weight : 591.34.

Functional Category : Tablet and capsule lubricant.

Structural Formula : $[CH_3(CH_2)_{16}COO]_2$ Mg.

Flowability : Poorly flowing, cohesive powder.

Melting Point : 126-130^{0}C.

Solubility : Practically insoluble in ethanol, ethanol (95%), ether and wter, slightly slouble in warm benzene and warm ethanol (95%).

Specific Surface Area : 1.6-14.8 m^2/g.

Description :

Magnesium stearate is a very fine, light white, percipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste.

Application :

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

Stability And Storage Condition :

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

Incompatibilities :

Magnesium stearate is incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials.

Handling Precautions :

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing. It should be handled in a well-ventilaed environment.

Safety :

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as baing nontoxic following oarl administration.

G) Talc

Nonproprietary Name : BP : Purifide talc.

PhEur : Talcum.

USP : Talc.

Synonyms : Altalc, magnesium calcium silicate, powdered talc, magsil star.

Chemical Name : Talc.

CAS Registry Number : 14807-96-6.

Empirical Formula : $Mg_6(SiO_5)_4\ (OH)_4$.

Functional Category : Anticaking agent, glidant, tablet and capsule diluent, tablet and capsule lubricant.

Description : Talc is very fine, white to grayish white, odorless, impalpable, crystalline powder. It adheres radily to the skin and is soft to the touch and free from grittiness.

pH : 7-10 for a 20% w/v aqueous dispersion.

Moisture Ccontent : Talc absorbs insignificant amounts of water at 25_0C and relative humidities up to about 90%.

Specific Surface Area : 2.41-2.42 m^2/g.

Specific Gravity :2.7-2.8.

Solubility **:** Practically insoluble in acids and alkalis, organic solvents, and water.

Application :

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

Concentrations of talc to be used in various applications :

Use	**Concentration (%)**
Dusting powder	90.0-99.0
Glidant and lubrucant	1.0-10.0
Tablet and capsule diluent	5.0-30.0

Stability And Storage Condition :

Talc is a stable material and may be sterilized by heating at 160^0C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities **:** Incompatible with quaternary ammonium compounds.

Handling Precautions :

Observe normal precautions appropriate to the circumstances and quantity of material handled. Talc is irritant if inhaled.

Safety :

Talc is used mainly in tablet and capsule formulations. Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material.

H) **Aerosil**

Nonproprietary Name : BP : Colloidal anhydrous silica.

PhEur : Silica colloidalis anhydrica.

USPNF : Colloidal silicon dioxide.

Synonyms : Cab-O-Sil, colloidal silica, fumed silica wacker HDK.

Chemical Name : Silica.

CAS Regstry Number : 7631-86-9.

Empirical Formula : SiO_2.

Molecular Weight : 60.08.

Structural Formula : SiO_2.

Functional Category : Adsorbent, anticaking agent, emulsion stabilizer, glidant, tablet disintegrant, thermal stabilizer.

Description : Aerosil is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white-coloured, odorless, tasteless, nongritty amorphous powder.

pH : 3.5-4.4 (4% w/v aqueous dispersion).

Flowability : 35.52%.

Refractive Index **:** 1.46.

Specific Gravity **:** 2.2.

Specific Surface Area **:** 200-400 m^2/g.

Solubility :

Practically insoluble in organic solvents, wter, and acids, except hydrofluoric acid, soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.

Application :

Aerosil is widely used in pharmaceuticals, cosmetics, and food products, Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting. Aerosil is also used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.

Stability And Storage Condition :

Aerosil is hygroscopic but adsorbs large quantities of water without liquefying. Aerosil powder should be stored in a well-closed container.

Incompatibilities :

Incompatible with diethylstilbestrol preparations.

Safety :

Aerosil is widely used in oral and topical pharmaceutical products. And is generally regarded as an essentially nontoxic and nonirritant exipient.

I) Mannitol

Nonproprietary Name : BP : Mannitol.

PhEur : Mannitolum.

USP : Mannitol.

Synonyms **:** Cordycepic acid, manna sugar, pearlitol.

Chemical Name **:** D-Mannitol.

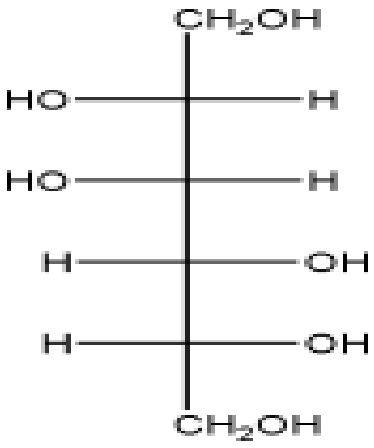
CAS Regstry Number **:** 69-65-8.

Empirical Formula **:** $C_6H_{14}O_6$.

Moleculer Weight **:**182.17.

Functional Category **:** Diluent, diluent for lyphilized preparations, sweetening agent, tablet and capsule diluent.

Structural Formula **:**



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.

Melting Point : 166-168^{0}C.

Specific Surface Area : 0.37-0.39 m^2/g.

Solubility : Mannitol is soluble in alkalis, ethanol (95%), water. It is practically insoluble in ether.

Application :

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10-90% w/w) in tablet formulations. Mannitol may be used in direct compression tablet applications, for which the granular and spray dried forms are available, or inwet granulations. 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.

Stability And Storage Condition :

Mannitol is stable in the dry state and in aqueous solutions. Solutions may strilized by filtration or by autoclaving. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities :

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. Mannitol is incompatible with xylitol infusion and may form comlexes with some metals such as ammonium, copper, and iron.

Safety :

Mannitol is a naturally occuring sugar alcohol found in animals and plants, it is present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities.

7. MATERIALS AND METHODS

7.1 MATERIALS

The following materials like Drug, Excipients and Chemicals were used for the formulation and evaluation studies of ODTs.

Table No. 7.1: List of materials and their suppliers.

Sr. No.	Materials	Manufacturer and Supplier of Materials
1	Metoclopramide HCL	Vaikunth Chemicals Pvt. Ltd., Bharuch.
2	Sodium Starch Glycolate	Vijlak Pharma Ltd., Mumbai.
3	Crospovidone	BASF Ltd., Pharmaco Mumbai.
4	Crosscarmellose Sodium	Ascot Pharma Ltd., Mumbai.
5	Microcrystalline Cellulose	Westurn Pharma, Mumbai.
6	Aspartame	Sinosweet Co. Ltd, Jaingsu, China.
7	Magnesium Stearate	Westurn Pharma, Mumbai.
8	Talc	Westurn Pharma, Mumbai.
9	Aerosil	Degussa, Westurn Pharma, Mumbai.
10	Pineapple Flavor	Vital Flavors, Mumbai.
11	Mannitol	Pharmaco, Mumbai.
12	Sodium Hydroxide	Qualigens Fine Chemicals, Mumbai.
13	Potassium dihydrogen Orthophosphate	Qualigens Fine Chemicals, Mumbai.
14	Hydrochloric Acid	Fisher Scientific India Pvt. Ltd., Mumbai
15	Potassium Chloride	Qualigens Fine Chemicals, Mumbai.
16	Potassium Bromide	S.D. Fine Chemical Ltd, Mumbai.

7.2 INSTRUMENTS USED

Table No. 7.2: List of instruments and manufacturer.

Sr. No.	Instruments	Manufacturer
1	Digital Balance	AX 200, Shimadzu, Japan.
2	Melting Point Apparatus	Scientific International SI-934, Delhi.
3	Double Beam UV- Spectrophotometer	Analytical technologies Ltd., Model No. 2080
4	Digital pH Meter	Equip-Tronics, Model EQ 610.
5	FTIR Spectrophotometer	Model No. 8400 S, Shimadzu, Japan
6	Tablet Compression Machine	Cadmach Machinery co. Pvt. Ltd., Ahmadabad.
7	Roche Friabilator	Scientific International, New Delhi.
8	Tablet Hardness Tester	Monsanto Hardness Tester, Magumps, Bombay.
9	Disintegration Apparatus	ED-2L Electrolab, Mumbai.
10	Dissolution Test Apparatus II	USPXXIII, (TDT-08L) Plus, Electrolab, India.
11	Vernier Caliper	Mitutoyo Digital Vernier Caliper, Japan.

7.3 METHODOLOGY

7.3.1 Preformulation Study

Identification of drug

B) Melting Point :

Melting point of pure Metoclopramide HCL was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Metoclopramide HCL by

repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically increase the temperature of heating bath at a rate 100^0C min rise of temperature per minute. The rise in temperature was viewed through magnifying lens. The temperature at which the drug started melting was recorded.

B) Infrared absorption spectrophotometer :

Identification of Metoclopramide HCL was determined by the infrared absorption spectrophotometer. The sample was heated in hot air oven for removing moisture content. The sample were prepared with potassium bromide by mixing it in mortar and pestle. The prepared sample was placed in FT-IR and scanned at range from 400 to 4000 cm^{-1} to obtain the spectrum. Theobtained spectrum was compared with the reference standard IR spectrum of metoclopramide HCL.

C) Ultra visible spectrophotometer :

A solution of Metoclopramide HCL containing concentration 50µg/ml was prepared in water and the solution was scanned in the range of 200-400nm. The obtained spectrum was compared with the reference standard UV spectrum of metoclopramide HCL.

D) Identification test :

Identification of metoclopramide HCL was determined by the chemical test for primary aromatic amines. Dissolve the drug about 2 mg in 2 ml of water the solution gives the reaction of primary amines (IP).

E) Solubility :

Solubility of Metoclopramide hydrochloride was performed in solvents water and alcohol.

7.3.2 Standard Calibration Curve of Metoclopramide HCL

Preparation of stock solution of Metoclopramide HCL

Weigh accurately 10 mg of Metoclopramide HCL and dissolve it in 100 ml of dilution media pH 6.8 buffer to obtain the stock solution of strength 100 µg/ml. and the respective dilutions were prepared by using stock solution. Same procedure was repeated for stock solution of metoclopramide HCL using pH 1.2 buffer as a dilution media.

Calibration curve of Metoclopramide HCL in pH 1.2 buffer

Procedure:

10 mg of Metoclopramide HCL was dissolved in 100 ml of the pH 1.2 buffer to obtain the working standard of 100 µg/ml. Aliquots of 0.2 ml to 1 ml from the stock solution representing 2 to 10 µg/ml of drug were transferred to 10 ml volumetric flask and the volume was adjusted to 10 ml with the pH 1.2 buffer. Absorbance of the above solutions was measured at 273 nm. by UV visible spectrophotometer against the blank solution prepared in the same manner without adding the drug. A graph of absorbance Vs concentration was plotted and was found to be linear over a range of 2 to 10 µg/ml indicating its compliance with Beer's law.

Calibration curve of Metoclopramide HCL in pH 6.8 buffer

Procedure:

10 mg of Metoclopramide HCL was dissolved in 100 ml of the pH 6.8 buffer to obtain the working standard of 100 µg/ml. Aliquots of 0.2ml to 1ml from the stock solution representing 2 to 10 µg/ml of drug were transferred to 10 ml volumetric flask and the volume was adjusted to 10 ml with the pH 6.8 buffer. Absorbance of the above solutions was measured at 273 nm. by UV visible spectrophotometer against the blank solution prepared in the same manner without adding the drug. A graph of absorbance Vs concentration was plotted and was found to be linear over a range of 2 to 10 µg/ml indicating its compliance with Beer's law.

Preparation of Buffer and Reagents

The reagents were prepared as per I.P.

Sodium Hydroxide (0.2M) solution :

Eight gram of sodium hydroxide (NAOH) was dissolved in 1000 ml volumetric flask containing about 700 ml of distilled water and volume was made up to the mark with distilled water.

Potassium Dihydrogen Phosphate (0.2M) solution :

Potassium dihydrogen phosphate (27.218g) was dissolved in 1000 ml volumetric flask containing about 700 ml of distilled water and volume was made up to the mark with distilled water.

Phosphate Buffer (pH 6.8) solution :

Fifty ml of 0.2 M Potassium dihydrogen phosphate solution was taken in a 200 ml volumetric flask, to which 22.4 ml of 0.2 M sodium hydroxide solution was added and volume was made up to the 200 ml with distilled water. The pH was adjusted to 6.8 with dilute sodium hydroxide solution.

0.2M Hydrochloric acid (HCL) solution:

Conc. HCl diluted with distilled water so that final solution contains 7.292 g of hydrochloric acid in 1000.0 ml to obtain 0.2M hydrochloric acid solution.

0.2M Potassium chloride (KCL) solution:

Dissolve approx. 14.911 g of potassium chloride in distilled water and diluted to 1000.0 ml with distilled water to obtain 0.2M potassium chloride solution.

pH 1.2 Hydrochloric acid buffer:

About 250.0 ml of 0.2M potassium chloride solution was placed in a 1000.0 ml volumetric flask. To this, about 425.0 ml of 0.2M hydrochloric acid was added and then volume was adjusted to 1000 ml with distilled water. Then prepared solution was tested using pH meter. The pH of solution was adjusted to pH 1.2 with the help of 0.2M hydrochloric acid.

7.3.3 Drug and Excipients Interaction Study

FTIR Spectroscopy :

The interaction between drug and excipients was studied by using FTIR spectroscopy. In the preparation of tablet formulation, drug and excipients may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-excipients interaction are therefore very critical in selecting appropriate polymer. FTIR spectroscopy was employed to ascertain the compatibility between Metoclopramide hydrochloride and the selected excipients. Potassium bromide, pure drug and the excipients were heated to 105^0C for one hour in a hot air oven to remove the moisture content. Then in presence of IR lamp, potassium bromide was mixed with drug and or excipients and the spectra were taken. FTIR spectrum of metoclopramide hydrochloride was compared with FTIR spectra of excipients.

7.4 Formulation Development

Selection of Superdisintegrants :

The best type of superdisintegrants are incorporated in the formulation of ODTs like, Sodium starch glycolate, Crospovidone, Cross carmellose sodium. Before the tablet formulation the superdisintegrants was screened out and taken into formulation with other excipients for compression by direct compression method. The superdisintegrant shows good properties like, when the tablet comes in contact with liquid, it breaks up into smaller particles because of

superdisintegrants are swells, hydrate, change the volume and produce a disruptive change in the tablet.

In this work, the direct compression method with aid of superdisintegrants was attempted for the formulation development of orodispersible tablets of Metoclopramide hydrochloride. The superdisintegrants like Sodium starch glycolate, Crospovidone, Cross carmellose sodium were taken for the formulation development. The Metoclopramide hydrochloride tablets are available in 5mg and 10mg doses in the market. Dose of 10mg is selected for the present study.

The development of the formulation of orodispersible tablets in the present study was mainly based on the type and concentration of superdisintegrants. Various superdisintegrants in different concentrations (2.6%, 4%, and 5.3%) were used so as to get tablets with good physical properties. Ingredients like Microcrystalline cellulose and mannitol as directly compressible diluents, magnesium stearate and talc as lubricant, aerosil as flow promoter, aspartame as sweetening agent and pineapple flavor as enhance the palatability. And Sodium Starch Glycolate (Carboxtmethyl Starch), Crospovidone (Polyplasdone XL) and Cross Carmellose Sodium (Ac-Di-Sol) were taken in the different concentrations such as 2.6%, 4%, and 5.3%.

The formulation design of orodispersible tablets of Metoclopramide HCL is shown in Table 7.3.

Table No. 7.3: Formulation design of Metoclopramide HCL orodispersible tablets.

Sr. No.	Ingredients (mg)	MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9
1.	Metoclopramide HCL	10	10	10	10	10	10	10	10	10
2.	Sodium starch glycolate	4	6	8	–	–	–	–	–	–
3.	Crospovidone	–	–	–	4	6	8	–	–	–
4.	Cross carmellose sodium	–	–	–	–	–	–	4	6	8
5.	Microcrystalline cellulose	50	50	50	50	50	50	50	50	50
6.	Aspartame	6	6	6	6	6	6	6	6	6

7.	**Magnesium stearate**	**1.5**	**1.5**	**1.5**	**1.5**	**1.5**	**1.5**	**1.5**	**1.5**	**1.5**
8.	**Talc**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
9.	**Aerosil**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**
10	**Pineapple flavour**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**
11	**Mannitol**	**76**	**74**	**72**	**76**	**74**	**72**	**76**	**74**	**72**
	Total	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Tablets were prepared in batch of 100

Metoclopramide HCL orodispersible tablets were prepared by direct compression method. The ingredients mentioned in table 7.3 were used for formulation such as, superdisintegrants in different concentration, Microcrystalline cellulose as diluent, mannitol as directly compressible diluent, aspartame was selected as sweetening agent due to its intense sweetness, magnesium stearate and talc as lubricant, aerosil as flow promoter and flavor (Pineapple flavor) was added it enhance the palatability of tablets.

Preparation of powder blend of drug and excipients :

The powder blend for orodispersible tablets were prepared by taking ingredients given in Table 7.3

All the ingredients were passed through 60 mesh sieve separately and collected. Then ingredients were weighed and mixed in a geometrical order. First Microcrystalline cellulose, Mannitol and Superdisintegrants were weighed and mixed together in glass mortar using a pestle. Then Drug and Aspartame were mixed and added in first mixer. Then Magnesium stearate, Talc and Aerosil were added and mixed. Finally flavor (Pineapple flavor) was added and mixed for 10-20 minutes.

Before tablets preparation, the mixture blends of all the formulations were subjected for compatibility studies (IR) and pre-compression parameter like Angle of repose, Bulk density, Tapped density, Percentage compressibility and Hausner ratio.

Preparation of Metoclopramide HCL Orodispersible Tablets by Direct Compression :

Metoclopramide HCL orodispersible tablets were prepared in nine formulations MF1 to MF9 using the ingredients given in the Table 7.3 keeping the total weight of the tablet (150mg) kept constant in all the formulations. All the ingredients were passed through 60 mesh sieve separately and collected. Then ingredients were weighed and mixed in a geometrical order. First

microcrystalline cellulose, mannitol and superdisintegrants were weighed and mixed together in glass mortar using a pestle. Then drug and aspartame were mixed and added in first mixer. The blend was then lubricated by mixing with magnesium stearate, talc and aerosil. Finally the mixture was blended with flavor. Then the powder blend was compressed. Tablets were prepared using 8 mm round flat-faced punches of the 16-station (Cadmach Machineries ltd.) rotary tablet compression machine. Compression force was kept constant for all formulation.

The Orodispersible tablets were prepared and subjected to post compression parameters likehardness, friability, thickness, weight variation,*In-vitro* dispersion time, wetting time, water absorption ratio, drug content, *In-vitro* disintegration time and *In-vitro* dissolution.

7.5 Pre-compression assessment of powder blend

Different parameters were evaluated for prepared powder blend using following methods.

Angle of repose

Angle of repose is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

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

The angle of repose is calculated by using fixed funnel method. In this method the funnel was fixed to a stand at definite height (h). The graph paper was placed on a flat horizontal surface. Then powder blend was allowed to fall freely on the paper through the funnel, until the apex of the conical pile just touches the tip of the funnel. The height and radius of pile was noted and from this angle of repose was determined with the help of given formula.

The formula for calculating angle of repose is – $\mathbf{\tan(\theta) = h / r}$

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

Where,

θ is the angle of repose

h is the height in cm.

r is the radius in cm.

Table No. 7.4: Angle of repose as an indication of powder flow properties:

Sr. No.	Angle of Repose (°)	Type of Flow
1	**<20**	**Excellent**
2	**20-30**	**Good**
3	**30-34**	**Passable**
4	**>34**	**Very poor**

Bulk Density

Bulk density is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the accurately weighed 2g of powder blend (passed through 20 mesh sieve) was placed in a 10ml graduated measuring cylinder. And then initial volume was observed, this initial volume is called as bulk volume. From this the bulk density was calculated by using the following formula.

$$\mathbf{D_b = M / V_b}$$

Where, D_b = Bulk density.

M= Mass of the powder.

V_b= Bulk volume of the powder.

Tapped Density

Tapped density is the ratio of total mass of powder to the tapped volume of powder. Accurately weighed amount of powder blend was placed in a measuring cylinder and the volume was measured by tapping of powder for 500 times and the tapped volume was noted. The tapped density was calculated by using following formula.

$$\mathbf{D_t = M / V_t}$$

Where, D_t = Tapped density.

M = Mass of the powder.

V_t = Tapped volume of the powder.

Compressibility Index

Compressibility index is indicates the powder flow properties. It is expressed in percentage. Compressibility index is based on the bulk density and tapped density, the percentage compressibility of the powder blend was determined by using the following formula.

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where,

I = Compressibility index.

D_t = Tapped density of the powder.

D_b = Bulk density of the powder.

Table No. 7.5: Relationship between % compressibility and flow ability.

% Compressibility	Flow ability
5 – 12	Excellent
12 – 16	Good
18 – 21	Fair passable
23 – 35	Poor
33 – 38	Very poor

Hausner Ratio

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

$$\text{Hausner ratio} = D_t / D_b$$

Where,

D_t = tapped density.

D_b = bulk density.

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

7.6 Post-compression assessment of powder blend

Hardness

Hardness of the tablet was determined by using Monsanto tablet hardness tester. Hardness or tablet crushing strength (f_c), the force required to break a tablet in a diametric compression. From each batch, hardness of 6 tablets was determined. The lower plunger is placed in contact with tablet, and a zero reading was taken. The upper plunger is then forced

against a spring by turning a threaded bolt until the tablet fractures. Hardness of tablet is expressed in kg / cm^2.

Friability

The friability test for tablets was performed to assess the effect of abrasion and shocks. Roche friabilator was used for the percent friability of the tablets. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre-weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Then the tablets were removed and de dusted by using a soft muslin cloth and reweighed. The weight lost should not exceed the limit 1.0%. The percentage friability was measured by using the following formula.

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

Where,

% F = Friability in percentage.

$W_{initial}$ = Initial weight of tablet.

W_{final} = Final weight of tablet.

Thickness

The thickness of tablets was measured by using vernier caliper. Five tablets from each batch were taken randomly and thickness was measured and average values were calculated. Thickness is expressed in mm.

Weight Variation

The weight variation test was performed as per I.P. Twenty tablets were randomly selected from each batch and individually weighed. And then average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight.The tablets passes the test for weight variation test if no more than two tablets are outside the percentage limit and if no tablet differs by more than two times the percentage limit. Weight variation specification as per I.P. is shown in Table no. 7.6.

Table No. 7.6: Weight variation tolerances for uncoated tablets.

Average weight of tablets (mg)	% Deviation
80 mg or less	**±10**
More than 80 mg and less than 250 mg	**±7.5**
250 mg or more	**±5**

***In-vitro* Dispersion Time**

In-vitro dispersion time was measured by dropping a tablet into a petridish containing 10ml of phosphate buffer pH 6.8 solution at 37± 0.5^0c. Three tablets from each batch were randomly selected and tested the time required for complete dispersion of a tablet was measured. The *in-vitro* dispersion time is expressed in seconds.

Wetting Time

A piece of tissue paper folded double was placed in a Petri dish (6.5cm) containing 6 ml of water .the tablet was placed on the paper, and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^0c.Wetting time corresponding to the time taken for the tablet to disintegrate when kept motionless on the Petri dish.

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a petri dish (6.5cm) containing 6 ml of water. A tablet was put on the tissue paper and the time required for the complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation.

$$R = 100 (Wa-Wb) / Wb$$

Where,

Wa = Weight of the tablet after absorption.

Wb = Weight of the tablet before absorption.

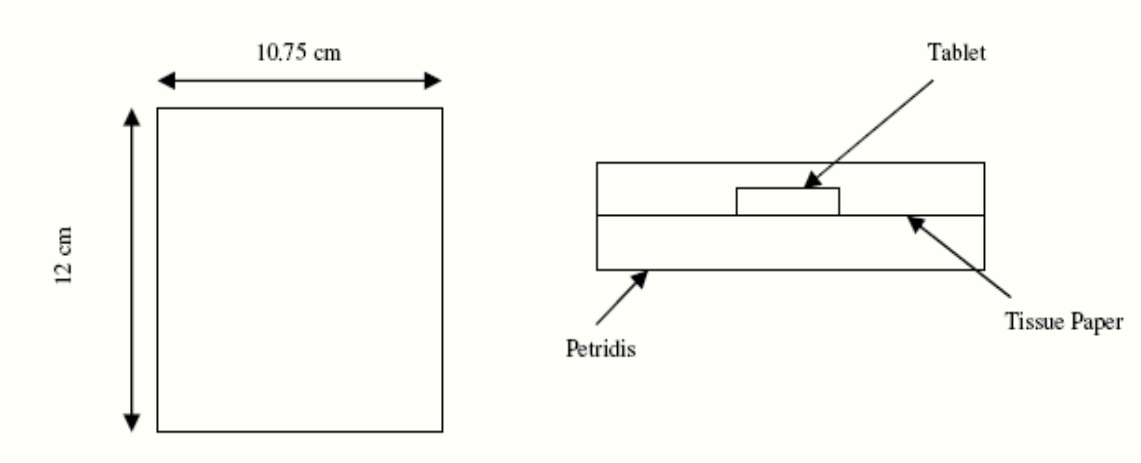


Figure No. 7.1: Method for measurement of wetting time and water absorption ratio.

Disintegration Time

The *in-vitro* disintegration time of a tablet was determined using disintegration test apparatus. One tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube and run the apparatus using distilled water at 37^0c ± 2^0c. And then complete disintegration of tablet with no palpable mass remaining in the apparatus was measured in seconds.

Drug Content

The drug content of the tablets was measured according to the procedure given in IP, 2007. It has been reported that metoclopramide HCl can be detected at 273 & 305 nm. Drug content uniformity was carried out at 305 nm because successive extraction was done using chloroform for which maximum absorption observed at 305 nm as reported in pharmacopoeia.

***In-vitro* Dissolution Studies**

In-vitro dissolution studies for orodispersible tablets of Metoclopramide HCL were carried out using USP apparatus type II at 50 rpm. The dissolution medium used was phosphate buffer pH 6.8 (900ml) maintained at 37 ± 0.5^oC.

Aliquots of dissolution media were withdrawn (10ml) at different intervals and content of Metoclopramide HCL was measured by determining absorbance at 273 nm. 10ml aliquot was withdrawn at the 0min, 1min, 2min, 3min .....to be continued at the 1min intervals and filter by whatmann filter paper. And analyzed at 273 nm using- visible spectrophotometer.

STABILITY STUDIES

Definition

Stability is defined as "the capacity of the drug product to remain within specifications established to ensure its identity, strength, quality and purity" (FDA 1987).

Stability studies of pharmaceutical products were done as per ICH guidelines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions. Basically, there are two types of stability studies:

1) Short -term stability studies

2) **Long - term stability studies**

Table 7.4 Stability conditions according to ICH guidelines

Types	**Conditions**		**Minimum time period at submission (month)**
	Temperature (^{0} C)	**Relative humidity (%)**	
Short-term testing	40 ± 2	75 ± 5	6
Long-term testing	25 ± 2	60 ± 5	12

Method:

Selected formulations were stored at different storage conditions at elevated temperatures such as 25^{o}C± 2^{0}C / 60% ± 5% RH, and 40^{0}C ± 2^{0}C/ 75% ± 5% RH for 90 days. The samples were withdrawn at intervals of 30 days and checked for physical changes, hardness, friability, drug content and percentage drug release.

8. RESULTS AND DISCUSSION

8.1 PREFORMULATION STUDIES

Identification test for Metoclopramide HCL:

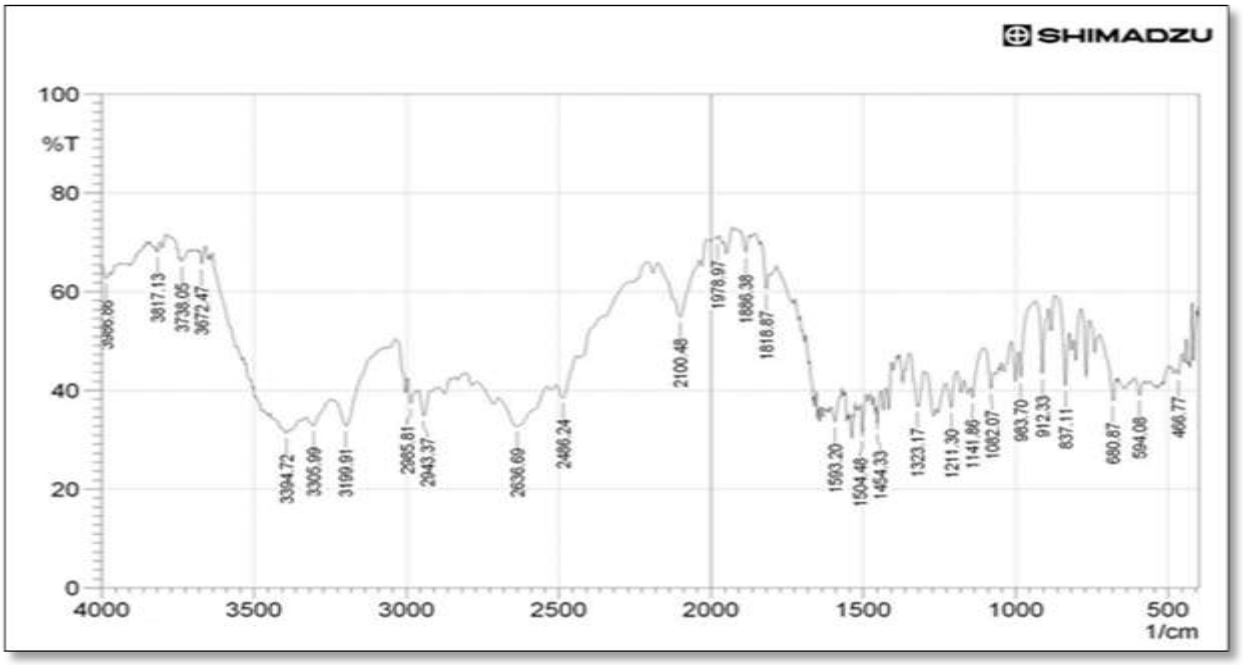
Identification of metoclopramide HCL was carried out by Melting Point, I.R. Spectroscopy, U.V. Spectroscopy, Identification test and solubility.

A) Melting Point :

The melting point of the metoclopramide HCL was found to be 184^0C, which complies with given in the official reference.

B) I.R. Spectroscopy :

Figure No. 8.1: FTIR Spectrum of Metoclopramide HCL



FTIR spectrum of metoclopramide HCL as shown in figure no 8.1, showed all the peaks corresponding to the functional groups presents in the structure of metoclopramide HCL.

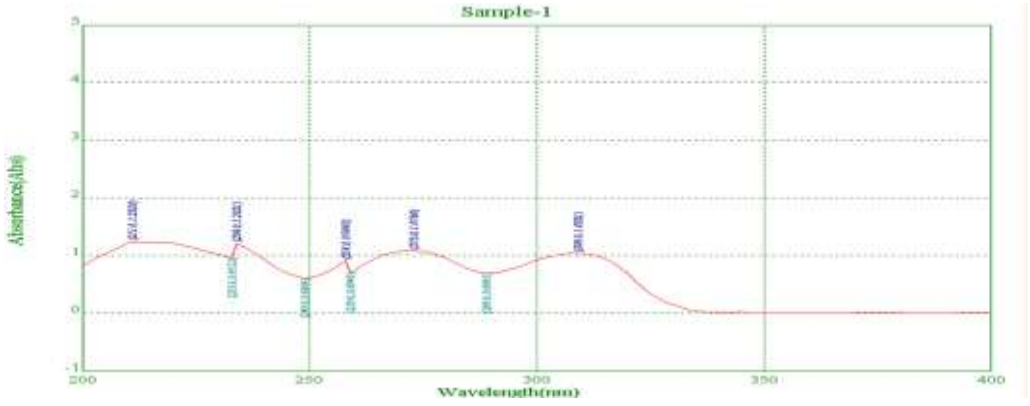
Table No. 8.1: Interpretation of FTIR spectrum of Metoclopramide HCL

Transition	IR Range	Drug
C=C	**1500-1600**	**1593.20**
O-H	**3400-2400**	**3394.72**
N-H	**3100-3500**	**3199.91**
C-O	**1300-1000**	**1141.86**
C-H	**3000-2850**	**2943.37**
C=O	**1680-1860**	**1818.87**
C-C	**800-1300**	**837.11**

C) UV Spectroscopy :

The λ_{max} of pure Metoclopramide HCL was found to be 273 nm and 309 nm after scanning on the spectrophotometer, which complies with the reference spectra of metoclopramide HCL. (Fig. No.8.2)

Figure No. 8.2: UV Spectrum of Metoclopramide HCL



D) Identification Test :

Identification test for Primary Aromatic Amines, the solution of drug was produced the red coloured precipitation after completion the reaction. It indicates the primary aromatic amine is present in the drug. (I.P.2007)

E) Solubility :

The Metoclopramide Hydrochloride was found to be freely soluble in water and alcohol.

8.2 Drug and Excipients Compatibility Study :

Fourier transformed infra-red (FTIR) spectra of Metoclopramide HCL and the physical mixture of drug with excipients was taken by using IR Spectrophotometer. The scanning range was 450 - 4000 cm^{-1} and the resolution was 1 cm^{-1}. The IR spectrum of pure drug and physical mixture of drug and excipients were studied. The characteristic absorption peaks of metoclopramide HCL and absorption peaks of physical mixture are corelates with each other. This indicate that the drug was compatible with the excipients.

Figure No. 8.3: FTIR Spectrum of Drug with Crospovidone

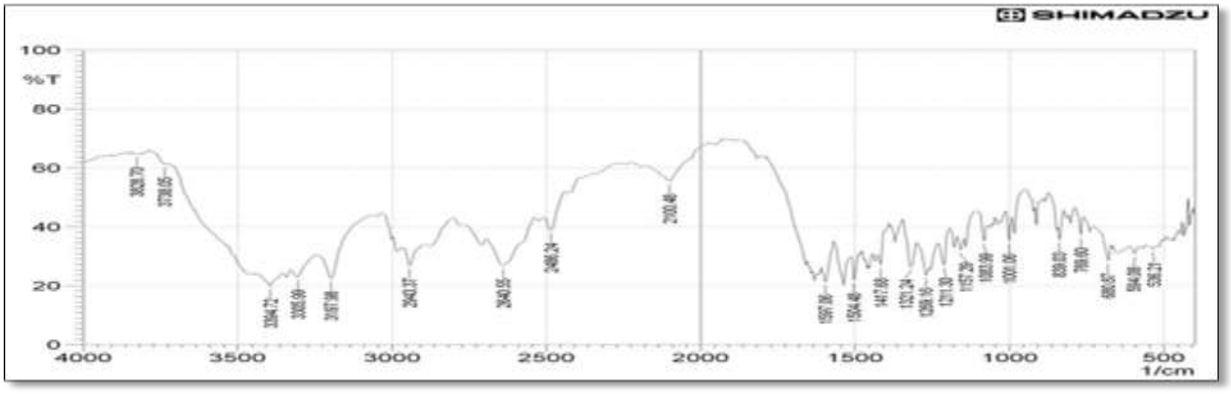


Figure No. 8.4: FTIR Spectrum of Drug with sodium starch glycolate

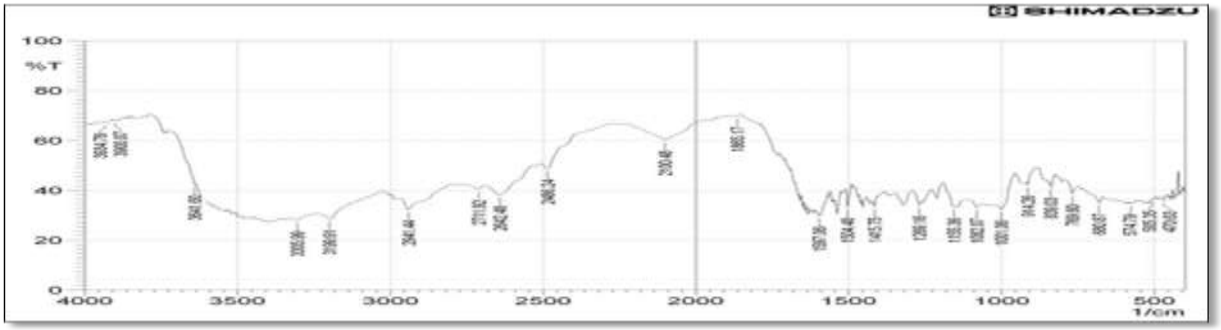


Figure No. 8.5: FTIR Spectrum of Drug with Cross Carmellose Sodium

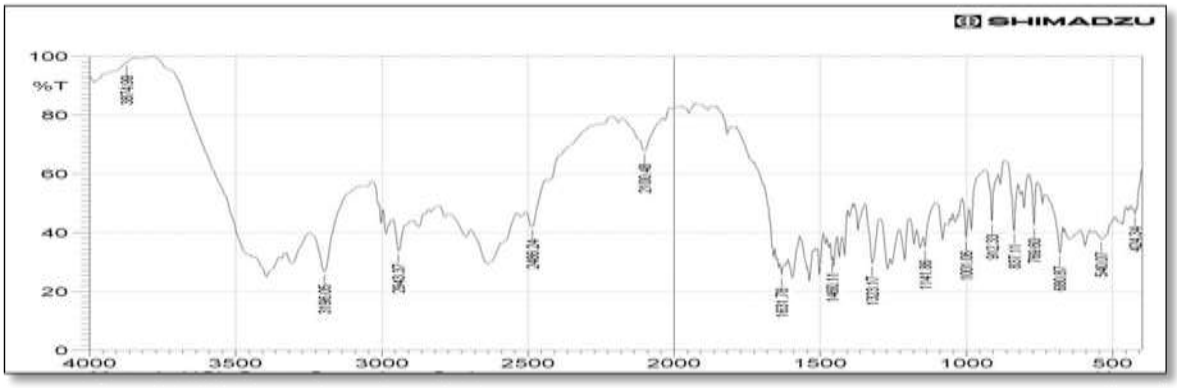


Figure No. 8.6: FTIR Spectrum of Metoclopramide HCL with all excipients

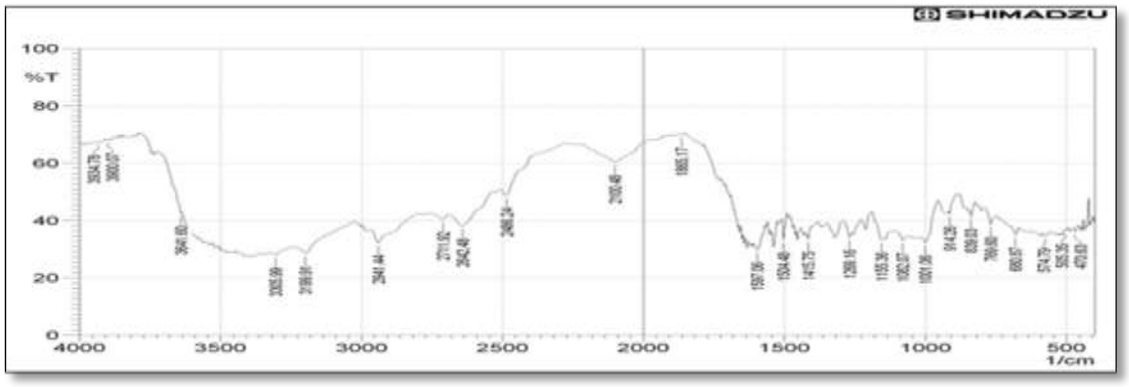


Table No. 8.2: FTIR spectra for the mixture of Metoclopramide HCL with various super disintegrants and with all excipients.

Transition	IR Range	Drug + Crospovidone	Drug + sodium starch glycolate	Drug + Cross Carmellose Sodium	Drug + all excipients
C=C	**1500-1600**	**1597.06**	**1597.06**	**-**	**1597.06**
C=O	**1820-1660**	**-**	**1865.17**	**-**	**1865.20**
C-C	**800-1300**	**839.03**	**839.03**	**837.11**	**837.10**
N-H	**3300-3500**	**3199.91**	**3199.91**	**3196.06**	**3199.92**
C-O	**1300-1000**	**1141.86**	**1155.36**	**1141.86**	**1141.85**
C-H	**3000-2850**	**2943.37**	**2941.44**	**2943.37**	**2941.37**

Figure shows the IR spectra of pure Metoclopramide HCL and its physical mixture (1:1) with Crospovidone, Cross Carmellose Sodium, sodium starch glycolate and with all excipients. The IR spectra did not show any significant difference from those obtained for their physical mixture. These obtained results indicate that there was no positive evidence for the interaction between Metoclopramide HCL and super disintegrants or Metoclopramide HCL and excipients. These results clearly indicate the usefulness of the utilized super disintegrants for preparation of orodispersible tablet of pure Metoclopramide HCL.

8.3 Standard Calibration Curve of Metoclopramide HCL :

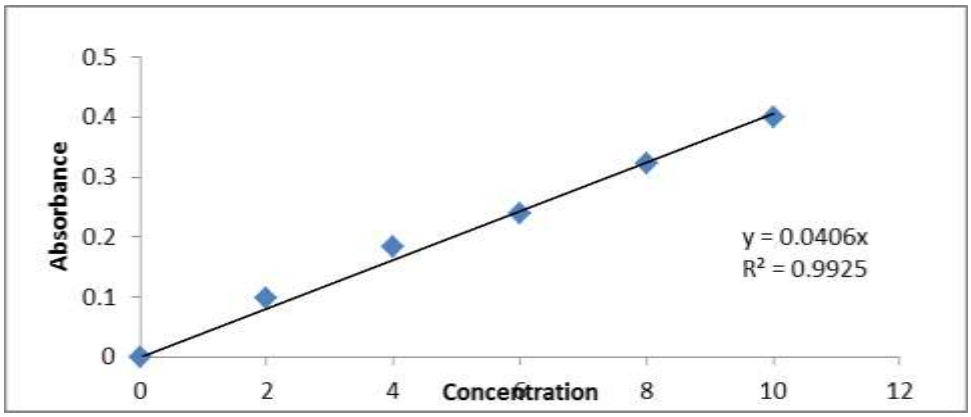
8.3.1 Preparation of standard calibration curve in hydrochloric acid buffer pH 1.2:

The standard calibration curve of Metoclopramide HCL was prepared by using hydrochloric acid buffer pH 1.2 as solvent. Standard calibration curve was obtained by plotting Absorbance Vs. Concentration. Table 8.3 shows the absorbance values of Metoclopramide HCL. The standard curve is shownin figure 8.7 the standard calibration curve shows the correlation coefficient of 0.9925. The curve was found to be linear in the concentration range of 2-10 µg/ml at 273.0 nm. Thus the standard curve followed the Beer- Lamberts Law.

Table No. 8.3: Absorbance values for standard calibration curve of Metoclopramide HCL in hydrochloric acid buffer pH 1.2

Sr.No.	Concentration (µg/ml)	Absorbance
1	**0**	**0**
2	**2**	**0.097**
3	**4**	**0.184**
4	**6**	**0.238**
5	**8**	**0.322**
6	**10**	**0.399**

Fig. No. 8.7: standard calibration curve for Metoclopramide HCL at 273.0 nm. in Hydrochloric acid buffer pH 1.2

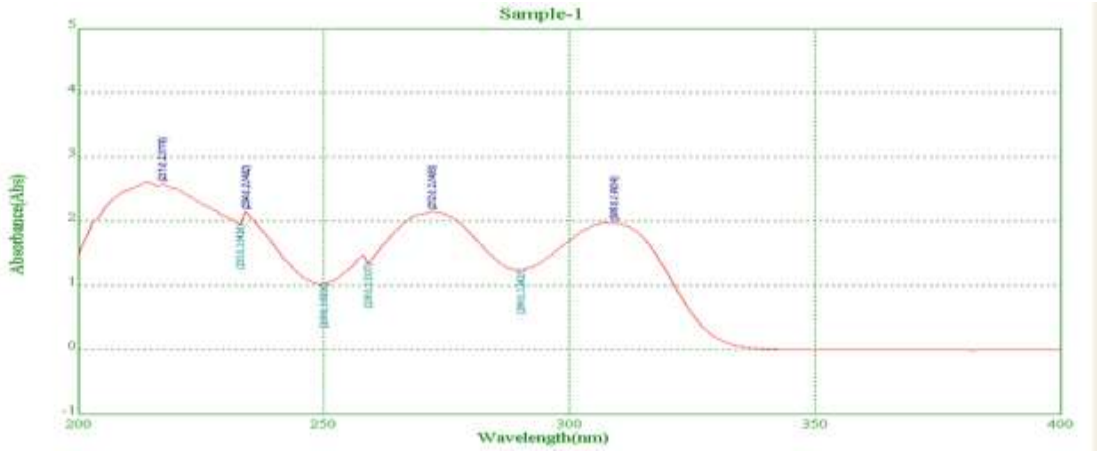


8.3.2 Calibration curve of Metoclopramide HCL in phosphate buffer pH 6.8:

1) UV Spectra of drug in phosphate buffer pH 6.8:

50 µg/ml solution of Metoclopramide HCL was prepared in phosphate buffer pH 6.8 and was subjected to scanning under UV visible spectrophotometer, between the range 200-400nm. The λ_{max} was found to be at 272 nm. (Fig. 8.8)

Figure No. 8.8: UV Spectrum of Metoclopramide HCL in phosphate buffer pH 6.8



2) Preparation of standard calibration curve in phosphate buffer pH 6.8:

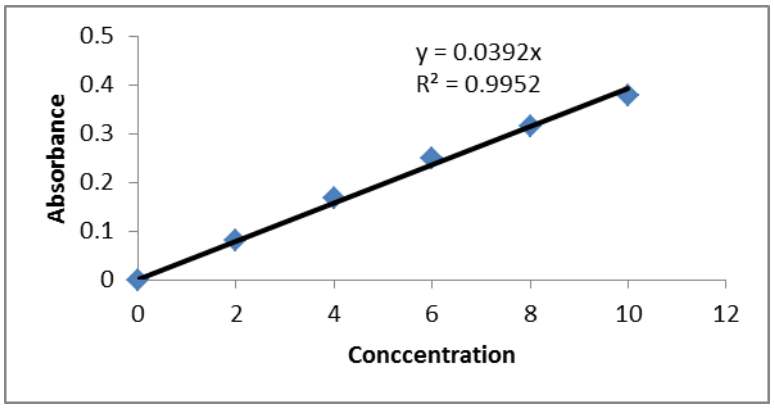
The standard calibration curve of Metoclopramide HCL was prepared by using phosphate buffer pH 6.8 as solvent. Standard calibration curve was obtained by plotting Absorbance Vs. Concentration. Table 8.4 shows the absorbance values of Metoclopramide Hydrochloride. The standard curve is shown in figure 8.9, the standard calibration curve shows

the correlation coefficient of 0.9952. The curve was found to be linear in the concentration range of 2-10 µg/ml at 273.0 nm. Thus the standrad curve followed the Beer-Lamberts Law.

Table No. 8.4: Absorbance values for standard calibration curve of Metoclopramide HCL in phosphate buffer pH 6.8

Sr. No.	Concentration (µg/ml)	Absorbance
1	**0**	**0**
2	**2**	**0.081**
3	**4**	**0.168**
4	**6**	**0.248**
5	**8**	**0.314**
6	**10**	**0.378**

Figure No. 8.9: Standard calibration curve of Metoclopramide HCL in pH 6.8 buffer.



8.4 Pre-compression study of tablet blend:

Nine formulations were prepared by using 2.6%, 4%, 5.3% concentration of super disintegration of superdisintegrants sodium starch glycolate, crospovidone and croscarmellose sodium. For each designed formulation, powder mixed blend of drug and excipients was prepared and evaluated for various parameters as follows.

Angle of Repose (θ):

The angle of repose of various powders mixed blend, prepared with different superdisintegrants, was measured by cylinder method. Angle of repose was found in the range from 25.80 to 32.36 the good flowability of powder blend was also evidenced with angle of repose which is indicated a good flowability. The result are given in table no. 8.5

Table no. 8.5: Angle of Repose

Batch code	Angle of repose (θ)
MF1	**30.61**
MF2	**32.12**
MF3	**31.60**
MF4	**29.60**
MF5	**32.20**
MF6	**32.36**
MF7	**31.16**
MF8	**25.80**
MF9	**28.50**

Bulk density: The bulk density of various powder mixed blends. Prepared with different superdisintegrants was measured by graduated cylinder. The bulk density was found in the range from 0.5 to 0.520. The result are given in table no. 8.6

Table no. 8.6: Bulk Density

Batch code	Bulk density (gm/cm^3)
MF1	**0.5**
MF2	**0.510**
MF3	**0.5**
MF4	**0.5**
MF5	**0.508**
MF6	**0.520**
MF7	**0.518**
MF8	**0.519**
MF9	**0.520**

Tapped density: The tapped density of various powder mixed blends prepared with different superdisintegrants, was measured by measuring cylinder. The tapped density was found in the range from 0.606 to 0.628. The result are given in table no. 8.7

Table no. 8.7: Tapped Density

Batch code	Tapped density (gm/cm^3)
MF1	**0.608**
MF2	**0.625**
MF3	**0.625**
MF4	**0.606**
MF5	**0.617**
MF6	**0.609**
MF7	**0.621**
MF8	**0.628**
MF9	**0.627**

Compressibility Index: The compressibility index of various powder mixed blends prepared with different superdisintegrants using bulk density and tapped density data, compressibility index was calculated. It was found in the range 14.61 to 20.00. The result are given in table no. 8.8

Table no. 8.8: Compressibility Index

Batch code	Compressibility Index (%)
MF1	**17.76**
MF2	**18.04**
MF3	**20.00**
MF4	**17.49**
MF5	**17.66**
MF6	**14.61**
MF7	**16.58**
MF8	**17.35**
MF9	**16.08**

Hausner ratio: The Hausner ratio of various powder mixed blends prepared with different superdisintegrants, it was calculated by using bulk density and tapped density data. It was found in the range of 1.17 to 1.25. The result are given in table no. 8.9

Table no .8.9: Hausner ratio

Batch code	Hausner ratio
MF1	**1.216**
MF2	**1.225**
MF3	**1.25**
MF4	**1.212**
MF5	**1.214**
MF6	**1.171**
MF7	**1.198**
MF8	**1.210**
MF9	**1.205**

8.5 Evaluation of orodispersible tablets of Metoclopramide HCl:

Hardness: Tablets were evaluated by using hardness tester. Hardness of the tablets was found in the range 1.90 to 2.20. The result are given in table no. 8.10

Table no. 8.10: Hardness

Batch code	Hardness (kg/cm2)
MF1	**1.98**
MF2	**1.98**
MF3	**2.02**
MF4	**1.95**
MF5	**1.96**
MF6	**2.0**
MF7	**1.90**
MF8	**2.20**
MF9	**1.96**

Friability: Tablets were evaluated by using Roche Friabilator and Friability of tablets was observed in acceptable range 0.48 to 0.81 (Less than 1%). The result are given in table no. 8.11

Table no. 8.11: Friability

Batch code	Friability (%)
MF1	**0.650**
MF2	**0.771**
MF3	**0.589**
MF4	**0.718**
MF5	**0.819**
MF6	**0.705**
MF7	**0.489**
MF8	**0.533**
MF9	**0.788**

Thickness uniformity: Tablets were evaluated by using verniercaliper. The thickness of tablets wasfound to be exact 2.5 uniform thickness was obtained due to uniform die fill.

Tablet no. 8.12: Thickness uniformity

Batch code	Thickness (mm)
MF1	**2.571**
MF2	**2.552**
MF3	**2.558**
MF4	**2.573**
MF5	**2.568**
MF6	**2.568**
MF7	**2.571**
MF8	**2.574**
MF9	**2.590**

Weight variation: Tablets were prepared using direct compression technique. Since the material was free flowing, tablets were obtained of uniforms weight due to uniform die fill. The tablets were obtained in the range with acceptable weight variations as per pharmacopoeia specifications less than 7.5%. The result are given in table no. 8.13

Table no. 8.13: Weight variation

Batch code	Weight (mg) ± S.D	Weight variation (7.5%)
MF1	**150.85 ±0.6**	**Passes**
MF2	**149.25±0.4**	**Passes**
MF3	**150.75±0.2**	**Passes**
MF4	**148.20±0.3**	**Passes**
MF5	**150.30 ±0.8**	**Passes**
MF6	**151.48 ±0.4**	**Passes**
MF7	**150.30 ±0.4**	**Passes**
MF8	**149.60 ±0.2**	**Passes**
MF9	**150.11±0.3**	**Passes**

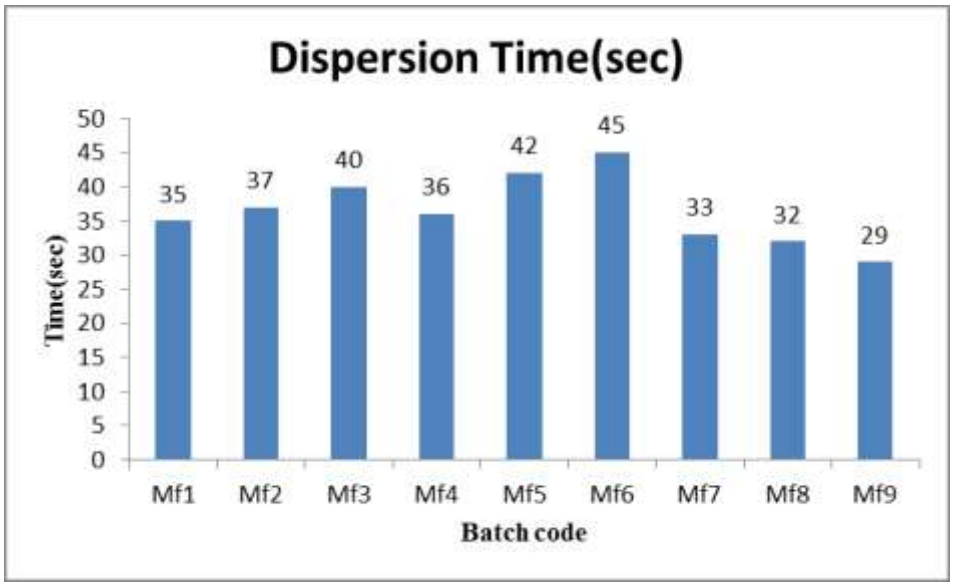
In-vitro dispersion time:

In-vitro dispersion time was measured by dropping a tablet into a petridish containing 10ml of phosphate buffer pH 6.8 solution at 37± 0.5^0c. The dispersion time was found in the range 29 to 45 for all batches. The batch MF9 showed the fast dispersion. The result are given in Table no. 8.14

Table no. 8.14: Dispersion Time

Batch code	Dispersion time (sec)
MF1	**35**
MF2	**37**
MF3	**40**
MF4	**36**
MF5	**42**
MF6	**45**
MF7	**33**
MF8	**32**
MF9	**29**

Figure No. 8.10 Dispersion Time



Water absorption ratio: A piece of tissue paper folded twice was placed in a small petri-dish (6.5cm)containing 6ml of water, a tablet was placed on the paper and the time forcomplete wetting was measured the wetted tablet was then weighed and thewater absorption ratio was calculated for each batch. The ratio was calculated for each batch. The ratios are given in table no. 8.15

Table no. 8.15: Water absorption ratio

Batch code	Water absorption ratio ±S.D
MF1	**62.65±5.90**
MF2	**91.03±2.42**
MF3	**67.76±6.04**
MF4	**62.60±2.50**
MF5	**67.56±5.40**
MF6	**97.10±1.94**
MF7	**83.81±5.77**
MF8	**84.10±2.45**
MF9	**61.65±5.90**

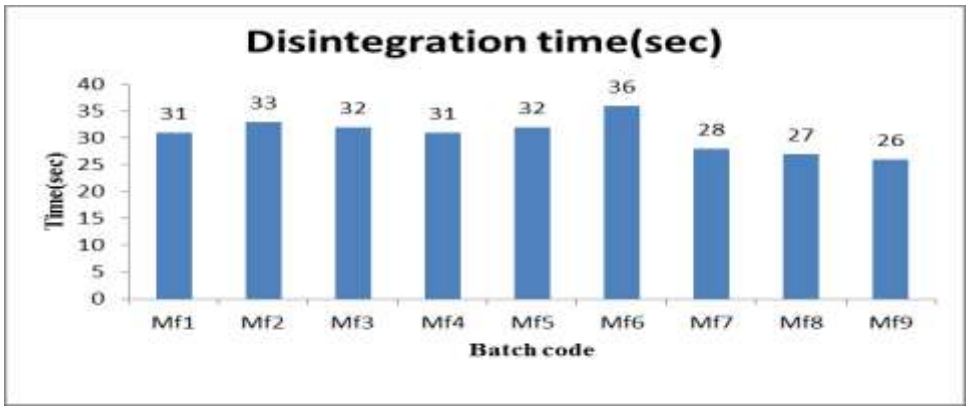
Disintegration time:

Tablets were evaluated for disintegration time in the disintegration test apparatus (I.P) The disintegration time was found in the range 26 to 36 for all the batches. The batch**MF9** showed the fastest disintegration. The result are given in table no. 8.16

Table no. 8.16: Disintegration Time

Batch code	Disintegration time (sec)
MF1	**31**
MF2	**33**
MF3	**32**
MF4	**31**
MF5	**32**
MF6	**36**
MF7	**28**
MF8	**27**
MF9	**26**

Figure No. 8.11 Disintegration Time



Content uniformity:

The results for content uniformity are presented in table no. 8.17 The results showed drug content were lying within the limits. The assay limit of Metoclopramide HCLtablets as per IP is 90-110%. The assays of the tablets were carried out as a process given in IP and data table are as follows.

Table no. 8.17: Content uniformity

Sr.no	Batch code	Content uniformity (%)
1	**MF1**	**98.96**
2	**MF2**	**99.02**
3	**MF3**	**100.30**
4	**MF4**	**99.16**
5	**MF5**	**97.91**
6	**MF6**	**98.95**
7	**MF7**	**99.03**
8	**MF8**	**99.30**
9	**MF9**	**98.93**

In-vitro release studies:

The Comparative analysis of each formulation was based on in vitro kinetic parameters, which elucidated the release profile. The in-vitro drug release of orodispersible tablets of Metoclopramide HCL for all formulation is given as follows.

***In vitro* drug release studies details:**

Apparatus used : USP II dissolution test apparatus

Dissolution medium : 6.8Buffer

Dissolution medium volume : 900 ml

Temperature : 37±0.5ºC

Speed of basket paddle : 50 rpm

Sampling intervals : 1 min

Sample withdrawn : 10 ml

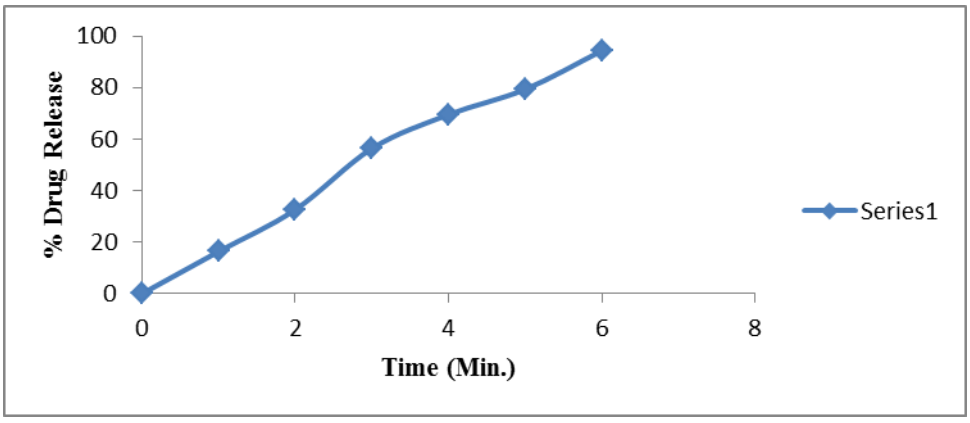
Absorbance measured : 273 nm

In-vitro release studies of batch MF1 in pH 6.8 buffer

Table no. 8.18 In-vitro release studies of batch MF1 in pH 6.8 buffer

Sr.no	Time (min)	Percent drug release
1	**0**	**0**
2	**1**	**16.39**
3	**2**	**32.62**
4	**3**	**56.39**
5	**4**	**69.53**
6	**5**	**79.36**
7	**6**	**94.35**

Figure No. 8.12: In-vitro release studies of batch MF1 in pH 6.8 buffer

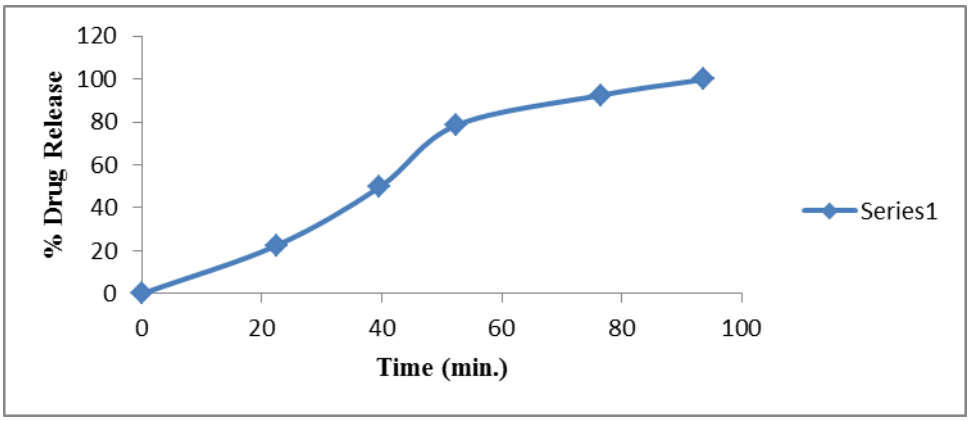


In-vitro release studies of batch MF2 in pH 6.8

Table No. 8.19: In-vitro release studies of batch MF2 in pH 6.8

Sr.no	Time (min)	Percent drug release
1	**0**	**00**
2	**1**	**22.39**
3	**2**	**39.62**
4	**3**	**52.39**
5	**4**	**76.56**
6	**5**	**93.65**

Figure No.8.13: In-vitro release studies of batch MF2 in pH 6.8

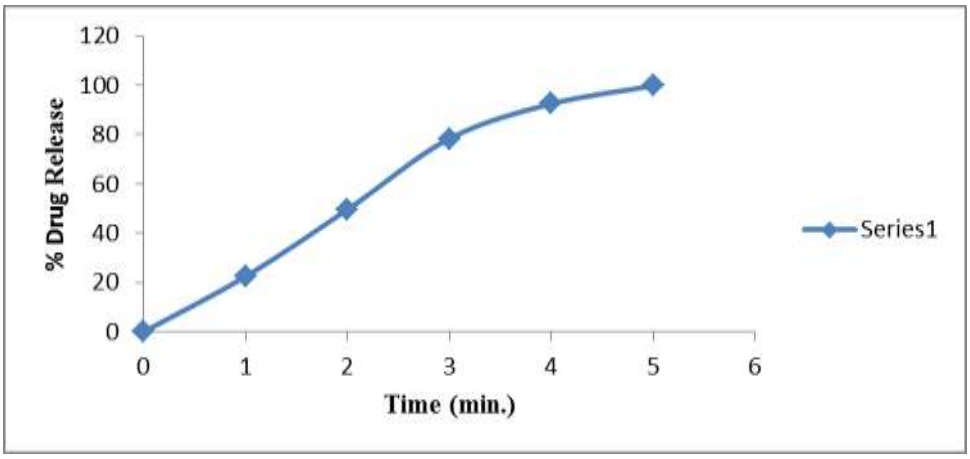


In-vitro release studies of batch MF3 in pH 6.8

Table No. 8.20: In-vitro release studies of batch MF3 in pH 6.8

Sr.no	Time (min)	Percent drug release
1	**0**	**00**
2	**1**	**22.39**
3	**2**	**49.62**
4	**3**	**78.39**
5	**4**	**92.50**
6	**5**	**99.79**

Figure No.8.14: In-vitro release studies of batch MF3 in pH 6.8

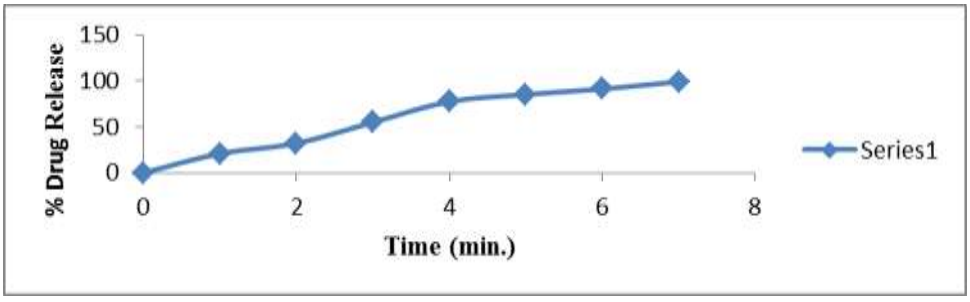


In-vitro release studies of batch MF4 in pH 6.8

Table No. 8.21: In-vitro release studies of batch MF4 in pH 6.8

Sr.no	Time (min)	Percent drug release(%)
1	**0**	**00**
2	**1**	**20.96**
3	**2**	**32.15**
4	**3**	**55.09**
5	**4**	**77.59**
6	**5**	**85.35**
7	**6**	**91.35**
8	**7**	**99.25**

Figure No.8.15: In-vitro release studies of batch MF4 in pH 6.8

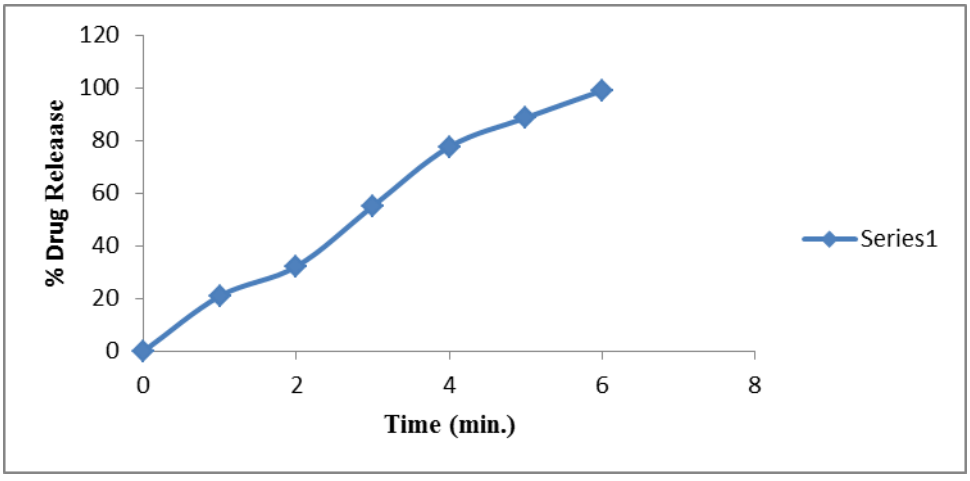


In-vitro release studies of batch MF5 in pH 6.8

Table No. 8.22: In-vitro release studies of batch MF5 in pH 6.8

Sr.no	Time (min)	Percent drug release(%)
1	**0**	**00**
2	**1**	**20.96**
3	**2**	**32.15**
4	**3**	**55.09**
5	**4**	**77.59**
6	**5**	**88.62**
7	**6**	**98.96**

Figure No. 8.16: In-vitro release studies of batch MF5 in pH 6.8

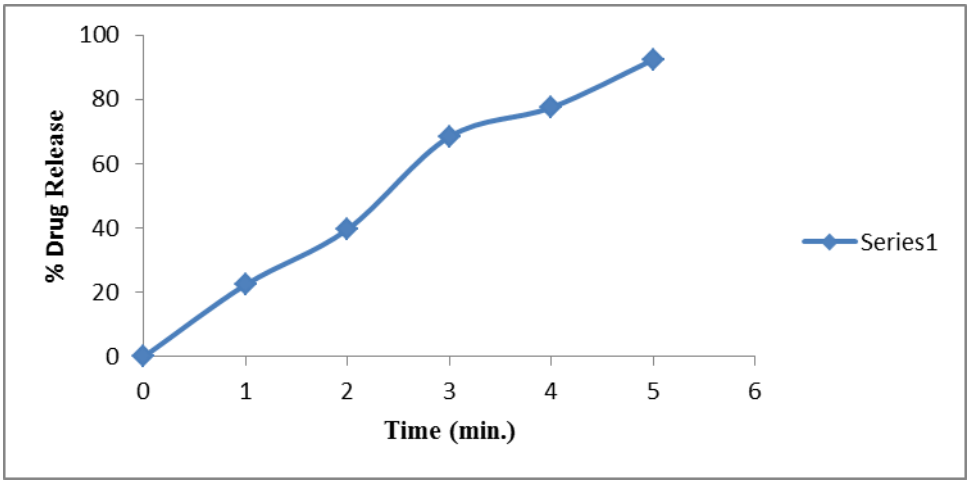


In-vitro release studies of batch MF6 in pH 6.8

Table No. 8.23: In-vitro release studies of batch MF6 in pH 6.8

Sr.no	Time (min)	Percent drug release
1	**0**	**00**
2	**1**	**22.39**
3	**2**	**39.62**
4	**3**	**68.39**
5	**4**	**77.5**
6	**5**	**92.36**

Figure No.8.17: In-vitro release studies of batch MF6 in pH 6.8

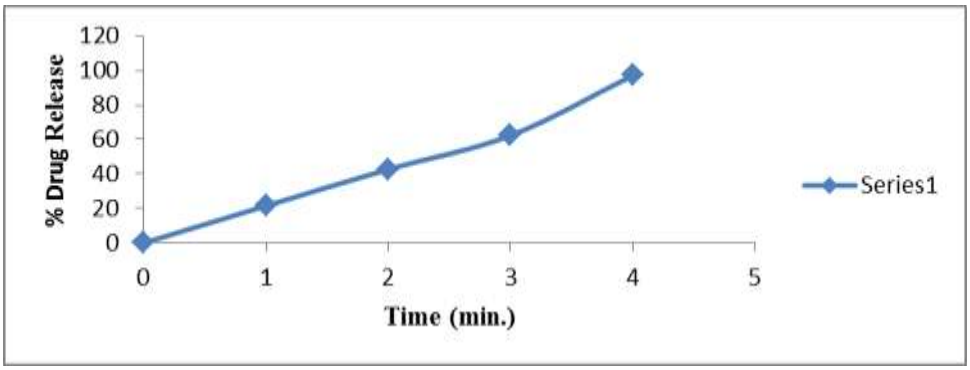


In-vitro release studies of batchMF7 in pH 6.8

Table No. 8.24: In-vitro release studies of batchMF7 in pH 6.8

Sr.no	Time (min)	Percent drug release
1	**0**	**0**
2	**1**	**21.51**
3	**2**	**42.70**
4	**3**	**62.35**
5	**4**	**97.15**

Figure No.8.18: In-vitro release studies of batchMF7 in pH 6.8

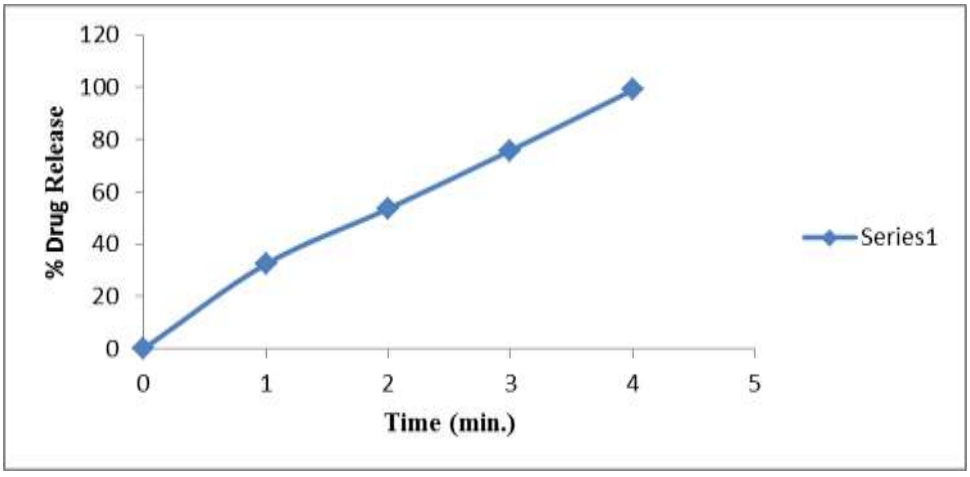


In-vitro release studies of batch MF8 in pH 6.8

Table No. 8.25: In-vitro release studies of batch MF8 in pH 6.8

Sr.no	Time (min)	Percent drug release
1	**0**	**0**
2	**1**	**32.39**
3	**2**	**53.58**
4	**3**	**75.86**
5	**4**	**98.97**

Figure No.8.19: In-vitro release studies of batch MF8 in pH 6.8

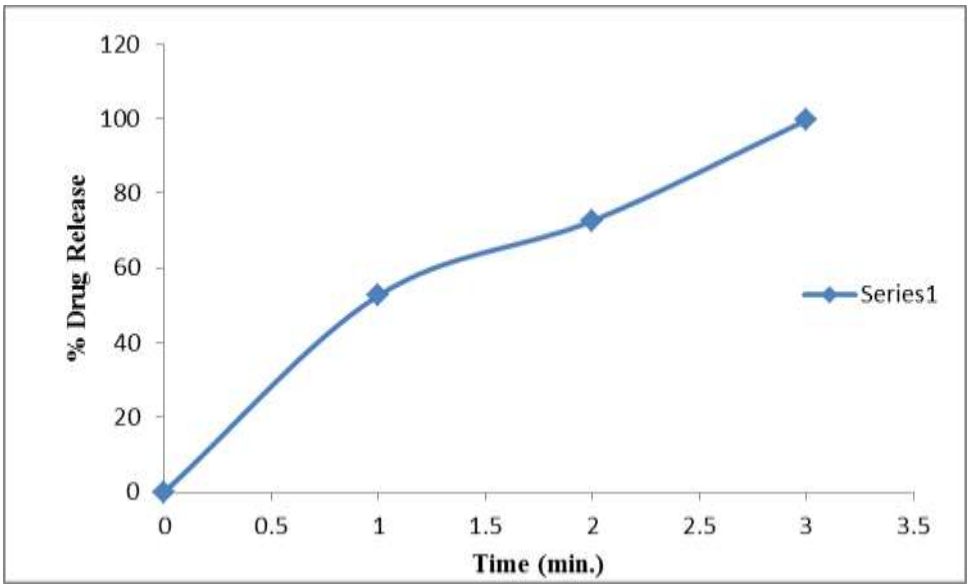


In-vitro release studies of batch MF9 in pH 6.8

Table No. 8.26: In-vitro release studies of batch MF9 in pH 6.8

Sr.no	Time (min)	Percent drug release
1	**0**	**00**
2	**1**	**52.63**
3	**2**	**72.63**
4	**3**	**99.60**

Figure No.8.20: In-vitro release studies of batch MF9 in pH 6.8



COMPARATIVE IN VITRO DRUG RELEASE PROFILE OF ORODISPERSIBLE TABLETS OF METOCLOPRAMIDE HCL IN pH 6.8 BUFFER

Table No. 8.27: Comparative in-vitro drug release profile of all batches

Sr. no	Time (MIN)	Percent drug release								
		MF1	MF2	MF3	MF4	MF5	MF6	MF7	MF8	MF9
1	0	00	00	00	00	00	00	00	00	00
2	1	16.39	22.39	22.39	20.96	20.96	22.39	21.51	32.39	52.63
3	2	32.62	39.62	49.62	32.15	32.15	39.62	42.70	53.58	72.63
4	3	56.39	52.39	78.39	55.09	55.09	68.39	62.35	75.86	99.60
5	4	69.53	76.56	92.50	77.59	77.59	77.5	97.15	98.97	
6	5	79.36	93.65	99.79	85.35	88.62	92.36			
7	6	94.35			91.35	98.96				
8	7				99.25					

From the above observation we can conclude that, as concentration of sodium starch glycolate, crospovidone, and cross carmellose sodium increase the disintegration time also increase. But the superdisintegrant cross carmellose sodium gives the minimum disintegrating time as compare to sodium starch glycolate or crospovidone. In the batch of cross carmellose sodium gives minimum disintegrating time and drug release in 3mins. at the concentration of 5.3% of cross carmellose sodium. And the batch of sodium starch glycolate and crospovidone (at the same conc. of superdisintegration i.e. 5.3%) gives the more disintegration time.

Figure No. 8.21: Comparative in vitro drug release profile of batches MF1 to MF4

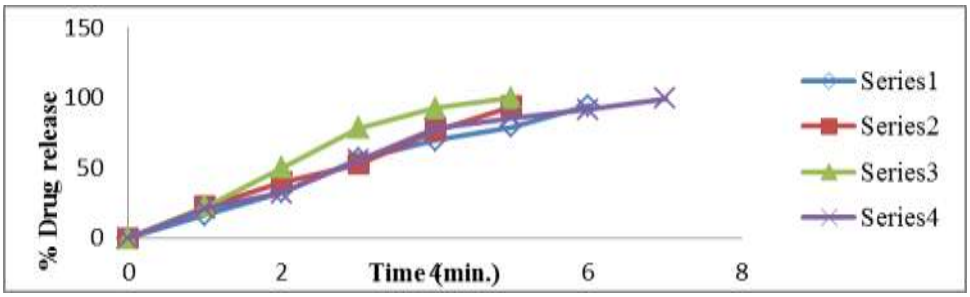
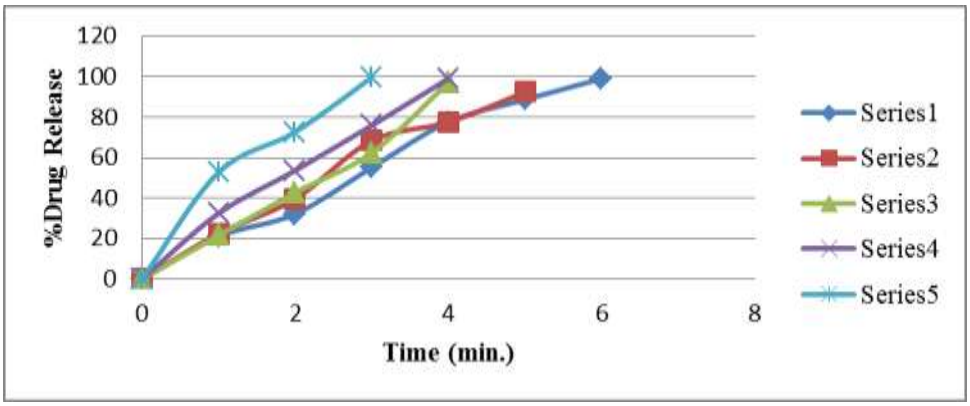


Figure No. 8.22: Comparative in vitro drug release profile of batches MF5 to MF9



STABILITY STUDIES:

Table No. 8.28: Showing the Stability Studies of Formulation MF9 at 25°C ± 2°C and 60% RH ± 5% RH

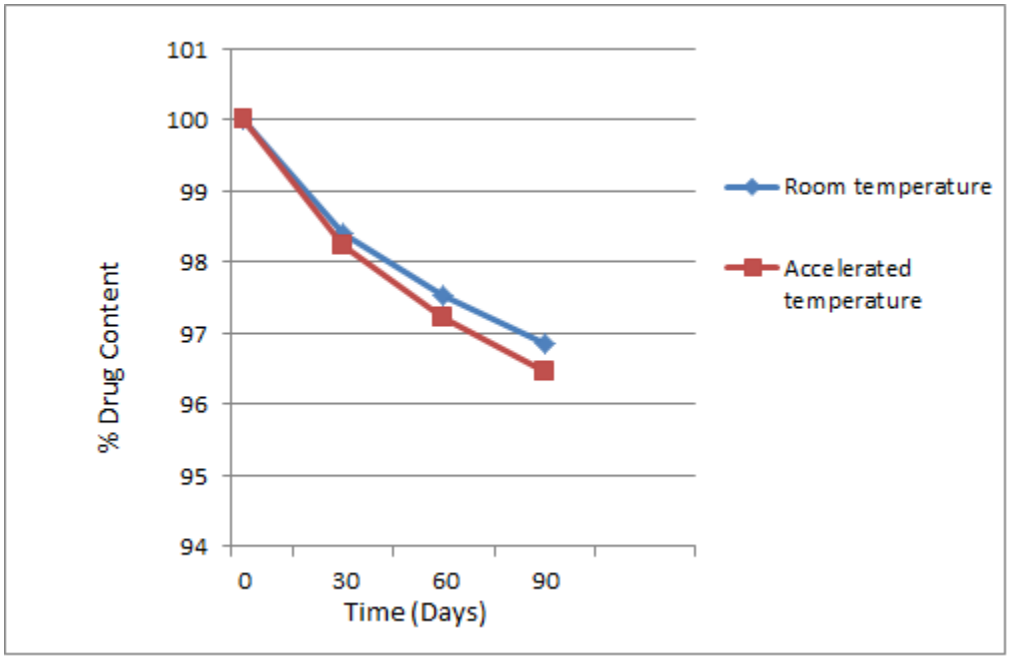
Time (days)	Drug content(%)	Hardness (Kg/cm^2)	Friability (%)
30	**98.41**	**1.94 ±0.12**	**0.58 ±0.012**
60	**97.53**	**1.90 ±0.11**	**0.56 ±0.012**
90	**96.87**	**1.89 ±0.11**	**0.55 ±0.012**

Table No. 8.29 Showing the Stability Studies of Formulation MF9 at 40°C ± 2°C and 75% RH ± 5% RH

Time (days)	Drug content(%)	Hardness (Kg/cm^2)	Friability(%)
30	**98.25**	**1.94 ±0.12**	**0.58 ±0.012**
60	**97.23**	**1.89 ±0.11**	**0.55 ±0.012**
90	**96.47**	**1.88 ±0.10**	**0.54 ±0.013**

Stability studies were carried out on optimized formulation (MF9) as per ICH guidelines. There was not much variation in the tablets at all the temperature conditions. There was no significant changes in drug content, physical stability, hardness, friability, drug release for the optimized formulation MF9 after 90 days at 25°C± 2°C / 60% ± 5% RH, and 40°C ± 2° / 75% ± 5% RH.

Figure No. 8.23: showing stability study for formulation MF9 at various temperature



9. SUMMARY AND CONCLUSION

9.1 Summary:

Metoclopramide hydrochloride is Antiemetics, Dopamine Antagonists, Prokinetic Agents used to treat nausea and vomiting, it blocks the D2 receptors in the Chemoreceptor Trigger Zone (CTZ) in the central nervous system. It is effective and popular drug for many types of vomiting. Gastrokinetic: to accelerate gastric emptying, Dyspepsia, Gastroesophageal reflux disease (GERD). On high dose it also shows the 5-HT3 receptor antagonist. Metoclopramide hydrochloride may used to be treat chemotherapy induced emesis.

The aim of present work was to prepare a suitable orodispersible tablet of Metoclopramide hydrochloride; once a day Metoclopramide hydrochloride dosage form could reduce the dosing frequency and improve patient compliance.

Sodium starch glycolate, crospovidone, cross carmellose sodium are use as superdisintegrant at minimum to maximum quantity which give better disintegration time with better releasing time was studied. Initially study gives the report that as we increase the concentration superdisintegrating agents, the disintegrating time and in-vitro drug release are also increases.

In the study all the formulation were subjected to physical parameters of tablets, like hardness, friability, weight variation, drug content of Metoclopramide hydrochloride. All the formulations resulted in acceptable limit except formulation MF3 and MF8 for hardness test marginally deviated. The final batch MF9 (contained Cross Carmellose Sodium 5.3%) can be considered as optimized batch as it has the disintegration time is minimum (26 sec) seems to be most promising formulation which gives the release up to **99.60**% in 3min.

The drug-excipients interaction studies were carried out by FTIR. No significant interaction of drug with excipients was observed. During stability studies, no significant variation in drug release was observed, indicating that formulation batch MF9 was stable over the chosen condition for 3 months.

The optimized formulation batch MF9 showed better drug release profile with other formulations.

9.2 Conclusion:

From the present study carried out on metoclopramide HCL orodispersible tablet using by direct compression method, the following conclusion can be drawn.

The total weight of MF9 batch was 150 mg contained metoclopramide HCL-6.6%, croscarmellose sodium-5.3%, microcrystalline cellulose-33.3%, aspartame-4%, magnesium stearate-1%, talc-0.6%, aerosil-0.3%, pineapple flavor-0.6%, mannitol-48%.

The Prefromulation study gives the following information of optimize batch Angle of Repose-$28^{0}.50^{'}$ Bulk density-0.520, Tapped density-0.627, Compressibility Index-16.08 good to flow, Hausner ratio-1.205.

Post parameter evaluation of tablets Hardness-1.96, Friability-0.788, Thickness-2.590, Weight variation-150.11±, Dispersion time-29 sec, Water absorption ratio-61.65, Disintegration time-26 sec, Content uniformity-98.93%, In-vitro drug release studies- in 3 min.

If the concentration of croscarmellose sodium is increases it gives quick the disintegration and dissolution was observed. So the results give information that Disintegration time in 26 sec and dissolution in 3 min. Croscarmellose sodium is the optimize batch on basis of disintegration time and in-vitro drug release.

The optimized formulation of batch MF9 gave the best in-vitro release of 99.60% in 3min in phosphate buffer pH 6.8. The release of drug followed matrix diffusion mechanism.

Our objective to cost effective orodispersible tablet by direct compression quickly disperse in oral cavity and it definitely gives the fast release action for its antiemetic activity. Fast disintegration of tablets formulated in this investigation may be help in administration of metoclopramide HCL in a palatable form without water during emesis. Formulation MF9 gives the quick disintegration and better drug release. Hence it can be concluded that the formulation MF9 is a stable and effective for quick action and it is alternative to the conventional tablets.

10. REFERENCES

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