"FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF METOCLOPRAMIDE HYDROCHLORIDE"

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THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY
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In partial fulfillment of the requirements for the award of the Degree of
MASTER OF PHARMACY
IN
PHARMACEUTICS

Submitted By
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Under the guidance of
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(Affiliated to the Tamilnadu Dr. M.G.R Medical University, Chennai)

Approved by the Govt. of Tamilnadu, Chennai
All India Council for Technical Education, New Delhi
Recognized by Pharmacy Council of India, New Delhi

CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF METOCLOPRAMIDE HYDROCHLORIDE"** Submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai, is a bonafide project work of **Reg. No: 261511001** carried out in the department of pharmaceutics, Cherraan's College of Pharmacy, Coimbatore, for the partial fulfillment for the degree of Master of Pharmacy under my guidance during the academic year 2016-2017.

This work is original and has not been submitted earlier for the award of any other degree or diploma of this or any other university.

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CHERRAAN'S COLLEGE OF PHARMACY

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Internal Examiner **External Examiner**

DECLARATION

The research work embodied in this work "**FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF METOCLOPRAMIDE HYDROCHLORIDE"** was carried out by me in the department of pharmaceutics, cherraan's College of Pharmacy, Coimbatore under the direct supervision of J. Karthikeyan, M.Pharm, Professor, Cherraan's college of Pharmacy, Coimbatore.

The dissertation submitted to The Tamilnadu Dr. M.G.R Medical University, Chennai, for the award of degree of Master of Pharmacy in Pharmaceutics during the academic year of 2016-2017.

Place: Coimbatore

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SYMBOLS AND ABBREVATIONS

Gm	Gram
Hrs	Hours
mg	Milligram
nm	Nanometer
mm	Micrometer
UV	Ultra-Violet
%	Percent/Percentage
RPM	Rotation per Minute
Abs	Absorbance
Conc.	Concentration
i.m	Intra Muscular
Min	Minute
L/kg	Litre/ Kilogram
pH	Negative logarithm of hydrogen ion
pKa	Negative logarithm of acid Dissociation constant
FTIR	Fourier transform infrared spectroscopy

Cm	Centimeter
RH	Relative Humidity
^{0}C	Degree Celsius
%	Percent/Percentage
RF	Retardation Factor
BPC	British Pharmacopoeia
I.P	Indian Pharmacopoeia
Ph. Eur	European Pharmacopoeia
USP	United State Pharmacopoeia
S.D	Standard Deviation
5HT	5 Hydroxy Tryptamine
API	Active Pharmaceutical Ingredient

CONTENTS

1. INTRODUCTION

An ideal dosage regimen in the drug therapy of any disease is the one which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for entire duration of treatment. This is possible through administration of conventional dosage form in a particular dose at a particular frequency. Thus drug may administered by variety routes in variety of dosage form[1].

Oral route is most common and popular route of administration of drug is oral route because of its systemic effect, patient compliance, less expensive to manufacture. Tablet provides high precision dosing. Tablet form is the most widely used dosage form because of self-administration and ease in manufacturing. In most of the cases immediate on set of action is required as compare to conventional therapy. To achieve the rapid onset of action and eliminate the drawbacks of conventional therapy immediate release dosage form is now a days popular and used as an alternative oral dosage form. Immediate release tablet are very quickly after administration. Basic approach used in development is the use of superdisintegrants which provide rapid disintegration of tablet after administration[2].

1.1. Types of Tablets [3, 4, 5]:

1. Tablets ingested orally

    a. Standard Compressed tablet

    b. Multiple compressed tablet

        i. Layered Tablet
        ii. Compression coated Tablet

    c. Repeat action Tablet

    d. Delayed action and enteric coated Tablet

    e. Sugar and chocolate coated tablet

    f. Film coated tablet

    g. Chewable Tablet

    h. Targeted tablet

        i. Floating tablet
        ii. Colon targeted tablet

These tablets are meant to be swallowed intact along with a sufficient quantity of potable water. Exception is chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction.

2. Tablets used in the oral cavity:

a. Buccal Tablet

b. Sublingual Tablet

c. Troches and Lozenges

d. Dental cones

e. Mouth dissolved tablet

The tablets under this group are aimed release API in oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity.

3. Tablets administered by other routes:

a. Implantation Tablet

b. Vaginal Tablets

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application.

4. Tablets used to prepare solution:

a. Effervescent Tablet

b. Dispensing Tablet

c. Hypodermic Tablet

d. Tablets Triturates

1.2. Immediate Release Dosage Form

Immediate release tablets are designed to disintegrate and release the drug in absence of any controlling features such as coating or other formulation techniques[6]. The solution containing the active ingredients is swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect[7].

1.3. Advantages of Tablets

- They are unit dosage form, and they offer the capabilities of all oral dosage forms for the dose precision and the least content variability during dosing.
- Accuracy and uniformity of drug content.
- Optimal drug dissolution and hence, availability from the dosage form for absorption consistent with intended use (i.e., immediate or extended release).
- Usually taken orally, but can be administered sublingually, rectally or intra-vaginally.
- Their cost is lowest of all oral dosage form.
- They are the most compact of all oral dosage forms.
- They are in general the easier and cheaper to package and ship as compare to other oral dosage forms.
- Product identification is simple and cheap, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They are ease to administer, does not require a specialist.
- They are better suited to large-scale production than other unit oral forms.
- They have the better properties of chemical, mechanical and microbiological stability.
- Easy to prepare.
- Provide prolonged stability to medicaments.
- Formulate as a special release products such as enteric or delayed release products.
- Easy to divide into halves and quarters whenever fraction dose is required.

1.4. Problems With Existing Oral Dosage Form [11,12]:

- Patient may suffer from tremors therefore they have difficulty to take powder and liquids. In dysphasia physical obstacles and adherence to an esophagus may cause gastrointestinal ulceration.

- Swallowing of solid dosage forms like tablet and capsules and produce difficulty for young adult of incomplete development of muscular and nervous system and elderly patients suffer from dysphasia.

- Liquid medicaments (suspension and emulsion) are packed in multidose container; therefore achievement of uniformity in the content of each dose may be difficult.

- Buccal and sublingual formation may cause irritation to oral mucosa, so patients refused to use such medications.

- Cost of products is main factor as parenteral formulations are most costly and discomfort.

1.5. Desired Criteria For Immediate Release Drug Delivery System [13,14]:

- In the case of solid dosage it should dissolve or disintegrate in the stomach within a short period.

- In the case of liquid dosage form it should be compatible with taste masking.

- Be portable without fragility concern.

- Have a pleasing mouth feel.

- It should not leave minimal or no residue in the mouth after oral administration.

- Exhibit low sensitivity to environmental condition as humidity and temperature.

- Be manufactured using conventional processing and packaging equipment at low cost.

- Rapid dissolution and absorption of drug, which may produce rapid onset of action.

1.6. Merits of Immediate Release Drug Delivery System [15]:

- Improved compliance/added convenience
- Improved stability, bioavailability
- Suitable for controlled/sustained release actives
- Allows high drug loading
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging machinery
- Cost- effective
- Improved solubility of the pharmaceutical composition
- Decreased disintegration and dissolution times for immediate release oral dosage forms.

Bulking Agents

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

Lubricants

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

Carrier Materials

For therapeutic purposes, the pharmaceutical compositions of the present invention comprise micronized drug in a desired amount in combination with one or more pharmaceutically-acceptable carrier materials appropriate to the indicated route of administration.

Oral dosage forms of the pharmaceutical compositions of the present invention preferably comprise micronized drug in a desired amount admixed with one or more carrier materials selected from the group consisting of diluents, disintegrants, binding agents and adhesives, wetting agents, lubricants, anti-adherent agents and/or other carrier materials. More preferably, such compositions are tableted or encapsulated for convenient administration. Such capsules or tablets can be in the form of immediate release capsules or tablets, or can contain a controlled-release formulation as can be provided.

For example, in a dispersion of drug in hydroxypropyl methylcellulose. Injectable dosage forms preferably are adapted for parenteral injection. Preferably, these dosage forms comprise micronized drug in aqueous or non-aqueous isotonic sterile injection solutions or suspensions, such as drug suspended or dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. These solutions and suspensions can be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration.

Super Disintegrants[33]

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

Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids.

Superdisintegrant improve disintegrant efficiency resulting in decreased use levels when compared to traditional disintegrants. Traditionally, starch has been the disintegrant of choice in tablet formulation, and it is still widely used. For instance, starch generally has to be present at levels greater than 5% to adversely affect compatibility, especially in direct compression. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants[8].

Mechanism of Disintegrants[9,10]:

1) High swellability

2) Capillary action and high swellability

3) Chemical reaction

When introduced to an aqueous environment of use, the tablet rapidly takes up water, leading to swelling of the disintegrant and rapid disintegration of the tablet before the dispersion polymer can form a hydrogel. The disintegrant should be chosen such that it:

(1) Swells rapidly when introduced into the use environment

(2) Has a low tendency to form or promote formation of a hydrogel.

The rate of swelling of the disintegrant is directly correlated to tablet disintegration times. Tablets containing disintegrants cause more rapid swelling have faster disintegration times at comparable disintegrant levels. The amount of work, W, or swelling energy, due to swelling can be measured using a dynamic mechanical analyzer (DMA). The swelling energy attributable to swelling of the disintegrant in the compact may be calculated from the following equation:

$$W=P\Delta V$$

Where,

W is the work or swelling energy of the disintegrant,

P is the pressure applied by the probe,

ΔV is the volume change of the sample.

To compare disintegrants, the swelling energy per mass of disintegrant is used. Preferably, the disintegrant generates a swelling energy of at least 0.05 J/g within about 10 minutes following addition of water to the liquid reservoir. The most popular disintegrants are corn starch, soluble starch etc. which have been well dried and powdered. Starches have great affinity for water and swell when moistened thus facilitating the rupture of the tablet matrix, its disintegration action in tablets is due to capillary action. Spherical shape of starch increases the porosity of tablet thus promoting capillary action.

Classification of "Superdisintegrant" may be organized into three classes based on their chemical structure. As shown in Table below.

Table No.1.1: Classification of Super disintegerants

Disintegerants	Concentration in granules (%)	Special comments
Starch USP	5-20	Higher amount is required, poorly compressible
Starch 1500	5-15	-
Avicel®(PH 101,PH 102)	10-20	Lubricant properties and directly compressible
Solka floc	5-15	Purified wood cellulose
Alginic acids	1-5	Acts by swelling
Na alginate	2.5-10	Acts by swelling
Explotab	2-8	Sodium Starch glycolate Superdisintegerant
Polyplasdone(XL)	0.5-5	Cross-linked PVP
Amberlite (IPR 88)	0.5-5	Ion exchange resin
Methyl cellulose, Na CMC HPMC	5-10	-
AC-Di-Sol	1-3	Direct compression
	2-4	Wet granulation

Advantages:

1. Effective in lower concentrations
2. Less effect on compressibility and flow ability
3. More effective intragranularly some super disintegrants are:

A. Sodium Starch Glycolate used in concentration of 2-8 % and optimum is 4%. **Mechanism of Action:** Rapid and extensive swelling with minimal gelling. Microcrystalline cellulose (Synonym: Avicel, celex) used in concentration of 2-15% of tablet weight. And Water wicking.

B. Cross-linked Povidone (crospovidone) used in concentration of 2-5% of weight of tablet. **Mechanism of Action**: Water wicking, swelling and possibly some deformation recovery. Rapidly disperses and swells in water, but does not gel even after prolonged exposure. Greatest rate of swelling compared to other disintegrants. Greater surface area to volume ratio than other disintegrants.

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

D. Cross linked carboxy methyl cellulose sodium (i.e. Ac-Di-sol) Croscarmellose Sodium **Mechanism of Action:** Wicking due to fibrous structure, swelling with minimal gelling. Effective Concentrations: 1-3% Direct Compression, 2-4% Wet Granulation Conventional.

Surfactants:

One very useful class of excipients is surfactants, preferably present from 0 to 10 wt %. Suitable surfactants include fatty acid and alkyl sulfonates; commercial surfactants such as benzalkonium chloride, dioctyl sodium sulfosuccinate, polyoxyethylene sorbitan fatty acid esters, natural surfactants such as sodium taurocholic acid, lecithin, and other phospholipids and mono- and diglycerides; and mixtures thereof. Such materials can advantageously be employed to increase the rate of dissolution by, for example, facilitating wetting, or otherwise increase the rate of drug release from the dosage form.

pH Modifiers:

Inclusion of pH modifiers such as acids, bases, or buffers may also be beneficial in an amount of from 0 to 10 wt %. Acidic pH modifiers (e.g., acids such as citric acid or succinic acid) retard the dissolution of the pharmaceutical composition when the dispersion polymer is anionic. Alternatively, basic pH modifiers (e.g., sodium acetate or amines) enhance the rate of dissolution of the same types of pharmaceutical composition.

Porosigen[34]:

The dosage form also includes a porosigen. A "porosigen" is a material that, when present in the formulation containing the solid amorphous dispersion, leads to a high porosity and high strength following compression of the blend into a tablet. In addition, preferred porosigen are soluble in an acidic environment with aqueous solubility typically greater than 1 mg/mL at a pH less than about 5.

Examples of porosigens include acacia, calcium carbonate, calcium sulfate, calcium sulfate dihydrate, compressible sugar, dibasic calcium phosphate, tribasic calcium phosphate, monobasic sodium phosphate, dibasic sodium phosphate, lactose, magnesium oxide, magnesium carbonate, silicon dioxide, magnesium aluminum silicate, maltodextrin, mannitol, methyl cellulose, microcrystalline cellulose, sorbitol, sucrose, xylitol and mixtures thereof.

Generally, the porosigen will comprise from 5 to 70 wt %. To ensure the tablet has sufficient porosity to allow adequate wicking of water into the tablet to cause rapid tablet disintegration and/or rapid release of drug, tablet porosity should be within 0.15-0.25. Accordingly, the disintegrant, porosigen should be selected so that the immediate release dosage form has high strength as well as the high porosity required to achieve rapid disintegration and/or release of drug.

Other Excipients

Excipients balance the properties of the actives in immediate release dosage forms. This demands a thorough understanding of the chemistry of these excipients to prevent interaction with the actives. Determining the cost of these ingredients is another issue that needs to be addressed by formulators. The role of excipients is important in the formulation of fast-melting tablets. These inactive food grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents[17].

1.7. Technique Used In the Preparation of Immediate Release Tablets[18]

- Tablet molding technique
- Granulation technique
- Direct compression technique
- Mass extrusion technique Tablet Molding

1.7.1. Tablet molding technique[27]

In this technology, water-soluble ingredients are used so that tablet disintegrate and dissolve rapidly. The powder blend is moistened with a hydro alcoholic solvent and is molded into tablet using compression pressure lower than used in conventional tablets compression. The solvent is then removed by air-drying. Molded tablets have a porous structure that enhances dissolution.

Two problems commonly encountered are mechanical strength and poor taste masking characteristics. Using binding agents such as sucrose, acacia or poly vinyl pyrrolidone can increase the mechanical strength of the tablet. To overcome poor taste masking characteristic Van Scoik incorporated drug containing discrete particles, which were formed by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium bicarbonate, lecithin, polyethylene glycol and active ingredient into a lactose based tablet triturate form.

1.7.2. Mass extrusion technique Tablet Molding[28]

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking

Immediate release solid dosage forms prepared by solid dispersions. When formulating such solid amorphous dispersions into immediate release solid dosage forms for oral administration to a use environment such as the GI tract of an animal such as a human, it is often desirable to maximize the amount of dispersion present in the dosage form. This minimizes the size of the solid dosage form required to achieve the desired dose.

Depending on the drug dose, it is often desired that the solid amorphous dispersion comprise at least 30 wt. %, preferably at least wt. %, and more preferably at least 50 wt % or more of the solid dosage form. Such high drug loadings of dispersion in a solid dosage form minimize the dosage form's size, making it easier for the patient to swallow it and tending to improve patient compliance.

The immediate release dosage forms containing a solid dispersion that enhances the solubility of a “low-solubility drug,” meaning that the drug may be either “substantially water-insoluble,” which means that the drug has a minimum aqueous solubility at physiologically relevant pH (e.g., pH 1-8) of less than 0.01 mg/mL, “sparingly water-soluble,” that is, has an aqueous solubility up to about 1 to 2 mg/mL, or even low to moderate aqueous solubility, having an aqueous-solubility from about 1 mg/mL to as high as about 20

to 40 mg/ml. The drug dispersions used in fabricating the high loading immediate release dosage forms of the present invention comprise solid dispersions of a drug and at least one concentration enhancing polymer.

1.7.3. Direct Compression Method[41,42,43]:

In this method, tablets are compressed directly from the mixture of the drug and excipients without any preliminary treatment. The mixture to be compressed must have adequate flow properties and cohere under pressure thus making pretreatment as wet granulation unnecessary. Few drugs can be directly compressed into tablets of acceptable quality. A type of disintegrant and its proportion are of prime importance. The other factors to be considered are particle size distribution, contact angle, pore size distribution, tablet hardness and water absorption capacity. All these factors determine the disintegration. The disintegrant addition technology is cost effective and easy to implement at industrial level.

Advantages

- Direct compression is more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.
- The most important advantage of direct compression is that it is an less economical process. Reduced processing time, reduced labor costs, fewer manufacturing step, and less number of equipments are required, less process validation, reduced consumption of power. Elimination of heat and moisture, thus increasing not only the stability but also the suitability of the process for thermolabile and moisture sensitive API.
- Particle size uniformity.
- Prime particle dissolution.
- In case of directly compressed tablets after disintegration, each primary drug particle is liberated. While in the case of tablets prepared by compression of granules, small drug particles with a larger surface area adhere together into larger agglomerates; thus decreasing the surface area available for dissolution.
- The chances of batch-to-batch variation are negligible, because the unit operations required for manufacturing processes is fewer.
- Chemical stability problems for API and excipient would be avoided.
- Provides stability against the effect of aging which affects the dissolution rates.

Disadvantages

Excipients Related

- Problems in the uniform distribution of low dose drugs. High dose drugs having high bulk volume, poor compressibility and poor flow ability are not suitable for direct compression for example, Aluminium Hydroxide, Magnesium Hydroxide.
- The choice of excipients for direct compression is extremely critical. Direct compression diluents and binders must possess both good compressibility and good flow ability.
- Many active ingredients are not compressible either in crystalline or amorphous forms.
- Direct compression blends may lead to unblending because of difference in particle size or density of drug and excipients. Similarly the lack of moisture may give rise to static charges, which may lead to unblending.
- Non-uniform distribution of color, especially in tablets of deep colors

1.7.4. Granulation[29]

Granulation may be defined as a size enlargement process which converts small particles into physically stronger & larger agglomerates. The objective of granulation is to improve powder flow and handling, decrease dustiness, and prevent segregation of the constituents of the product.

Granulation method can be broadly classified into two types:

1. Wet granulation and
2. Dry granulation Ideal characteristics of granules

The ideal characteristics of granules include spherical shape, smaller particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-2%), good flow, good compressibility and sufficient hardness. The effectiveness of granulation depends on the following properties:

- Particle size of the drug and excipients
- Type of binder (strong or weak)
- Volume of binder (less or more)

- Wet massing time (less or more)
- Amount of shear applied
- Drying rate (Hydrate formation and polymorphism)

(i) Wet granulation [30]

Wet granulation is a commonly used unit operation in the pharmaceutical industry. Wet granulation is often carried out utilizing a high-shear mixer. The high-shear granulation process is a rapid process which is susceptible for over wetting. Thus, the liquid amount added is critical and the optimal amount is affected by the properties of the raw materials. Power consumption of the impeller motor and the impeller torque have been applied to monitor the rheological properties of the wet mass during agglomeration and, thereby, have been used to determine the end-point of water addition. However, these methods are affected by the equipment variables. Hence, additional process monitoring techniques would be valuable. Important steps involved in wet granulation.

- Mixing of drug(s) and excipients.
- Preparation of binder solution.
- Mixing of binder solution with powder mixture to form wet mass.
- Coarse screening of wet mass using a suitable sieve (6-12 screens).
- Drying of moist granules.
- Screening of dry granules through a suitable sieve (14-20 screen).
- Mixing of screened granules with disintegrant, glidant, and lubricant. Limitation of wet granulation.

Advantages

- Rapid process.
- Ability to be operated continuously.
- Suitable for heat sensitive product.

Disadvantages

- The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements.
- Loss of material during various stages of processing
- Stability may be a major concern for moisture sensitive or thermo labile drugs.
- An inherent limitation of wet granulation is that any incompatibility between Formulation components is aggravated. It is a unique granulation technique that directly converts liquids into dry powder in a single step. This method removes Moisture instantly and converts pumpable liquids into a dry powder.

(ii) Dry granulation [30, 31]

In dry granulation process the powder mixture is compressed without the use of heat and solvent. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain granules. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is pre-compressed and the resulting tablets or slugs are milled to yield granules. The other method is to pre-compress the powder with pressure rolls using a machine such as chilsonator.

Advantages:

The main advantages of dry granulation or slugging are that it uses less equipment's and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step required for wet granulation. Slugging can be used for advantages in the following situations:

- For moisture sensitive material
- For heat sensitive material
- For improved disintegration since powder particles are not bonded together by a binder.

Disadvantages:

- It requires a specialized heavy duty tablet press to form slug.

- It does not permit uniform color distribution as can be achieved with wet granulation where the dye can be incorporated into binder liquid.
- The process tends to create more dust than wet granulation, increasing the potential contamination.

Steps in dry granulation:

1. Milling of drugs and excipients
2. Mixing of milled powders Compression into large, hard tablets to make slug
3. Screening of slugs
4. Mixing with lubricant and disintegrating agent
5. Tablet compression two main dry granulation processes:

a. Slugging process

Granulation by slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly. The accuracy or condition of slug is not too important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling.

b. Roller compaction

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

1.7.5. By solid dispersions [35,36]:

Dispersion of one or more active ingredients in an inert carrier or matrix in solid state, and insoluble or bland matrices may be used to mask the taste of bitter taste. Carriers used in solid dispersion systems include povidone, polyethelene glycols, hydroxypropyl methyl cellulose, urea, mannitol and ethyl cellulose.

When formulating such solid amorphous dispersions into immediate release solid dosage forms for oral administration to a use environment such as the GI tract of an animal

such as a human, it is often desirable to maximize the amount of dispersion present in the dosage form. This minimizes the size of the solid dosage form required to achieve the desired dose. Depending on the drug dose, it is often desired that the solid amorphous dispersion comprise at least 30 wt %, preferably at least wt %, and more preferably at least 50 wt % or more of the solid dosage form. Such high drug loadings of dispersion in a solid dosage form minimize the dosage form's size, making it easier for the patient to swallow it and tending to improve patient compliance.

The immediate release dosage forms containing a solid dispersion that enhances the solubility of a "low-solubility drug," meaning that the drug may be either "substantially water-insoluble," which means that the drug has a minimum aqueous solubility at physiologically relevant pH (e.g., pH 1-8) of less than 0.01 mg/mL, "sparingly water-soluble," that is, has an aqueous solubility up to about 1 to 2 mg/mL, or even low to moderate aqueous-solubility, having an aqueous-solubility from about 1 mg/mL to as high as about 20 to 40 mg/mL.

The drug dispersions used in fabricating the high loading immediate release dosage forms of the present invention comprise solid dispersions of a drug and at least one concentration-enhancing polymer. The concentration-enhancing polymer is present in the dispersions used in the present invention in a sufficient amount so as to improve the concentration of the drug in a use environment relative to a control composition. At a minimum, the dispersions used in the present invention provide concentration enhancement relative to a control consisting of crystalline drug alone. Thus, the concentration-enhancing polymer is present in a sufficient amount so that when the dispersion is administered to a use environment, the dispersion provides improved drug concentration relative to a control consisting of an equivalent amount of crystalline drug, but with no concentration-enhancing polymer present. Various approaches for preparation of solid dispersion are described below:

A. Melting Method

In this method, the drug or drug mixture and a carrier are melted together by heating. The melted mixture is cooled and solidified rapidly in an ice bath with vigorous stirring. This final solid mass is crushed and pulverized.

B. Solvent Method

In this method, the active drug and carrier are dissolved in a common solvent, followed by solvent evaporation and recovery of solid dispersion.

C. Melting-Solvent Method

In this method the drug, in solution form, is incorporated into a molten mass of polyethylene glycol at a temperature below 70^0c without removing the solvent.

1.6. Emesis[37]

Vomiting can also be referred to as emesis, and consists of the following stages:

Nausea

Nausea is an unpleasant sensation of wanting to vomit, and is often associated with cold sweat, pallor, salivation, loss of gastric tone, duodenal contraction, and the reflux of intestinal contents into the stomach. Nausea generally precedes vomiting, but can occur by itself. The system that brings about the loss of gastric tone, of gastric relaxation, is the efferent part of the long loop intestinal reflex that relaxes the gut during food intake.

Retching

Retching is a strong involuntary effort to vomit, and usually follows nausea. During retching, the abdominal muscles, chest wall and diaphragm all contract without any expulsion of gastric contents.

Vomiting

Vomiting is the forceful expulsion of the contents of the gastrointestinal system out through the mouth. From an evolutionary perspective, it is thought to have evolved as a defense mechanism of the body, serving a protective function to rid the body of noxious substances that have been ingested, rather than allowing them to be retained and absorbed by the intestine.

Contrary to popular belief, the stomach itself does not actively expel its contents during vomiting. The stomach, oesophagus, and their relevant sphincters are all in fact relaxed during vomiting. Most of the force that expels the contents arises from the contraction of the diaphragm, which is the major respiratory muscle, and the abdominal muscles, which are the muscles involved in active expiration.

1.7. Mechanisms of emesis

The mechanisms of emesis can be divided into three components:

Afferent inputs go to the central nervous system (CNS), relaying the signals of emetic stimuli; these signals are received, recognized, and centrally processed. They then form integrated emetic efferent signals coming from the CNS; these motor and chemical efferent pathways relay signals that lead to the coordinated respiratory, gastrointestinal and abdominal muscle expulsive actions of vomiting.

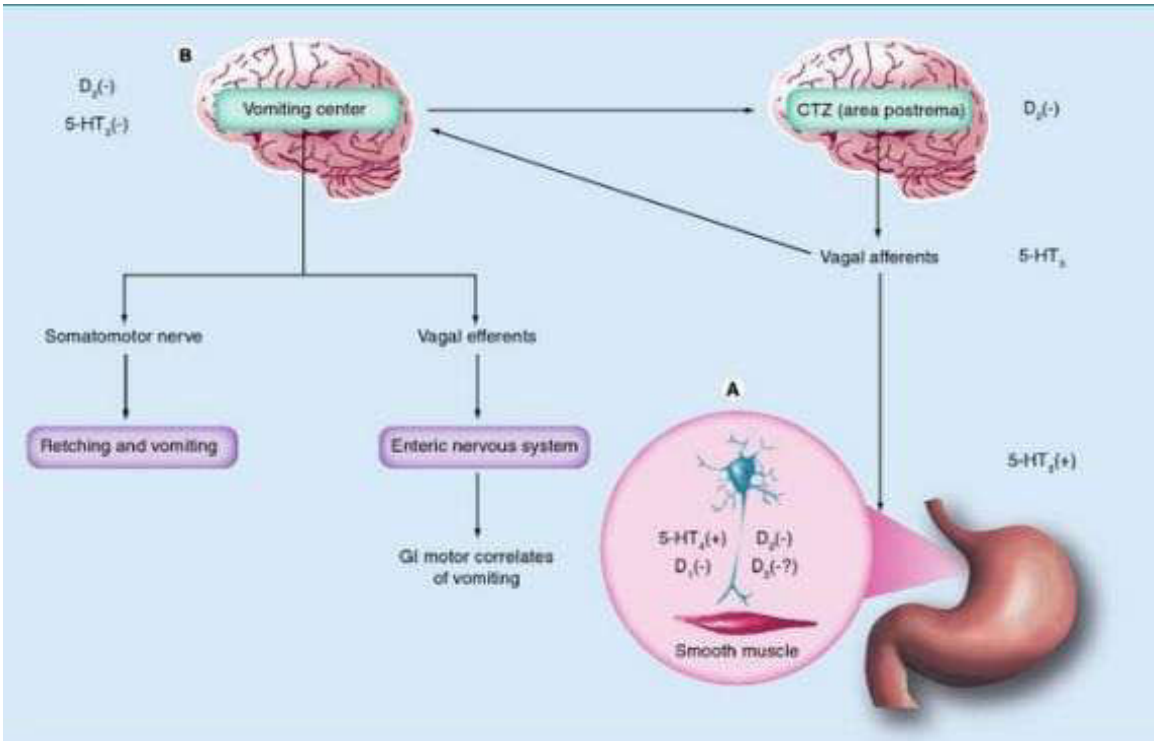


Figure No.1.1: Mechanism of Action of Emesis

Central nervous system control

There are two medullary centers of vomiting in the brain known as the sensory "chemoreceptor trigger zone (CTZ)" and the integrative centre.

i. Chemoreceptor trigger zone (CTZ)

The CTZ is located in the medulla of the brain. It has a defensive blood-brain barrier for detecting circulating toxins in the blood and cerebrospinal fluid (CSF), and is sensitive to a number of circulating emetic agents, including morphine, intravenous copper sulphate, and certain circulating metabolic emetic agents associated with uremia, infections and radiation. When activated, the CTZ does not initiate vomiting itself, but relays stimuli to the integrative vomiting centre which produces the actual act of emesis.

ii. Integrative vomiting centre

The integrative vomiting centre coordinates activities of the nearby neural structures to produce a complex patterned response, resulting in the processing and action of the vomiting reflex. The centre is located in the medulla. The motor component of the vomiting centre is controlled by both somatic and autonomic systems, meaning that both voluntary and involuntary systems are involved in the process. Their inputs are coordinated by the vomiting centre.

Somatic efferent pathways control respiratory and abdominal musculature, and visceral efferent components mediating changes in gastric tone and motility, while salivation, pallor and sweating are autonomic epiphenomena. The autonomic nervous system is not essential for the mechanical act of vomiting, but the activation of efferent nerves of the abdominal organs in the emetic process is proportional to the duration and intensity of the nausea that accompanies the process.

Afferent pathways[38]

The vomiting centre is predominantly activated by three different mechanisms:

- By nervous impulses from the stomach, intestinal tract, and other portions of the body, resulting in a reflexive activation;
- By stimulation from the higher brain centres;
- By the chemoreceptor trigger zone (CTZ) sending impulses.

Afferent impulses may also arise from other sites, such as unpleasant sights and odours, as well as severe parietal pain. The most common afferent pathways are in the viscera, or abdominal organs. Vomiting can be provoked by occlusion of the coronary vessels, distension of the intestine, and irritation of the gastrointestinal mucosa. In the gastrointestinal tract, mechanoreceptors in the intestinal wall are activated by abnormal contractions, distension or physical damage. Potentially harmful chemical stimuli can also activate chemoreceptors located in the intestinal wall. These receptors then release information to the vomiting centre.

Efferent pathways

The neural pathways involved in the motor act of vomiting are associated mainly with the phrenic nerve to the diaphragm, the spinal nerves to the abdominal and intercostal muscles, efferent visceral autonomic fibres to the gut, and the viscera efferent fibres to parts of the voluntary muscles of the pharynx and larynx. The vomiting reflex is mediated by both

the autonomic and somatic systems, and consists of two phases:

Prodomal phase (pre-ejection): Relaxation of gastric muscles followed by small intestinal retrograde peristalsis;
Ejection phase: Comprises of retching and vomiting including expulsion of gastric contents.

Stimuli for vomiting: Pain, sight, smell, taste, emotion

The experience of these sensations leads to information sent to the higher centres in the brain, and then information relayed to the vomiting centre and CTZ via chemicals that transmit information to the brain, hence the name 'neurotransmitters'. The one that is most commonly responsible is acetylcholine, or Ach. Neurotransmitters stimulate and activate the vomiting reflex through the afferent pathways previously described.

1.8. Motion sickness[39]

Motion sickness is due to labyrinth stimulation. The labyrinth is a part of the inner ear involved in balance and perception of movement. Labyrinth stimulation leads to impulses passing along the vestibular nerve to the central nervous system, where it activates the CTZ to produce emesis. Neurotransmitters such as histamine or Ach are also released to the CTZ, which itself can releases chemicals such as dopamine and serotonin (5HT) that go on to stimulate the vomiting centre, which releases Ach, which then leads to the feelings of nausea and actions of vomiting.

1.9. Opioid medications

Opioids such as codeine, morphine, pethidine, fentanyl, methadone, oxycodon, and tramadol can cause nausea and vomiting through a number of different possible mechanisms such as stimulation of CTZ, increased vestibular sensitivity, gastric stasis, or impaired intestinal motility and constipation.

1.10. Radiotherapy[40]

Whether radiation therapy causes nausea and vomiting depends on the part of the body being treated, the amount of radiation given, and how often the treatment is given.

When the area of the body being treated includes a large part of the abdomen, specifically, the small intestine (or small bowel), there is a greater chance of nausea and vomiting occurring. About 50% of the people with cancer who receive standard doses (180 to 200 centiGray) of radiation to their abdomen will have nausea and vomiting. These symptoms can occur 1 to 2 hours after treatment and can last for several hours.

Of those being treated with total body radiation therapy, used in bone marrow transplants, about 60% to 90% will develop nausea and vomiting if not given medicines to prevent nausea and vomiting. These people may also receive high doses of chemotherapy to prepare for the transplant.

The combination of radiation therapy and chemotherapy increases the chance of nausea and vomiting. People who receive one large dose of radiation therapy have a greater chance of nausea and vomiting than those who receive radiation therapy in smaller doses.

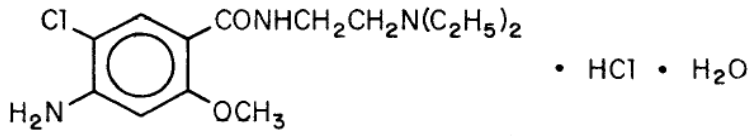
1.11. Hormonal changes during pregnancy

Symptoms of nausea and vomiting are common during the first trimester of the stages of pregnancy. The exact mechanisms of pregnancy-induced nausea and vomiting still is not clear, however it is thought that elevated level of pregnancy hormones can play a role in inducing nausea and vomiting. Adequate hydration should be advised. Dietary modification such as small, frequent, high-carbohydrate, low-fat meals may help.

2. DRUG PROFILE

METOCLOPRAMIDE HYDROCHLORIDE

Table No.2.1: Metoclopramide Drug Profile

Classification	Prokinetic Agent
Chemical Name	4-Amino-5-chloro-N-[2-(diethylamino)ethyl]-o-anisamide mono-hydrochloride Monohydrate;4-amino-5-chloro-N-[2-(diethylamino)-ethyl]-2-methoxybenzamidem monohydrochloride monohydrate.
Structural Formula	
Empirical Formula	$C_{14}H_{22}ClN_3O_2$. HCl .H2O
Category	Antiemetic drug.
Molecular Weight	354.27
Melting Point	182-185^{0}c
Description	A white or almost white, crystalline powder; odorless or almost odorless.

Identification test	Shake a quantity of the powdered tablets containing 50 mg of anhydrous metoclopramide hydrochloride with 5ml of water. Filter and add to the filtrate 5ml of a 1% w/v solution of 4-methylaminobenzaldehyde in 1 M hydrochloride acid, a yellow color is produced.
Solubility	Very soluble in water, Freely soluble in alcohol, sparingly soluble in chloroform, practically insoluble in ether.
pKa	9.71 (Teritiary aliphatic amine), 0.42(Primary aromatic amine)
Pre-systemic metabolism	32-98%
pH range	4.6-6.5 of 10% solution
Plasma protein binding	2.6-5.4hr
Oral absorption	Metoclopramide is rapidly and well absorbed. Relative to an intravenous dose of 20 mg, the absolute oral bioavailability of metoclopramide is 80% ± 15.5% [19].
Dose	10 mg (Children 0.25-0.5/kg) TDS oral or i.m.
Volume of distribution	2.2-3.4 L/kg

Plasma half life mean	2.6-5.4hr
Storage	Metoclopramide hydrochloride should be kept in a well-closed container, protected from light.
Indications	➢ Diabetic Gastroparesis (Diabetic Gastric Stasis). ➢ The Prevention of Nausea and Vomiting Associated with Emetogenic Cancer Chemotherapy. ➢ The Prevention of Postoperative Nausea and Vomiting Associated with Small Bowel Intubation and in cancer Therapy . ➢ Radiological Examination. ➢ In dyspepsia. ➢ In treatment of migraine.
Mechanism of action	➢ **Dopamine antagonists:** metoclopramide which block the effects of dopamine in the central nervous system and at the chemoreceptor zone. Because of this last action they are effective anti-emetics. They stimulate peristalsis by releasing acetylcholine since their actions are antagonized by atropine, a muscarinic blocker. ➢ **$5HT_4$ agonist**: It acts in the GIT to enhance acetylcholine release for myenteric neurons. This result from $5HT_4$ receptor activation on inter neuron which promote acetylcholine release from the primary motor neurons innervating the smooth muscles. ➢ **$5HT_3$ antagonism**: At high concentrations of metoclopramide can block $5HT_3$ receptor present on inhibitory myentericinterneurones and in NTS/CTZ. The pheripheral action can augment acetylcholine release in gut, but appears to be minor. The central action appears to be minor.

Pharmacology	➢ Metoclopramide stimulates motility of the upper gastrointestinal tract without stimulating gastric, biliary, or pancreatic secretions. Its mode of action is unclear. It seems to sensitize tissues to the action of acetylcholine. it can be abolished by anticholinergic drugs[45]. ➢ Metoclopramide increases the tone and amplitude of gastric contractions, relaxes the pyloric sphincter and the duodenal bulb, and increases peristalsis of the duodenum and jejunum resulting in accelerated gastric emptying and intestinal transit. It increases the resting tone of the lower esophageal sphincter. It has little, if any, effect on the motility of the colon or gallbladder. ➢ In patients with gastroesophageal reflux and low LESP (lower esophageal sphincter pressure), single oral doses of metoclopramide produce dose-related increases in LESP [46]. ➢ The onset of pharmacological action of metoclopramide is 1 to 3 minutes following an intravenous dose, 10 to 15 minutes following intramuscular administration, and 30 to 60 minutes following an oral dose; pharmacological effects persist for 1 to 2 hours[47].
Contraindications	➢ Metoclopramide should not be used whenever stimulation of gastrointestinal motility might be dangerous, e.g., in the presence of gastrointestinal hemorrhage, mechanical obstruction, or perforation. ➢ Metoclopramide is contraindicated in patients with pheochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumor. Such hypertensive crises may be controlled by phentolamine. ➢ Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug. ➢ Metoclopramide should not be used in epileptics or patients receiving other drugs which are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased.

Pharmacokinetic	Metoclopramide undergo variable first pass metabolism following oral administration resulting in considerable inter individual variation in peak plasma concentration. Gastro-intestinal absorption may also be affected by conditions such as vomiting and migraine. Attempts to overcome these factors and achieve more predictable plasma concentration have been investigated using other route of administration[23,24,25]. In a single dose study of 12 subjects, the area under the drug concentration-time curve increased linearly with doses from 20 to 100 mg. Peak concentrations increase linearly with dose; time to peak concentrations remains the same; whole body clearance is unchanged; and the elimination Clinical Pharmacokinetics of Metoclopramide[21]. Renal impairment affects the clearance of metoclopramide. The reduction in clearance as a result of renal impairment suggests that adjustment downward of maintenance dosage should be done to avoid drug accumulation[22].
Distribution	Apparent volume of distribution Metoclopramide Hydrochloride is 2.2-3.4 litres/ kg in adults. The drug crosses the blood brain barrier and placenta. It is weakly bound to plasma protein.
Elimination	Elimination half life ($t_{1/2}$) is 4-6 hours. The $t_{1/2}$ is prolonged in patient with renal failure. It is excreted in urine, about 85% of a dose being eliminated in 72 hours, 20-30% as unchanged. Metoclopramide and the remainder as sulfate or glucuronide conjugate. About 5% of a dose is excreted in faeces via the bile[20].

Adverse Effect	➢ Metoclopramide is a dopamine antagonist and may cause extrapyramidal symptoms which are usually occur as acute dystonic reactions especially in young female patient. Parkinsonism and tarditive dyskinesia have occasionally occurred, usually during prolonged treatment in elderly patient. ➢ Other adverse effect includes restlessness, drowsiness, dizziness, head ache and bowel upsets such as diarrhoea. Hypotension and hyper tension and depression may occur and there are isolated reports of blood group, hypersensitivity reaction malignant syndrome and urinary incontinence.
Administration for Cancer chemotherapy	➢ Early studies showed that high doses of metoclopramide could control nausea and vomiting associated with the administration of highly emetic cytotoxic agents, cisplatin[26]. The dose of metoclopramide was 2mg per kg body weight by intravenous over 15 minutes, or 1mg per kg for 6 doses in patient receiving lower doses of cisplatin. The anti-emetic protection has been reported to maintain with subsequent courses to upto 8 consecutive cycles of chemotherapy[28, 29]. ➢ High dose of oral administration of metoclopramide 2mg per kg given 1 hour before and 1,3,5,8, and 11 hours after initiation of cisplatin chemotherapy has been also found to be of benefit[34, 35]. ➢ Metoclopramide is not effective in all patient and various anti-emetic regimens have been investigated which combine drugs with different mechanism of action to increase antiemetic protection[36]. Dexamethasone and lorazepam has been reported to enhance the antiemetic effect of metoclopramide. . However, the addition of diazepam to a standard regimen of metoclopramide maybe associated with increased vomiting[38].

Administration in renal failure	Total clearance of metoclopramide is significantly reduced in patients with renal failure and the elimination half-life is prolonged to up to 19 hours. This may be due to impaired metabolism or to an alteration in enterohepatic circulation of metoclopramide in renal failure. Cumulation of metoclopramide could therefore occur in renal failure with a possible increased risk of side effects .Dosage reduction of at least 50% have therefore been recommended in patients with moderate to severe renal impairement[49].
Administration for Amenorrhea	Metoclopramide 5 mg four times daily for 10days followed by 2.5mg three times daily for 20 days, and then this whole sequence is repeated twice , Produced menstrual bleeding in 7 of 8 women with amenorrhoea associated with normoprolactinaemia. Regular menstruation was restored in patient[50].
Administration for Aspiration syndrome	Metoclopramide has been investigated for the prevention of aspiration pneumonitis since it can increase lower oesophageal sphincter tone, increase gastric emptying and reduce emesis. A dose of 10 mg by mouth or intramuscularly has been reported to promote gastric emptying , thus reducing gastric fluid volume , during labour and prior to laproscopy[51].
Log p	2.667
Therapeutic Uses	➢ Antiemetic. ➢ Gastrokinetic ➢ Gastroparesis ➢ Hiccup. ➢ Orthostatic hypotension ➢ Gastroesophageal reflux disease(GERD) ➢ Diabetis Gastroparesis

Allergic Reactions	A few cases of rash, urticaria, or bronchospasm, especially in patients with a history of asthma. Rarely, angioneurotic edema, including glossal or laryngeal edema.
Over Dose	➢ Symptoms of over dosage may include drowsiness, disorientation and extrapyramidal reactions. Anticholinergic or antiparkinson drugs or antihistamines with anticholinergic properties may be helpful in controlling the extrapyramidal reactions. Symptoms are self-limiting and usually disappear within 24 hours. ➢ Hemodialysis removes relatively little metoclopramide, probably because of the small amount of the drug in blood relative to tissues. Similarly, continuous ambulatory peritoneal dialysis does not remove significant amounts of drug. It is unlikely that dosage would need to be adjusted to compensate for losses through dialysis. Dialysis is not likely to be an effective method of drug removal in overdose situations. ➢ Methemoglobinemia has occurred in premature and full-term neonates who were given overdoses of metoclopramide (1-4 mg/kg/day orally, intramuscularly or intravenously for 1-3 or more days). Methemoglobinemia can be reversed by the intravenous administration of methylene blue. However, methylene blue may cause hemolytic anemia in patients with G6PD deficiency, which may be fatal.
Marketed Product	Reglan 10mg, 20mg, Perinorm 10mg, Vominorm 10mg, Actinorm 10mg,

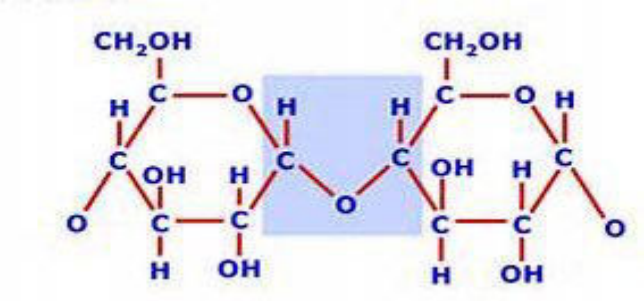
3. EXCIPIENT PROFILE

3.1. STARCH

Synonyms: Starch 1500, Starch I.M

Nonproprietary Names: Amylum, Polysacharide

Chemical Structure:



Molecular weight: 162.14g/mol

Empirical formula: ($C_6H_{12}O_5$)

Chemical Name: (2R,3S,4S,5R,6R)-2-(hydroxyl methyl)-6-[(2R,3S,4R,5R,6S)-4,5,6-trihydroxy-2-(hydroxyl methyl)oxan-3-yl]oxy-oxane-3,4,5-triol.

Physical Description

White colour, Odorless, Tasteless

Functional Category

Thickening agent, stiffening agent, gluing agent, Disintegerant.

Identification Test

Boil with 15 times its weight of water and cool; a translucent viscous fluid or jelly is produced which is coloured deep blue by solution of iodine; the colour disappears on warming and reappears on cooling.

Incompatibilities

Incompatible with strong acids and alkali. Avoid mixing with strong oxidizing agents.

Application

Binder,Disintegrant, Flow aid lubricant.

3.2. LACTOSE

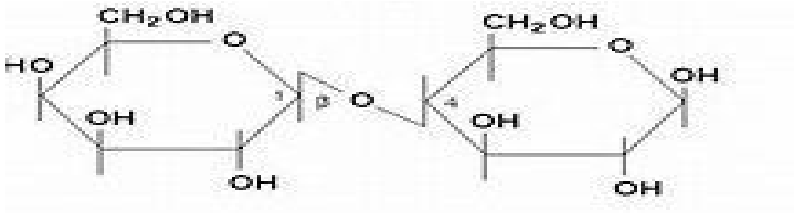
Synonyms

Fast flow, Lactochem, Tablettose, Zeparox, granulac, Microfine, Pharmatose.

Non- Proprietary Name:

Lactose monohydricum, Lactose monohydrate.

Chemical Structure:



Molecular weight : 360.31

Empirical Formula: $C_{12}H_{22}O_{11 \cdot H2O}$

Chemical name :

O- β-D-galactopyranosil-(1-4)-α-D-glycopyranose monohydrate

Physical Description

It is a white to off-white crystalline powder. It is odourless and slightly sweet tasting.

Functional Category:

Diluents for dry powder, inhaler, tablets and capsule.

Identification Test

On heating it melts, swells up and burns, giving off an odour of burnt sugar and leaves bulky carbonaceous residue.

Incompatibilities

Lactose is incompatible with aminoacids, aminophylline, ametamines, and lisinopril.

Applications

Lactose is widely used as filler or diluent in tablets, capsules. It also used as carrier for inhalation and lyophilized products.

3.3. PROPYL PARABEN

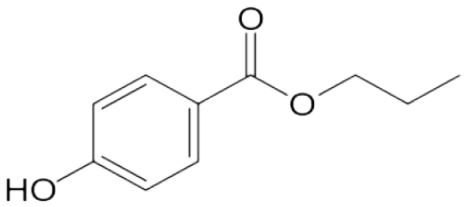
Synonym:

Propyl butex, Propyl chemosept, Propyl 4-hydroxybenzoate.

Non- proprietary names:

Propyis parahydroxy benzoates, Propyl 4-hydroxy benzoates, Propyl (parahydroxy benzoates)

Chemical structure



Molecular weight: 180.2

Empirical formula: $C_{10}H_{12}O_2$

Chemical Name: Hydroxy benzoic acid propyl ester.

Physical Description

White crystalline powder, colourless crystals or white powder or chunky white solid odourless or faint aromatic odour, low toxicity and tastes.

Functional Category

Preservatives, Food additive.

Identification Test

Boil 10mg with 10 ml of water cool and add 0.05 ml of ferric chloride solution, a reddish white colour is produced.

Incompatible

Incompatible with alkalis and metal salts.

Applications

An antimicrobial preservative in packed foods, pharmaceuticals, cosmetics.

3.4. METHYL PARABEN

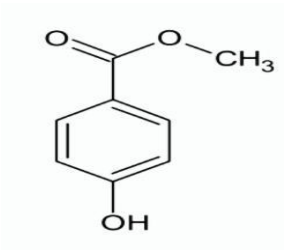
Synonym

Methyl 4-OH benzoate, Nipaginm.

Nonproprietary names:

Sodium methyl parahydroxy benzoates, Methyl paraben sodium salt.

Chemical structure



Molecular weight: 152.149g/mol

Empirical formula: $C_{10}H_{12}O_2$

Chemical Name:

Methyl p- hydroxyl benzoate

Physical Description

Soluble in water at 25^0c, slightly soluble in benzene, CCl_4, ethanol, Ether, acetone, DMSO, methanol.

Functional Category: Preservatives

Identification Test

Boil 10mg with 10 ml of water cool and add 0.05 ml of ferric chloride solution, a reddish white colour is produced

Incompatible

Incompatible with alkalis and metal salts.

Applications

It is an antifungal agent, often used in variety of cosmetics and personnel care products. It is used as food preservatives

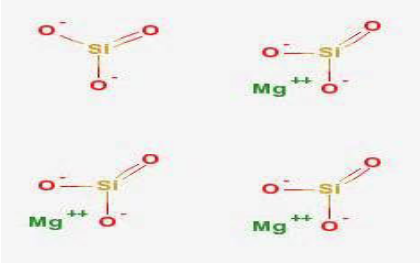
3.5. TALC

Synonyms

Altac ; E553b; hydrous magnesium calcium silicate; Purified French chalk.

Nonproprietary Names: Purified Talc, JP: Talc, PhEur :Talc ,USP :Talc.

Chemical Structure:



Molecular weight: 379.259 g/mol

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

Chemical Name : Talc.

Physical Description

Talc is a very fine, white to greyish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to touch and free from grittiness.

Functional Category

Anticaking agents; glidant ; tablet and capsule diluent; tablet and capsules lubricant.

Identification test:

In a lead or platinum crucible and using a copper wire, mix the sample with about 10 mg of sodium fluoride and a few drops of sulphuric acid to give a thin slurry. Cover the crucible with a thin transparent plate of plastic under which a drop of water is suspended, and warm gently. It will give a white ring is rapidly formed around a drop of water.

Incompatible

Mostly compatible with all other tabulating ingredients.

Applications

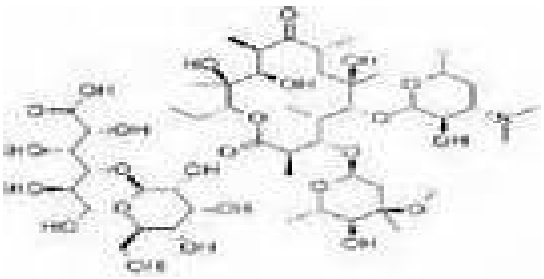
Talc was widely used in oral solid dosage formulations as lubricant and diluent. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

3.6. SODIUM STARCH GLYCOLATE

Synonyms
Sodium salt of carboxy methyl ester of starch.

Nonproprietary names
Explotab, Vivastar

Chemical Structure:



Molecular weight:
500000- 11000000

Empirical formula:
C_2H_5ONa

Chemical Name:
Sodium salt of a cross-linked partly O-carboxymethylated potato starch.

Physical Description
Weight to off white, Tasteless, Odorless, Relatively free flowing powder.

Functional Category
: Super Disintegerant, Dissolution aid, Suspending agent.

Identification Test
Heat 5 gm. with shaking, with 40 ml of dilute sulphuric acid and cool. Filter off the fatty acid liberated, the filtrate gives the reaction of magnesium.

Incompatible
Mostly compatible with all other tabulating ingredients.

Applications
It is an antifungal agent, often used in variety of cosmetics and personnel care products. It is used as food preservatives. It is also used as super disintegerant.

3.7. MAGNESIUM STEARATE

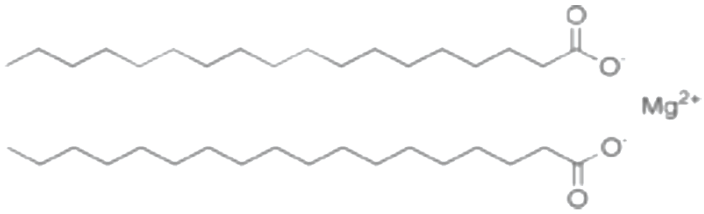
Synonyms

Dibasic magnesium stearate, magnesium distearate, magnesia stearas.

Nonproprietary names

BP: Magnesium Stearate, JP: Magnesium Stearate, PhEur : Magnesium Stearate.

Chemical Structure



Molecular weight: 591.24

Empirical Formula: $Mg\ (C_{18}H_{35}O_2)_2$

Chemical Name: Octadecanoic acid magnesium salt

Physical Description

Magnesium stearate is a very fine, light white, precipitated oromilled, impalpable powder of low bulk density, having a faintodorof stearic acid and a characteristic The powder is easy to touch and readily adheres to skin.

Functional Category: Tablet and capsule lubricant.

Identification Test

To 5.0 add 50 ml of peroxide-free ether, 20ml of dilute nitric acid and 20ml of water and heat under a reflux condenser until dissolution is complete. Cool and separate the aqueous layer in a separating funnel and shake with ether in 2 quantities, each of 4ml, of water. Combine the aqueous layer, wash with 15ml of peroxide free ether and dilute to 50ml with water. Evaporate the organic layer to dryness and dry the residue at 105^0C. this residue has a freezing point not less than 53^0C.

Incompatibilities

Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials.

Applications

Magnesium stearate is widely used in cosmetics food and pharmaceuticals formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentration between 0.25% and 5.0% w/w. It is also used in barrier cream.

3.8. INNOVATOR CHARACTERISTICS

Brand Name	Perinorm
Content Name	Metoclopramide
Dose	10mg
Route of Administration	Oral
Dosage	Immediate release tablet dosage form
Packing Description	Blister Packing, 10 tablets in one strip.
Storage Condition	Store in a cool and dry place
Manufacturer	IPCA Laboratories

4. LITERATURE REVIEW

1. **EL Parrot[3].:** This article deals with the study of the energetic relationships during compaction and the properties of tablets produced from a co-processed excipient based on starch. ®. The study also includes the mixtures of StarCap 1500® and the granulated directly compressible lactose. The tablet properties tested included tensile strength and disintegration time, examined in dependence on compression force, and also a 0.4% addition of magnesium stearate. The results show a better compressibility of StarCap 1500 in comparison with Starch 1500 and a lower elastic component of energy. The tablets were stronger and disintegrated more rapidly, but the substance possessed a higher sensitivity to an addition of a lubricant than Starch 1500. Increasing portions of StarCap 1500 in the mixtures with Pharmatose DCL 15 increased the tensile strength of tablets, disintegration period as well as the sensitivity to an addition of a lubricant. From the energetic viewpoint, energy for friction was decreasing, while the energy accumulated by the tablet during compaction and the elastic component of energy were increased[3].

2. **Rudolph M navari et.al[20]**: The localization of substance P in brain stem regions associated with vomiting, and the result of studies in ferrets, led us to postulate that a neurokinins-1-receptor antagaonist would be an antiemetic in patient receiving anticancer chemotherapy. The neurokinin-1—receptor antagonist with gransetron plus dexamethasone improves the prevention of acute emesis.

3. **Paul J Hesketh el.at[25]:** New sight into the pathophysiology of chemotheraphy-induced nausea and vomiting, a better understanding of patient at risk, and the availability of new antiemetic agents have all contributed to substantial improvement in emetic control. This review focuses on our current understanding of chemotherapy induced nausea and vomiting and the status of pharmacologic interventions in its prevention and treatment.

4. **Monica R P Rao[31]:** The development of immediate release tablet formulations is based on the use of super disintegrants separately or in combination. Seven formulations were prepared using simplex centroid mixture design where sodium starch glycolate, cross carmellose sodium and pre-gelatinised starch were selected as independent variables and dependent variables. Response surface plots were drawn, and optimum formulations were selected by grid search method. Formulations 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, which confirms the predictability of the model.
5. **Bhandari Neeraj el. At[51]:** The basic approach used in this study is that development tablets is the use of superdisintegrants which provide instantaneous disintegration of tablet after administration. The development of immediate release tablets also provides an opportunity for a line extension in the market place. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity

in a new and improved dosage form. Now a day, immediate release formulations are similar to many sustained release formulations that are now commonly available..

6. **Nyol Sandeep[36]:** Immediate drug release dosage forms disintegrate rapidly after administration with enhanced rate of dissolution. The basic approach used in development of tablets is the use of superdisintegrants like Sodium starch glycolate (Primogel, Explotab). These superdisintegrants provide instantaneous disintegration of tablet after administration in stomach. In this field immediate release liquid dosage forms and parenteral dosage form have also been introduced for treating patients. In liquid dosage form can be suspensions with typical dispersion agents like hydroxypropyl methylcellulose, AOT etc. The development of immediate release therapy also provides an opportunity for a line extension in the marketplace, a wide range of drugs e.g., neuroleptics, cardiovascular drugs, analgesics, antihistamines and other drugs can be considered candidates for this dosage form. As a drug entity nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen.

7. **Molassiotis, A. et al.[38]:** He evaluated acute chemotherapy-induced nausea and vomiting (CINV) prophylaxis; provided sufficient information to permit determination of the emetogenicity of the antineoplastic therapy administered or the study investigators stated the emetogenicity of the chemotherapy administered; included an implicit or explicit definition of complete acute CINV response; described the antiemetic regimen in full; and reported the complete acute CINV response rate as a proportion. The findings of several randomized trials were used to update recommendations for the prevention of acute CINV.

8. **Ripamonti. C.et al.[39]:** The aim of this paper is to review the existing literature related to the management of nausea and vomiting (N & V) in advanced cancer and derive clinical evidence-based recommendations for its management. These new guidelines, based on the existing (but poor) evidence, could help clinicians manage more effectively the complex and challenging symptoms of N & V in advanced cancer.

9. **H.C. Stewart et.el.[40]:** The causes of nausea, vomiting and retching and how these are brought about are explained, and the present views on the mechanism of vomiting are discussed. The sites of action of sensory stimuli causing vomiting are linked in a figure with the probable sites of action of anti-emetic drugs. Three main groups of anti-emetic drugs are discussed, general sedatives and tranquillizers, oscine and atropine, and certain antihistamines. The results of some clinical trials are considered and suggestions made for the best combination of drugs. Undesirable side effects, particularly those of the phenothiazines, are stressed so that suitable precautions can be taken in their use.

10. **Gupta et al.[52]:** The principal aim of this work was to find out the effect of sodium starch glycol ate and β – cyclodextrin on the dissolution profile of immediate release telmisartan tablets and to optimize their values by a 2^2 full factorial design. Other excipients used in the study are microcrystalline cellulose (Avicel PH-101) and magnesium stearate. Both sodium starch glycolate and β – cyclodextrin had contribution towards the immediate release but the effect of sodium starch glycolate is more pronounced from response surface plot as well as from the contour plot. The optimised amount of sodium starch glycolate and β – cyclodextrin were found to be 55.714 mg and 30 mg respectively for 70 % drug release at 30 minutes.

11. **V. M. Thakare et al.[53]:** In this work, orodispersible tablets of Metoclopramide HCl were prepared by direct compression techniques using complex of drug with various superdisintegrant. Before formulation of tablets, the best superdisintegrant among Tulsion 339, Ac-Di-Sol, and Sodium starch glycolate was formulated with drug and tested. For taste masking ion exchange resin Tulsion 339 Drug: Tulsion339, 1:2.25 ratios was used. The blends were examined for precompression parameters. The result were complies with Pharmacopeial and non-official limits. The prepared batches of tablets were evaluated for post compression parameters. Formulations were tested for *in vitro* drug release pattern (in pH 6.8 buffer), Batch F5 containing Tulsion 339 showed better disintegrating character along with the immediate release .

12. **Margret C R et.al.[54]:** It was studied Effect of formulated ingredients on rapidly disintegerating oral tablets prepared by the crystalline transition method.

13. **Yunxia B et.al[57]:** Tablets were prepared by direct compression technique. The granules were evaluated for angle of repose, bulk density, tapped density, bulkiness, compressibility index and hausners ratio. The tablets were evaluated for hardness, thickness, uniformity of weight, friability, wetting time, water absorption ratio, disintegeration time and drug content. In vitro release studies were performed using USP-II (paddle method) in 900ml of pH 1.2 at 50 rpm. The physical properties of the prepared tablets did not show any significant varitions and were found to have good physical integrity. Tablets prepared with pharmaburst B2 and carmellose sodium showed a lesser disintegerationtime and wetting time of 27±0.10 and 38±0.13 seconds respectively.

14. **Prakash khadka et. al.[65]**: in this study showed that Pharmaceutical particle technology is employed to improve poor aqueous solubility of drug compounds that limits in vivo bioavailability owing to their low dissolution rate in the gastrointestinal fluids following oral administration. The particle technology involves several approaches from the conventional size reduction processes to the newer, novel particle technologies that modify the solubility properties of the drugs and produce solid, powdered form of the drugs that are readily soluble in water and can be easily formulated into various dosage

forms. This review highlights the solid particle technologies available for improving solubility, dissolution and bioavailability of drugs with poor aqueous solubility.

15. **Samran et al.[66]:** The objective of the study was to characterise STE as excipient and to use STE as excipient in the formulation of ODT by lyophilisation method. The ingredients were glutinous rice used to form tapai and the liquid extract of tapai which was used to make STE. STE was used as excipient by combining STE with dextrose and avicel. Metoclopramide HCl was used as a drug model. The design of formula used the simplex lattice design (SLD) model with a three components mixture: STE, dextrose and avicel as excipients. The parameters of lyophilised ODT (LODT) were hardness and friability, wetting time, disintegrating time and dissolution rate. The results showed STE can be used as filler and binder for LODT. STE could also function as disintegrant and formed porosity in the lyophilised method.

16. **vander Meer .et .al .[67]:** Regulatory agencies in North America and Europe recently re-evaluated the safety of metoclopramide. This re-evaluation resulted in recommendations and restrictions in order to minimize the risk of neurological and other adverse reactions associated with the use of metoclopramide. In the ICU, off-label prescription of metoclopramide is common. We have reviewed the evidence for safety, effectiveness and dosing of metoclopramide in critically ill patients. Furthermore, tachyphylaxis is addressed and alternatives are summarized. Finally, recommendations are presented not to abandon use of metoclopramide in ICU patients, because metoclopramide is considered effective in enhancing gastric emptying and facilitating early enteral nutrition.

5. AIM AND OBJECTIVE

5.1 Aim of the Study:

The main aim of the present study is to develop a pharmaceutically equivalent, low cost, quality improved formulation of immediate release dosage form of Metoclopramide Hydrochloride 10 mg for the treatment of emesis. Evaluation and optimization of process parameters as well as finished dosage form also form part of this work comparable to innovator product.

The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. These tablets which disintegrate rapidly and get dissolved to release the medicaments. It may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release or absorption.

5.2 Objective

The main objective of this study was:

A. To formulate and evaluate immediate release of Metoclopramide hydrochloride tablets.

B. To study the release profile of the dosage form and to compare their drug release profiles with the innovator.

C. To determine the best fit dissolution profile for dosage form.

D. To study the stability of dosage form.

6. PLAN OF WORK

The present work was carried out to formulate and evaluate the immediate release tablet of Metoclopramide tablets.

A. Preformulation Studies:

- Description
- Melting Point
- Thin layer Chromatography
- pH Range
- Drug Excipient Compatibility Studies (FTIR)

B. Method of Drug Analysis

C. Evaluation Parameters

- ✓ Bulk Density
- ✓ Tapped Density
- ✓ Angle of Repose
- ✓ Carr's Index
- ✓ Hausner Ratio
- ✓ Sieve Analysis
- ✓ Physical Stability of Admixture.

D. Formulation of Metoclopramide Hydrochloride Immediate release Tablets.

E. Preparation of Metoclopramide Hydrochloride Tablets.

F. Post Compression Parameters

- Thickness
- Hardness
- Weight Variation
- Friability
- Wetting time
- Drug Content Uniformity

G. In vitro disintegeration time

H. In vitro dissolution study

I. Stability studies of the optimized formulation

J. Comparison of Formulated and Marketed Tablets.

7. MATERIALS AND METHODOLOGY

Table No. 7.1: List of Materials

S. No	Materials	Use	Sources
1	Metoclopramide Hydrochloride	Active Ingredient	Valkunth Chemicals Pvt .Ltd
2	Starch	Disintegerant and Binder	Universal Starch Chem Allied Limited.
3	Lactose	Diluent	Saputo Ingredients Inc.
4	Methyl paraben	Preservatives	Nebula Healthcare
5	Propyl paraben	Preservatives	Nebula HealthCare
6	Talc	Lubricant	Neelkanth Minechem
7	Magnesium Stearate	Glidant	Legend Industries
8	Sodium starch glycolate	Super disintegerant	Maple Biotech Pvt.Ltd

Chemicals

1	Hydrochloric acid	Mercks Laboratories Pvt.Ltd
2	Sodium hydroxide	Mercks Laboratories Pvt.Ltd
3	Sodium sulphate	Mercks Laboratories Pvt.Ltd
4	Potassium hydroxide	Mercks Laboratories Pvt.Ltd
5	Potassium dihydrogen phosphate	Mercks Laboratories Pvt.Ltd

Equipments

Table No.7.2: List of Equipment

S. No	Instrument Used	Manufacturer
1	Electronic weighing balance	Mettler, Switzerland
2	Max mixer	Innofab India pvt.ltd, Hyderabad
3	Fluidized bed dryer	Alliance, Bombay
4	Cadmill	Cadmach, Ahemedabad
5	Tablet Compression Machine 45 station double rotary	Cadmach, Ahemedabad
6	Friability Tester	Veego, Mumbai
7	Tablet Hardness Tester	Electrolab, Mumbai
8	Bulk density apparatus	Electrolab, Mumbai
9	Blender	Bhuvaneswari, Mumbai
10	Dissolution Apparatus	Veego, Mumbai
11	Tablet Disintegeration Apparatus	Veego, Mumbai
12	FT-IR Spectrophotometer	Perkin Elmer, USA

METHODOLOGY

7.1. Preformulation Studies[44]

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

Objective[45]

The overall objective of preformulation testing is to generate information useful in developing the formulation which is stable and bioavailable. Further the use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product. For any drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug like description, solubility, identification test, melting point, molecular weight.

Description:

The drug sample was analysed for physical appearance, color, and odour.

Melting point[48]

Determination of Melting Point: Melting point of drug was determined by capillary method. Fine powder of drug was filled in a glass capillary tube (previously sealed at one end). The capillary tube is tied to thermometer and the thermometer was placed in the Thieles tube and this tube is placed on fire. The powder at what temperature it will melt was noticed.

Thin Layer Chromatography:

Standard Preparation: Dissolve USP Metoclopramide Hydrochloride in Methanol and mix to obtain a solution having a known concentration of 1mg per mL

Test Preparation: Dissolve an accurately quantity of Metoclopramide Hydrochloride in methanol to obtain a solution containing 50 mg per mL. Dilute a portion of this preparation quantitatively with methanol to obtain a solution containing 500 µgm per ml. Apply 10µL in a chromatographic plate coated with silica gel mixture. Allow the spot to dry and Position the plate in a chromatographic chamber containing the solvent system consisting of a mixture of

chloroform, methanol, toluene and ammonium hydroxide until the solvent front has moved about the three fourth of the chromatographic plate. Then examine the plate under UV light and compare the intensity. Test preparation is more intense than standard preparation and sum of all intensities of all secondary preparation is not more than 1%.

pH Range :

pH of a 0.10 g/mL solution in carbon-dioxide-free water R, 4.5-6.5.

FTIR analysis[63]:

The FTIR spectra of the pure drug were recorded in between 4000 to 400 cm^{-1}. The drug sample and the excipients were characterized using FTIR analysis. FTIR spectra for, lactose, starch shown in figure.

7.2. Method of Drug Analysis[62]:

Preparation of standard stock solution:

Standard drug solution of Metoclopramide Hydrochloride was prepared by dissolving 10 mg metoclopramide hydrochloride in deionized water, phosphate buffer pH 6.8 and simultated Gastric Fluid (pH1.2) separately and the volume was made upto 100ml to obtain stock solution of 100 µg/ml concentration. Ultrasonication was done to obtain a clear solution.

UV Spectroscopic scan:

1. A stock solution of Metoclopramide hydrochloride tablet of concentration 100 µg/ml prepared in deionised water. The UV spectrum was recorded in the range of 200-400nm. The wavelength of maximum absorption was found to be 273.0nm.
2. A stock solution of Metoclopramide hydrochloride tablet of concentration 100 µg/ml prepared in phosphate buffer pH 6.8. The UV spectrum was recorded in the range of 200-400nm. The wavelength of maximum absorption was found to be 273.80nm.
3. A stock solution of Metoclopramide hydrochloride tablet of concentration 100 µg/ml prepared in 0.1 N HCL. The UV spectrum was recorded in the range of 200-400nm. The wavelength of maximum absorption was found to be 273.50nm.

Construction of calibration curve:

Aliquots of 0.5 to 3.5 ml portion of stock solution was transferred to a series of 10 ml volumetric flask, and volume made upto the mark with deionised water, Phosphate buffer pH 6.8 and simultated gastric pH 1.2 and prepared solution of 5,10,15,20,25,30 and 35 µg/ml. The solution was analysed using UV Spectrometer and calibration curve was plotted. The result shown in

7.3 Evaluation Parameters

Determination of bulk density and tapped density[46]

It refers to a measurement to describe packing of particles and also used to determine the amount of drug that occupies the volume in mg/ml before tapping and after tapping.

An accurately weighed quantity of the powder (W), was carefully poured into the graduated cylinder and the volume (V_o) was measured, then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 500 taps and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density and tapped density were calculated using the following formula:

$$\text{Bulk density} = W / V_o$$

$$\text{Tapped density} = W / V_f$$

Where,

W = weight of the powder
V_o = initial volume
V_f = final volume

Flow Properties[49]

The flow properties are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose.

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

Angle of repose was determined by using fixed funnel method. The fixed funnel method employ a funnel that was secured with its tip at a given height (2cm), above the graph paper that was placed on a flat horizontal surface. Granules or tablet blend were carefully poured through the funnel until the apex of the conical pile just touches the tip of the funnel. Thus, with r being the radius of the base of the conical pile.

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

Where,

h=height of pile.
r= radius of the base of pile.
θ =angle of repose.

Table No. 7.3: Relationship belongings angle of repose and powder flow

S. NO	Angle of repose (θ)	Flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	40 & Above	Very Good

Compressibility Index

Compressibility was calculated from the powder density using the following formula:

$$CI = \frac{(TD - BD)\ TD \times 100}{TD}$$

Where,

TD – Tapped density
BD – Bulk density

Table No. 7.4: Compressibility Index range

S.No	Percentage Compressibility Index	Flow ability
1	5-15	Excellent
2	12-16	Good
3	18-21	Passable
4	23-35	Poor
5	33-38	Very poor
6	<40	Very Very poor

Hausner Ratio:

It indicates the flow property of the powder and measured by the ratio of tapped density to bulk density.

Table No. 7.5: Hausner Ratio Properties

Hausner Ratio	Properties
0-1.2	Free flowing
1.2-1.6	Cohesive powder

Sieve analysis

The main aim of sieve analysis is to determine the different size of drug particles present. A series of standard sieve were stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed by sieves with smaller pore size (greater sieve number towards the bottom).

Table No. 7.6: Relationship belongings Nature of sample and different particle size.

S. No	Nature of Sample	Result of Determination
1.	Coarse powder	NLT 95% of the sample mass pass through 14# and NMT 40% pass through 36#
2.	Moderately coarse Powder	NLT 95% of the sample mass pass through 25# and NMT 40% pass through 60#
3.	Moderately fine powder	NLT 95% of the sample mass pass through 36# and NMT 40% pass through 40#
4.	Fine powder	NLT 95% of the sample mass pass through 100# and NMT 40% pass through 150#
5.	Very fine powder	NLT 95% of the sample mass pass through 150# and NMT 40% pass through 200#
6.	Super fine powder	NLT 95% by number of particles less than 10

7.4. Formulation of Metoclopramide Hydrochloride Tablets

Metoclopramide Hydrochloride Tablets Immediate Release tablets were prepared by wet granulation method.

Table No. 7.7: Formulation of Metoclopramide Hydrochloride Tablets

S. No	Ingredients (in mg)	Formulations								
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	Metoclopramide Hydrochloride	10	10	10	10	10	10	**10**	10	10
2	Starch	54.2	59.2	64.2	54.2	59.2	64.2	**54.2**	52.2	64.2
3	Lactose	29.5	24.5	19.5	30	4.5	19	**29**	24	19
4	Methyl paraben sodium	0.18	0.18	0.18	0.18	0.18	0.18	**0.18**	0.18	0.18
5	Propyl paraben sodium	0.12	0.12	0.12	0.12	0.12	0.12	**0.12**	0.12	0.12
6	Starch for paste	4	4	4	4	4	4	**4**	4	4
7	Talc	1	1	1				**1**	1	1
8	Magnesium stearate	1	1	1	1	1	1	**1**	1	1
9	Sodium starch glycolate				0.5	1	1.5	**0.5**	1	1.5
10	Total weight (in mg)	100	100	100	100	100	100	**100**	100	100

7.5. Preparation of Metoclopramide Hydrochloride Tablets

1. Sieving

The active ingredients and the other excipients are passed through sieve no #22. After sieving, they are collected to suitable baskets.

2. Dry Mixing

Above sieved materials are collected and then add into MCG. Dry mixing is achieved by low speed for 15 min.

3. Wet granulation

i. Preparation of Binder solution

Take the calculated amount of Starch in a S.S vessel and dissolved it in specified amount of water and then boils at 100^0C. Then this solution is added to another solution containing required amount of Methyl Paraben and Propyl Paraben which is heated at 60^0C. Stir it well.

ii. Mixing

Add binder solution to the above sieved material which mixing for 5-15 min in MCG in slow speed. Change the mixer speed to fast and mix for 5- 15 min till the end point achieved. Then pass through the cad mill to achieve required type of granules. Then scrap the materials from the cad mill.

4. Drying

Load the powder in the fluidized bed dryer. Dry the moist granules. Check the loss on drying at more than 0.5%.

5. Pulverization

Pass the dried granules through the cad mill with Super disintegerant, lubricants and glidants. Then collect the required type of granules by passing through the 14#150 mesh and get uniform sized granules.

6. Lubrication

All the above ingredients are collected and lubricated by using double cone blender.

7. Compression

i. Then the lubricated dry blends were subjected to punching using a tablet punching machine with Punch size: 6mm round punches

ii. Tablet weight : 100mg

iii. Hardness: 3.6 - 3.8Kg/cm^2

iv. Thickness: 2.7mm

v. Friability: NMT 0.80%w/w

Parameters like average weight, hardness and friability were checked during compression as in process quality measures.

7.6. Post Compression Parameters

A. Thickness and diameter[50]:

Control of physical dimension of the tablet such as thickness and diameter is essential for consumer acceptance and tablet uniformity. The thickness and diameter of the tablet was measured using Vernier calipers. It is measured in mm. A ± 5% may be allowed depending on the size of the tablet.

B. Hardness test[51]:

One tablet was placed vertically between the anvil and the punch of Strong Cobb Hardness tester. The tablet was clamped by turning the regulator screw until the signal "stop" lighted, and then the button was pressed until the tablet broke. After the tablet broke, the scale number was recorded. The tablet hardness was the figure of the needle on the scale. Hardness test was performed for 6 tablets.

C. Weight variation test[52]:

The weight of the tablet being made in routinely measured to ensure that a tablet contains the proper amount of drug. The USP weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meet the USP test if not more than 2 tablets are outside the percentage

limits and if no tablets differs by more than 2 times the percentage limit. USP official limits of percentage deviation of tablet are presented in the following table,

Table No.7.8: Weight variation limits[53]:

Sl.No	Average weight of a tablet (mg)	Maximum difference allowed (%)
1	130 or less	10
2	130-324	7.5
3	324 or more	5

$$PD = \frac{(W_{avg}) - (W_{initial})}{(W_{avg})} X\ 100$$

Where,

PD = Percentage deviation,

W_{avg}= Average weight of tablet,

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

D. Friability test[54]:

Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface. Friability test is carried out to access the ability of the tablet to withstand abrasion in packaging, handling and transport. Roche friabilator was employed for finding the friability of the tablets. 20 tablets from each formulation were weighed and placed in Roche friabilator that rotated at 25 rpm for 4 minutes. The tablets were deducted and weighed again. The percentage of weight loss was calculated again. The percentage of weight loss was calculated using the formula.

$$\% \text{ Friability} = \frac{(W1 - W2)}{W1} \times 100$$

Where,

W1= Weight of tablet before test

W2 = Weight of tablet after test

E. Wetting time

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10cm diameter were placed in a petri dish with a 10cm diameter. Ten milliliters of water containing eosin, a water-soluble dye, was added to the petridish. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time.

G. Drug content uniformity[56]:

Weigh and powder 20 tablets. Weigh accurately a quantity of the powder equivalent to 10 mg of anhydrous Metoclopramide hydrochloride, add 50 ml of 0.1M hydrochloric acid, heat on a water-bath at 70^0C for 15 minutes, cool, dilute to 100.0 ml with water and filter. To 20.0 ml of this solution add 15 ml of 1.25M sodium hydroxide and extract with three quantities, each of 30 ml, of chloroform, dry each extract with anhydrous sodium sulphate and filter. Dilute the combined extracts to 100.0 ml with chloroform and mix. Measure the absorbance of the resulting solution at the maximum at about 305 nm.

H. In-vitro Disintegration time[57]:

The in-vitro disintegration time 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. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds. Tablet was added to water at 37±0.5°c. Time required for complete disintegration of tablet was measured.

I. In-vitro dissolution study[58]:

In vitro drug release study of Metoclopramide HCl was performed in USP dissolution apparatus Type 2 (paddle).Phosphate buffer pH 1.2 was used as a dissolution media. The bowls of the dissolution tester was filled with 900 ml of phosphate buffer PH 1.2 and allows to attaining a temperature of 37±0.5ºc and 50 rpm. Dissolution apparatus was started. At predetermined time interval. 5ml sample withdrawal and addition of fresh dissolution media. The collected samples were filtered and absorbance of the solution was measured at 273.5 nm. The concentration of Metoclopramide HCl was calculated using slope of calibration curve and cumulative percentage release was calculated.

7.7. Stability study

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, retest periods and shelf lives to be established[59].

FDA's Current Good Manufacturing Practice regulations include sections on stability and stability testing of pharmaceutical components and finished pharmaceutical products. In addition, FDA and International Conference on Harmonization guidelines and guidance's provide working recommendations to support the regulatory requirements. Among these are the following [60]:

- "Stability Testing of New Drug Substances and Products"
- "Quality of Biotechnological Products: Stability Testing of Biotechnology/Biological Drug Products"
- "Photo stability Testing of New Drug Substances and Products"
- "Stability Testing of New Dosage Form.

Drug and drug product stability testing during every stage of development is critical to the quality of the product. For a marketed drug product, assurance of stability is vital to its safety and effectiveness during the course of its shelf life and use[61].

7.8. Storage condition

In general, a drug product should be evaluated under storage condition that tests its stability and if applicable, its sensitivity to moisture or potential for solvent loss. The long term testing should cover a minimum of 12 months study or at least three batches at the time of submission and should be continued for a period of sufficient time till it covers the proposed shelf life. Stability studies were conducted at different conditions of 40ºc/ 75% RH and 25ºc/ 60% RH for about 3months in stability chamber (thermo lab). Samples were collected at 1st month, 2nd month and 3rd month.

7.9. Comparison Study

The precompression parameters and the postcompression parameters of drug are compared between the optimized tablet and marketed tablet

8. RESULTS AND DISCUSSION

8.1. Preformulation Studies of Metoclopramide Hydrochloride

a. Organoleptic character

All the organoleptic character of paroxetine Hydrochloride was studied and it was found that all the character complies with USP standards.

Table No. 8.1: Characterization of Drug

Test	Specification	Result
Colour	White	Confirms
Odour	Odourless	Confirms
Physical State	Crystalline Powder	Confirms
Melting point	182^0C-185^0C	183^0C
Thin Layer Chromatography	Test Preparation is more intense than Standard Preparation	Confirms
pH of Water Solution	4.5- 6.5	Confirms

1. The FTIR Spectrum of Metoclopramide Hydrochloride

The FTIR absorption of Metoclopramide Hydrochloride (Pure drug) were recorded in between 4000 to 400 cm^{-1}. Characteristics peak and chemical group present in IR spectrum of Metoclopramide was showed in .

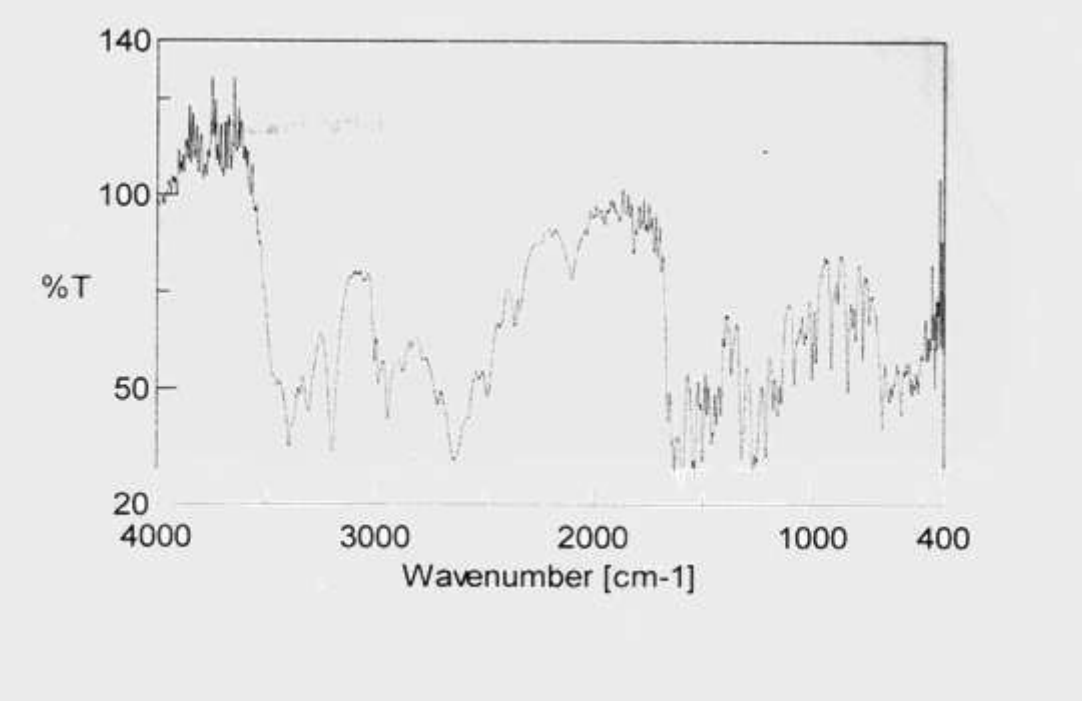


Figure No. 8.1: FTIR spectra of metoclopramide hydrochloride

Table No .8.2: Spectral assignment of metoclopramide hydrochloride

S. No	Functional Group	Frequency (cm^{-1})
1	C=O	1600
2	O-H, N-H	3200, 3300,3340, 3400,3460.
3	NH (Amide)	1540
4	C-O	1270
5	C-Cl	700

Figure No. 8.2: FTIR spectra of Metoclopramide Hydrochloride and Starch

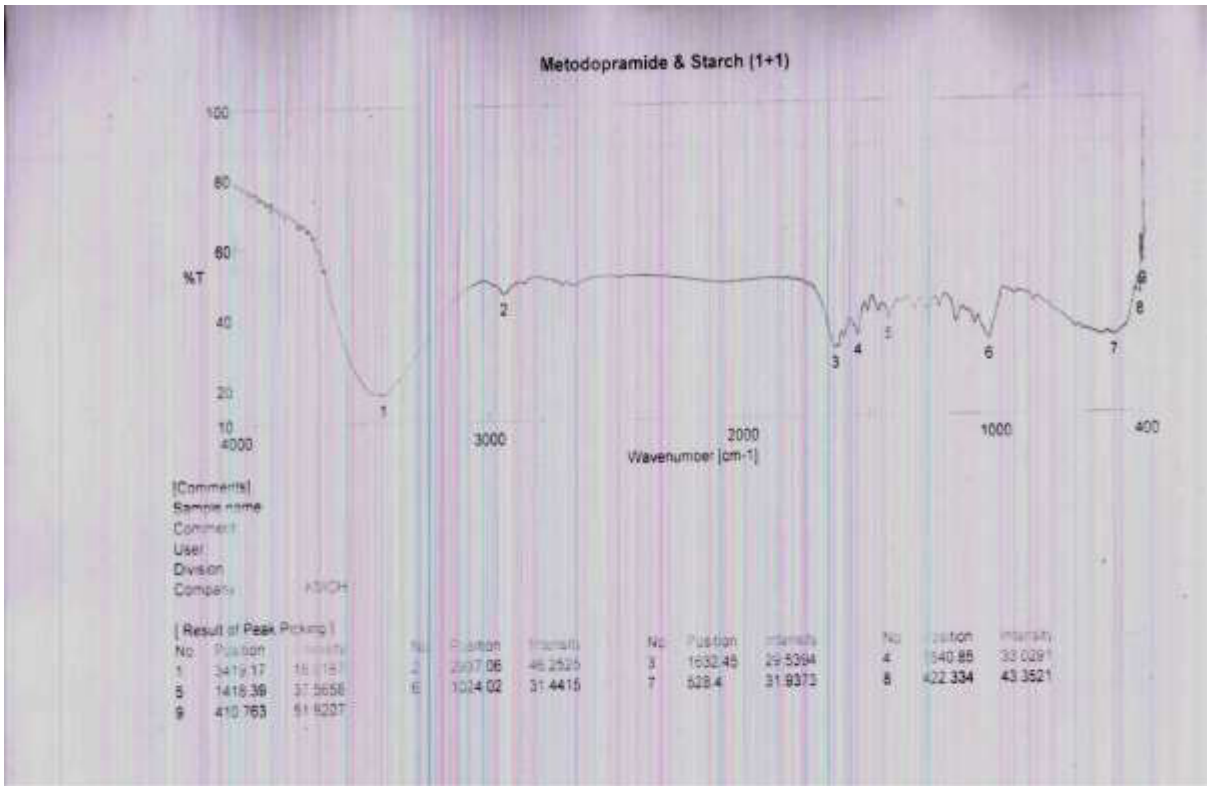
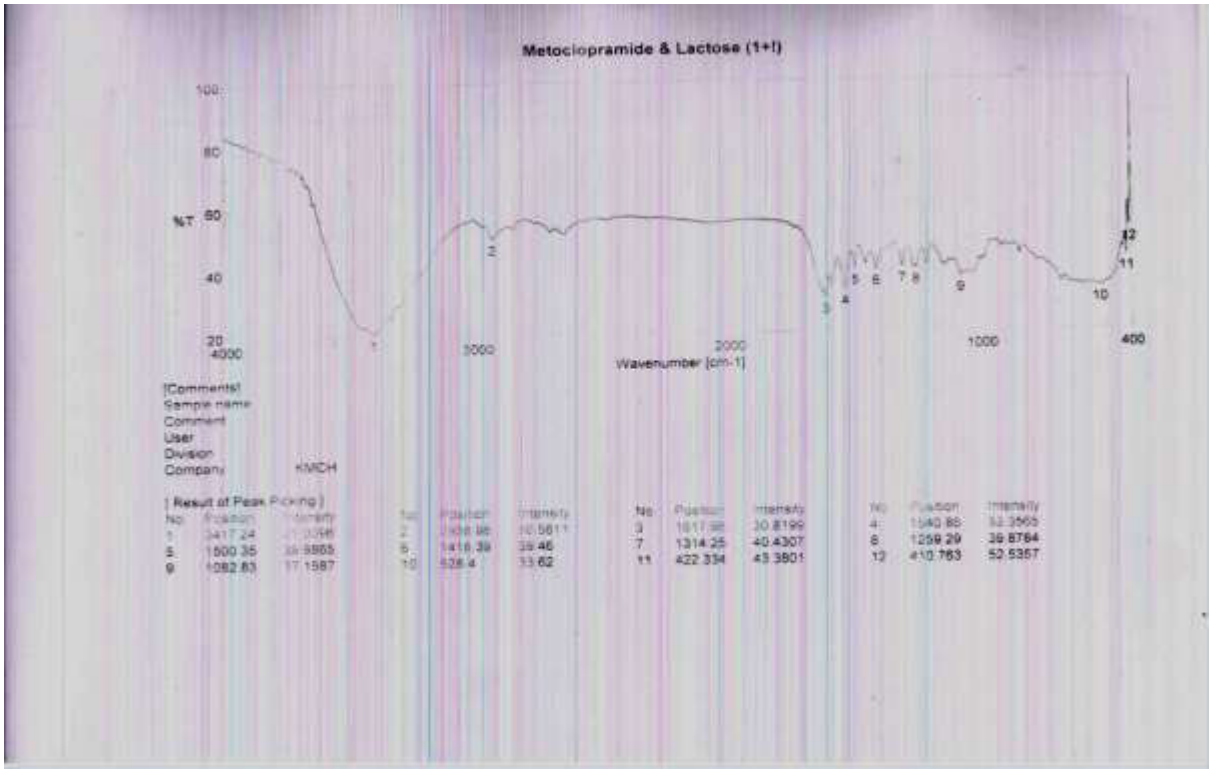


Figure No. 8.3: FTIR spectra of metoclopramide hydrochloride and Lactose



The FTIR of drug and Starch shown intense band at 3413 cm-1, 1418 cm-1, 1024, 422 cm-1 indicates no change in the functional groups NH, C=Cl and C=O, C-O. The FTIR of Drug and Lactose showed intense band at 3417 cm-1, 1500 cm-1, 1082, 528 cm-1. From the above interpretation it is understood that there is no major shifting in the frequencies of above said functional groups. Hence these drug and excipients are compatible with each other.

b. Method of Drug Analysis

Construction of Calibration Curve in Deionised Water

As shown in the figure, the calibration curve of Metoclopramide Hydrochloride follows linear relationship and the curve obeyed Beer-Lambert law within concentration range of 5-35 ugm/ml. The correlation coefficient value (R^2) was found to be 0.9987.

Table No. 8.3: Calibration curve in Deionized Water

SL. No	Concentration (µgm/ml)	Absorbance (nm)
1	5	0.286
2	10	0.561
3	15	0.826
4	20	1.061
5	25	1.312
6	30	1.621
7	35	1.934

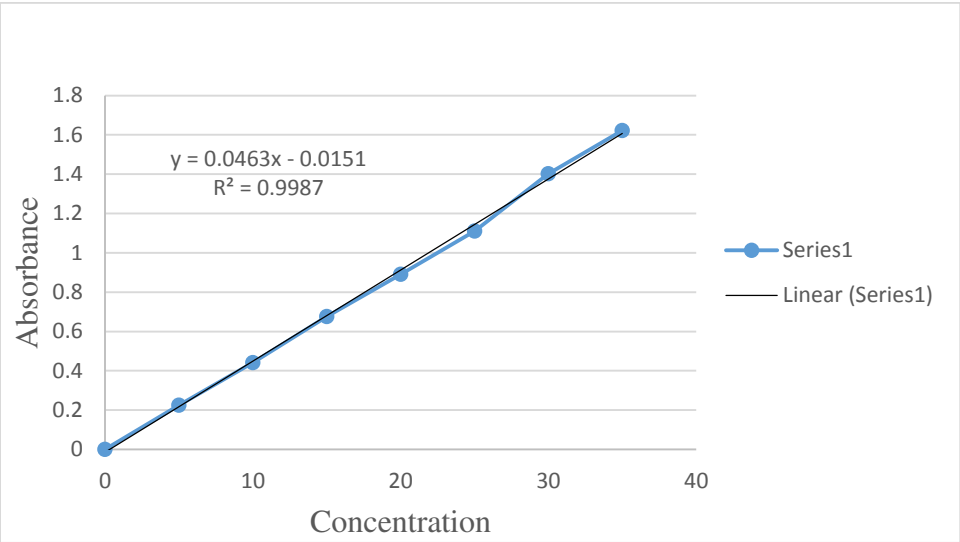


Figure No: 8.4: Calibration curve of Metoclopramide Hydrochloride in Deionised water.

In Phosphate Buffer pH 6.8

As shown in the figure, the calibration curve of Metoclopramide Hydrochloride follows linear relationship and the curve obeyed Beer-Lambert law within concentration range of 5-35 ugm/ml. The correlation coefficient value (R2) was found to be 0.9987.

Table No. 8.4: Calibration Curve in Phosphate Buffer pH 6.8

Sl. No	Concentration (µgm/ml)	Absorbance (nm)
1	5	0.224
2	10	0.442
3	15	0.676
4	20	0.891
5	25	1.11
6	30	1.402
7	35	1.622

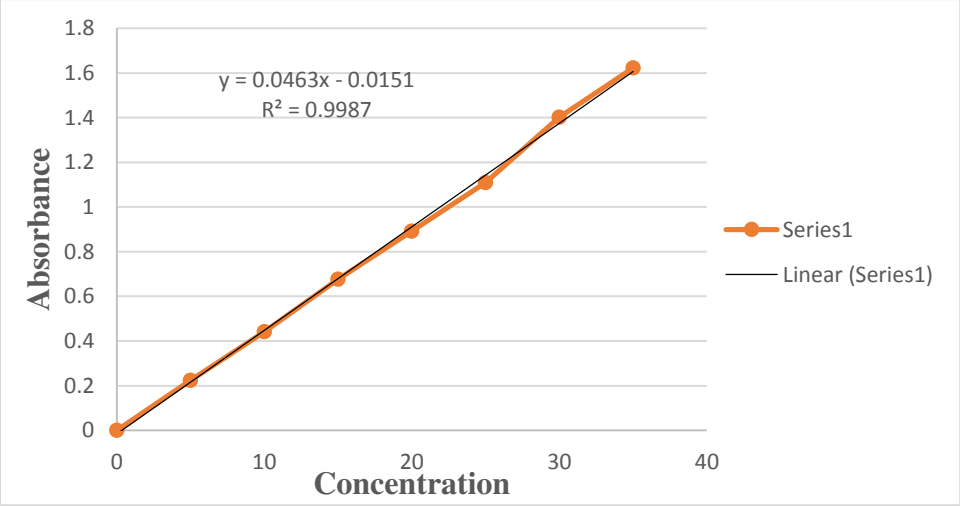


Figure No. 8.5: Calibration curve in phosphate buffer

In Stimulated Gastric pH (0.1N HCl)

As shown in the figure, the calibration curve of Metoclopramide Hydrochloride follows linear relationship and the curve obeyed Beer-Lambert law within concentration range of 5-35 (µgm/ml). The correlation coefficient value (R2) was found to be 0.9989.

Table No. 8.5: Calibration curve in simulated Gastric Fluid

SL. No	Concentration (µgm/ml)	Absorbance (nm)
1	5	0.160
2	10	0.312
3	15	0.456
4	20	0.616
5	25	0.746
6	30	0.938
7	35	0.972

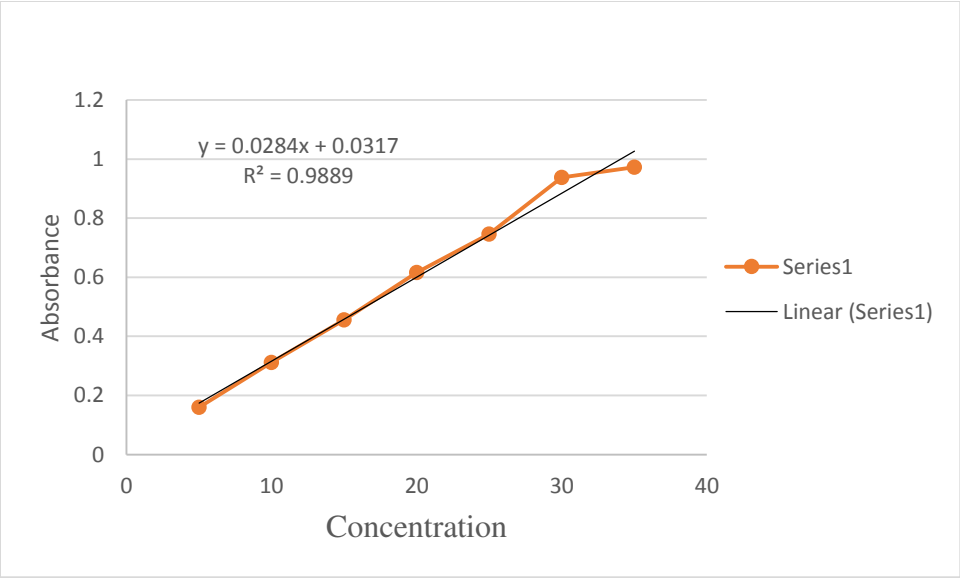


Figure No. 8.6: Calibration curve in simulated Gastric Fluid

8.2. Evaluation Parameters:

a. Pre-compression parameters

The Metoclopramide hydrochloride granules was prepared and subjected to pre-compression parameters like bulk density, Tapped density, carr's index, sieve analysis and angle of repose. All the pre-compression parameters was evaluated and reported in table no: 8.6.

Bulk Density and Tapped Density

The bulk density of all the powder blend batch of Metoclopramide hydrochloride was found to be 0.59g/cm^3 to 0.66g/$cm^3$and the tapped density of the entire powder blend batch was found to be 0.71g/cm^3 to 0.80g/cm3showing good flow property.

Angle of Repose

The angle of repose of the drug and excipients was evaluated. The angle of repose of the entire powder blend of each formulation was found in between 25-29^0 which reveals the blend has a good flow property. Hence it is confirmed that all blends has free flow property.

Carr's Index

The measurement of free flowing powder can also be done by Carr's index. The Carr's index for all the formulations was found to be 12-14.6 which reveals that the blends have fair flow character.

Hausner Ratio

The Hausner ratio of drug and Excipients was done as per procedure. The hausner ratio of the entire powder blend of each formulation was found in between 1.14-1.2 which reveals that the blend is free flowing. So it is confirmed that all the blend has free flow property.

Table No. 8.6: Results of Pre-compression parameters

Parameters	Bulk Density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (%)	Angle of Repose (θ)	Hausner Ratio
F1	0.59	0.75	12	25.25	1.2
F2	0.63	0.73	13.69	26.27	1.15
F3	0.61	0.71	14.08	27.32	1.16
F4	0.60	0.70	13.79	26.65	1.16
F5	0.62	0.71	12.67	28.42	1.14
F6	0.64	0.74	13.51	29.96	1.15
F7	0.63	0.72	12.5	25.07	1.14
F8	0.66	0.76	13.15	26.56	1.15
F9	0.64	0.75	14.66	27.60	1.17

Sieve Analysis

The sieve analysis was determined by Mechanical sieve shaker. Since 80% drug particles were retained in sieve no 50, and about 18.5% of drug particles were retained on sieve no 18. Hence the particles lay between sieves no 50 and 18. The drug has a particle size lies between 297μm to 1mm.

Table No.8.7: Particle size determination of Metoclopramide hydrochloride

Sieve No	Microns	Wt of drug + sieve (g)	Wt of the drug retained (g)	% of drug retained	Cumulative % of drug (µ) retained
#18	1000	389.7	3.7	18.5	18.5
#50	297	360	16	80	98.5
#70	210	331.3	0.3	1.5	100
#120	125	340	0	0	0
#140	105	338	0	0	0
#170	88	325	0	0	0
#200	74	320	0	0	0
#200 Pass		460	0	0	0
			20	100	

Physical Stability of the Admixture

The drugs along with the excipients were kept under conditions specified and the results are given

Table No. 8.8: Drug – Excipient stability profile

S. No	Items	1 Month/Control	1Month/ 60^0C
1	API	No change	No change
2	API+ Lactose	No change	No change
3	API+ Starch	No change	No change
4	API+ Talc	No change	No change
5	API+ Magnesium stearate	No change	No change

There was no physical change observed in the admixture after one month at 60 ºC

8.3. Post Compression Parameters

The tablets of different formulations of Metoclopramide Hydrochloride were subjected to various evaluation tests, such as hardness, thickness weight variation, friability and drug content. All the result is shown in Table 8.9.

Thickness

The thickness of the tablets was found out using Vernier Caliper and the thickness found to be in the range of 4.02-4.12mm for the uncoated tablets (F1-F6). For the enteric coated tablets the thickness ranged from 4.21-4.30.Thus all formulations showed uniform thickness.

Hardness test

The hardness of tablet was measured by Monsanto hardness tester. Ten tablets from the batch were used for hardness studies and results showed they were in between 3.5- 4.2 Kg/cm2.

Weight variation test

In a weight variation, the pharmacopoeial limit for the percentage deviation for tablets of more than 250 mg is ±5%. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements.

Friability test

The Friability of all the formulation was below 1% as per IP specification.

Wetting Time

The wetting time of tablet was measured and the result found in between 35- 45 seconds.

Drug content analysis

Metoclopramide Hydrochloride tablet was tested for their drug content and all the formulation showed drug content 90 to 110%.

All the tablet formulations showed acceptable pharmaco-technical properties and complied with the in-house specifications for weight variation, drug content, hardness, and friability.

Table No. 8.9: Results of post compression parameters

Evaluation of Post Compression Parameter							
Formulation Code	**Hardness (kg/cm^2)**	**Friability (%)**	**Weight variation Test (%) ±S.D**	**Uniformity of Drug Content (%) ± S.D**	**Thickness of Tablets (mm) ± S.D**	**Wetting Time (Seconds)**	**Disintegration Time (sec) ± S.D**
F1	3.7	0.69	102.3±0.15	98.94±0.25	2.7	36	42±0.73
F2	3.9	0.71	101.2±0.66	99.46±0.24	2.7	39	51±0.58
F3	4.2	0.68	98.9±0.301	99.65±0.33	2.7	45	55±0.65
F4	3.6	0.71	100.6±0.23	99.45±0.12	2.7	38	34±0.59
F5	3.5	0.74	102.1±0.18	99.25±0.31	2.7	40	41±0.85
F6	4.1	0.72	101.3±0.26	99.52±0.06	2.8	43	45±0.71
F7	3.7	0.69	101.6±0.22	99.86±0.39	2.7	35	30±0.64
F8	3.9	0.71	99.5±0.18	99.78±0.35	2.7	39	32±0.48
F9	4.1	0.70	100.8±0.21	99.42±0.14	2.8	42	35±0.40

8.4 .Drug Release Study

Innovator drug release profile

Cumulative percent drug released from the tablet were shown

Table No. 8.10: In-vitro Drug release profile of Innovator

S. No	Time (Min)	Percentage cumulative drug release
1	3	35.50
2	6	46.40
3	9	79.40
4	12	92.68
5	15	99.58

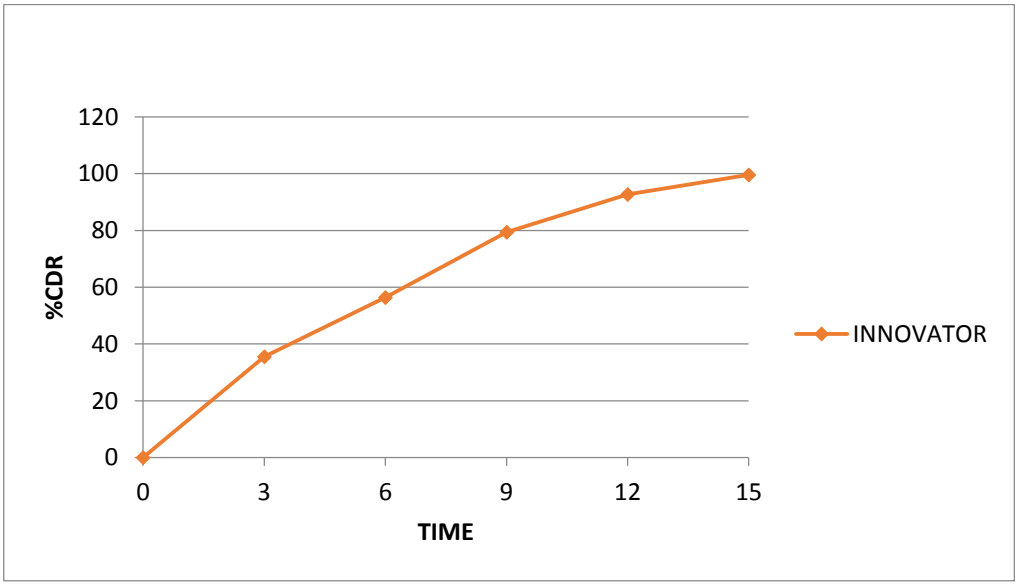


Figure No. 8.7: In-vitro Drug release profile of Innovator

Result of Drug release for F5 formulation

Cumulative percent drug released from the tablet were shown

Table No. 8.11: In-vitro Drug release profile of F5 batch

S. No	Time (Min)	Percentage cumulative drug release	
		F5	Innovator
1	3	30.24	35.50
2	6	61.18	46.40
3	9	89.12	79.40
4	12	93.92	92.68
5	15	94.42	99.58

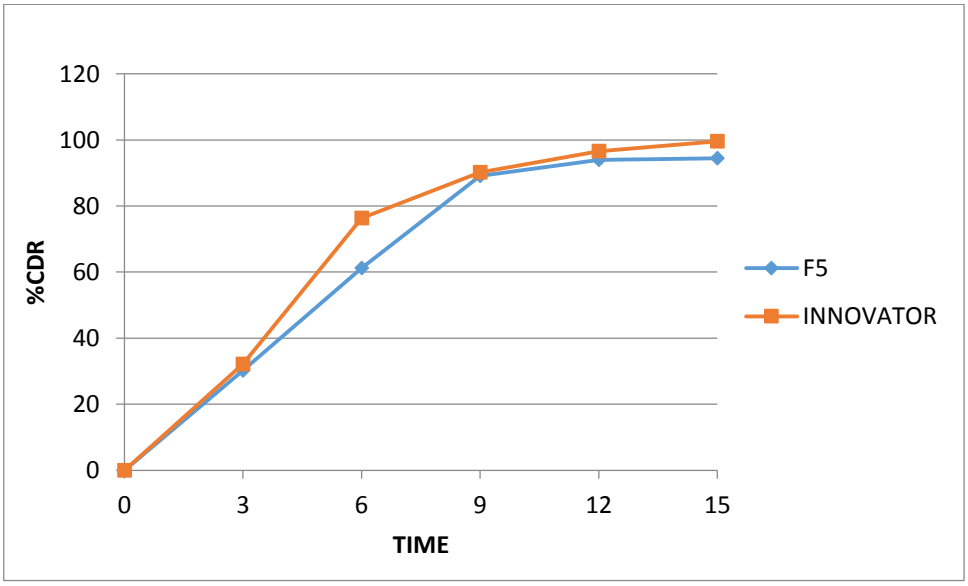


Figure No. 8.8: In-vitro Drug release profile of F5 batch

Result of Drug release for F6 formulation

Cumulative percent drug released from the tablet were shown

Table No. 8.12: In-vitro Drug release profile of F6 batch

S. No	Time (Min)	Percentage cumulative drug release	
		F6	Innovator
1	3	31.11	35.50
2	6	73.56	46.40
3	9	89.38	79.40
4	12	92.18	92.68
5	15	93.76	99.58

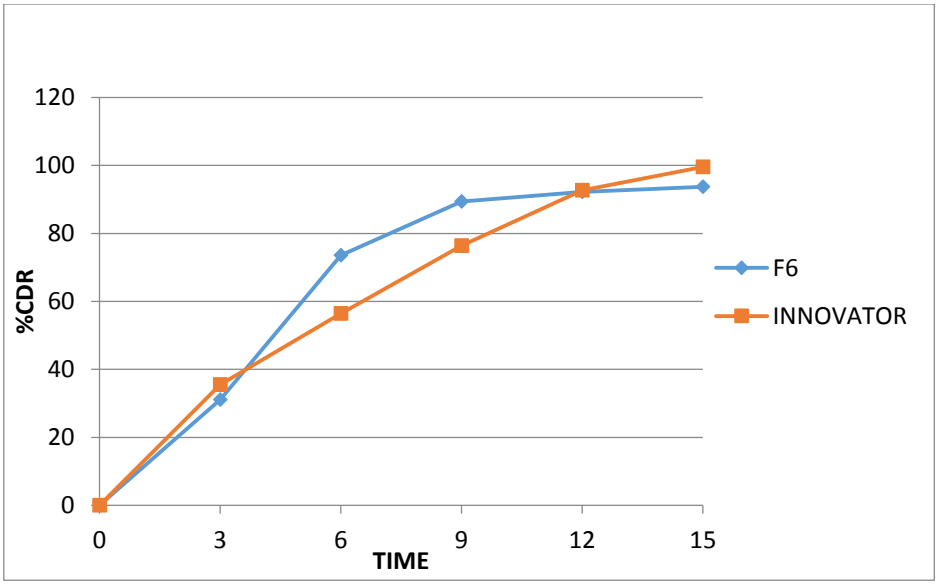


Figure No. 8.9: In-vitro Drug release profile of F6 batch

Result of Drug release for F7 formulation

Cumulative percent drug released from the tablet were shown

Table No. 8.13: In-vitro Drug release profile of F7 batch

S. No	Time (Min)	Percentage cumulative drug release	
		F7	Innovator
1	3	32.46	35.50
2	6	76.11	46.40
3	9	90.18	79.40
4	12	97.34	92.68
5	15	99.10	99.58

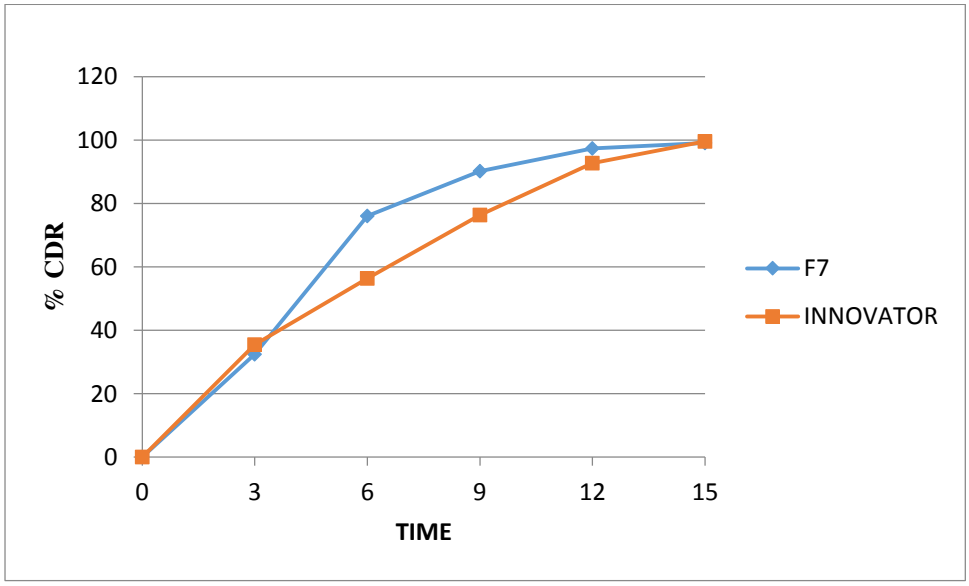


Figure No. 8.10: In-vitro Drug release profile of F7 batch

Result of Drug release for F8 formulation

Cumulative percent drug released from the tablet were shown

Table No. 8.14: In-vitro Drug release profile of F8 batch

S. No	Time (Min)	Percentage cumulative drug release	
		F8	Innovator
1	3	32.24	35.50
2	6	63.18	46.40
3	9	90.12	79.40
4	12	95.92	92.68
5	15	96.26	99.58

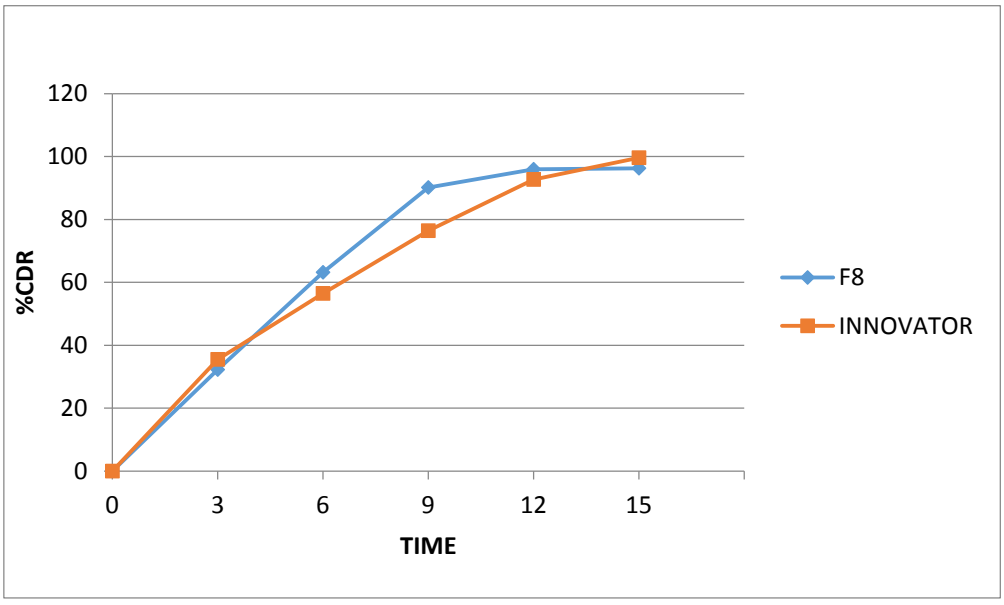


Figure No. 8.11: In-vitro Drug release profile of F8 batch

Result of Drug release for F9 formulation

Cumulative percent drug released from the tablet were shown

Table No. 8.15: In-vitro Drug release profile of F9 batch

S. No	Time (Min)	Percentage cumulative drug release	
		F9	Innovator
1	3	32.18	35.50
2	6	73.56	46.40
3	9	88.56	79.40
4	12	94.24	92.68
5	15	95.16	99.58

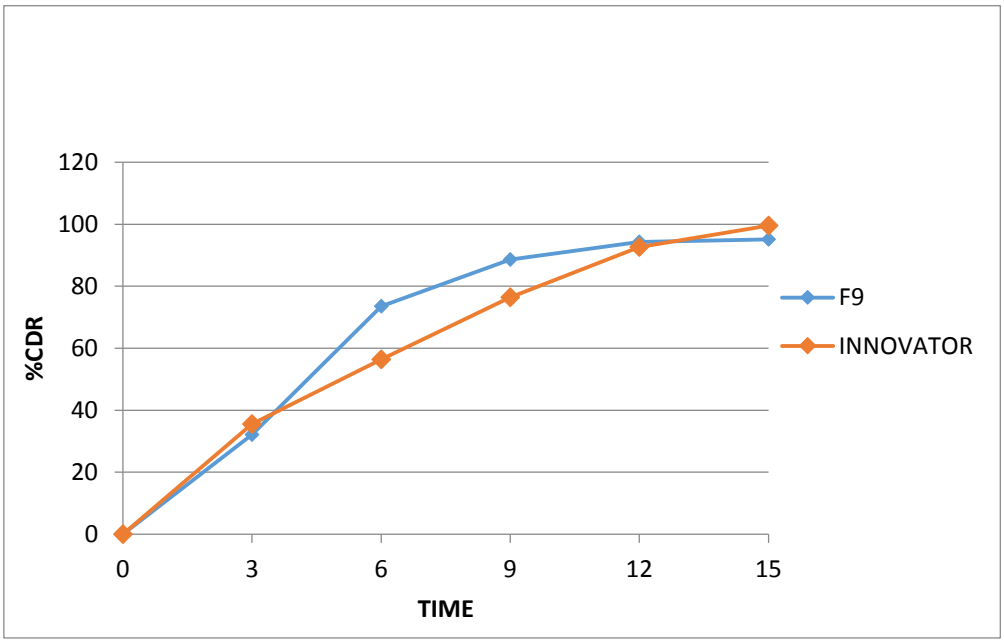


Figure No. 8.12: In-vitro Drug release profile of F9 batch

Drug Release of various formulation

Table No. 8.16: In-vitro Drug release profile of various formulation and innovator

Time (Min)	Formulation					
	F5	F6	F7	F8	F9	Innovator
3	30.24	31.11	32.46	32.24	32.18	35.50
6	61.18	73.56	76.11	63.18	73.56	56.40
9	89.12	89.38	90.18	90.12	88.56	76.40
12	93.92	92.18	97.34	95.92	94.24	92.68
15	94.42	93.76	99.10	96.26	95.16	99.58

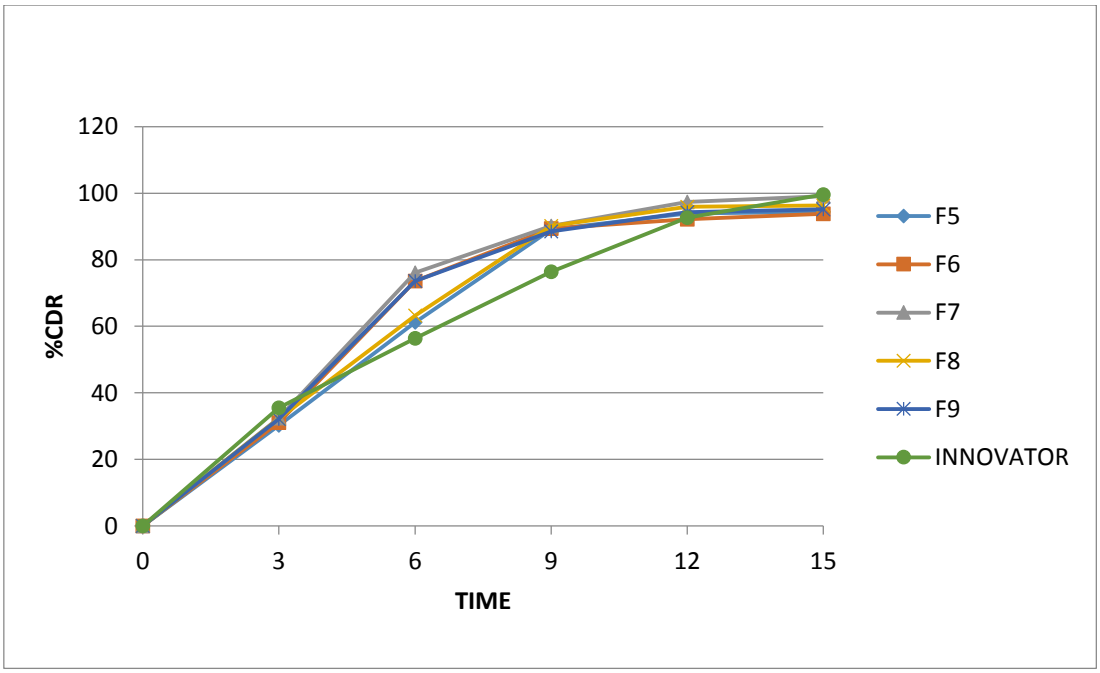


Figure No. 8.13: Comparison of In-vitro Drug release profile with Marketed Product

8.5. Stability Study

Aging studies of formulated immediate release tablet of Metoclopramide Hydrochloride at 25^0C/ 60% RH (2 month)

Table No .8.17: Stability studies of optimized formulation F7 at 25^0C/ 60% RH.

S. No	Evaluation Parameters	Observation		
		Initial	1 Month	2 Months
1	Physical Appearance	White	White	White
2	Weight variation (%)	101.6±0.22	101.9±0.22	101.9±0.22
3	Friability (%)	0.69	0.71	0.71
4	Thickness (mm)	2.7±0.051	2.7±0.046	2.7±0.056
5	Hardness (kg/cm^2)	3.70±0.18	3.68±0.27	3.68±0.29
6	Disintegeration Time (sec)	30±0.64	28±0.54	28±0.59
8	Drug content (%)	99.86±0.25	99.85±0.15	99.85±0.23

Stability Study

Aging studies of formulated immediate release tablet of Metoclopramide Hydrochloride at 40^0C/ 75% RH (2 month.)

Table No .8.18: Stability studies of optimized formulationF7 at 40^0C/ 75% RH.

S. No	Evaluation Parameters	Observation		
		Initial	1 Month	2 Months
1	Physical Appearance	White	White	White
2	Weight variation (%)	101.6±0.22	101.8±0.35	101.8±0.22
3	Friability (%)	0.69	0.71	0.72
4	Thickness (mm)	2.7±0.053	2.7±0.42	2.7±0.048
5	Hardness (kg/cm^2)	3.70±0.21	3.65±0.26	3.65±0.29
6	Disintegeration Time (sec)	30±0.62	28±0.54	28±0.60
8	Drug content (%)	99.86±0.28	99.86±0.35	99.85±0.39

8.6. Stability study of in-vitro dissolution for formulation F7 stored at different temperature

Table No .8.19: Stability study of In-vitro dissolution of optimized formulation

Time (Min)	Cumulative% Drug Release			
	Stored at 25^0C Temperature		Stored at 40^0C Temperature	
	After 1 Month	After 2 Months	After 1 Month	After 2 Months
3	31.42	31.08	31.38	30.96
6	74.85	74.52	74.45	74.36
9	89.18	88.98	88.84	88.53
12	96.34	96.12	96.38	95.97
15	98.98	98.97	98.94	98.91

8.7. Comparison of Formulated and Marketed Tablets

The Precompression parameters of drug are compared between the formulated tablet F7 and Marketed tablet are shown below:

Table No 8.20: Comparison of Formulated and Marketed Tablets

Sl. No	Parameters	F7	Marketed Tablet
1	Average weight of Tablet(mg)	101.6±0.22	140±0.58
2	Hardness (kg/cm2)	3.7±0.16	3.9±0.21
3	Friability (%)	0.69	0.26
4	Wetting Time (%) ±S.D	35±0.64	32±0.58
5	Uniformity of Drug Content (%) ± S.D	99.86±0.32	99.80±0.28
6	Disintegration Time (sec) ± S.D	30±0.62	25±0.53
7	Thickness(mm)	2.7±0.043	2.2±0.064
8	Drug Release (%)	99.58	99.10

8.8. Formulation of Immediate Release tablets of Metoclopramide Hydrochloride

Figure No. 8.15: Formulation of Immediate Release tablets of Metoclopramide Hydrochloride

9. SUMMARY

The present study was under taken to formulate and evaluate the immediate release tablets of Metoclopramide hydrochloride by using wet granulation technique with various disintegerants. The study involves pre-formulation ofdrug and excipients, formulation, evaluation and stability studies.

Nine formulations of metoclopramide were prepared by using various disintegerant in different concentration. The optimized formulation was selected according to the result found from the evaluation parameter of each formulation. Estimation of drug was carried out spectrometrically by UV method. Pre-formulation study involving FTIR showed no interaction between drug and excipients.

The selected drug Metoclopramide was taken and formulated with different concentration of starch, talc and sodium starch glycolate. The tablets were prepared by wet granulation method and then it is punched after subjecting the blend to pre-compression parameters like Angle of repose (25.07^0), Bulk density (0.63gm/cm), Tapped density($0.72g/cm^3$), Carr's Index (12.5%), Hausner ratio (1.14). The results obtained were satisfactory. The Post compression parameters like Hardness ($3.7kg/cm^2$), Weight variation (101.6%), Friability (0.69%), Drug content analysis (99.86%), Disintegeration time (30sec) and In-vitro dissolution studies (99.10 at 15 min) were also carried out and tabulated. Among all these formulations F_7 was selected as optimized formulation.

The selected optimized formulation was characterized with stability studies. These tablets were subjected to pre-compression parameters and post-compression parameters. These results were compared with the predetermined optimized formulation results. The formulation was found to be stable.

The prepared in-vitro dissolution studies of prepared immediate release tablet were compared with that of marketed formulations and were found to be better than them.

10. CONCLUSION

The Present study was conducted to formulate and evaluate the immediate release tablet of Metoclopramide hydrochloride. Pre-formulation study was carried out initially with study of selection of superdisintegrants was done and different formulations were prepared using sodium starch glycolate and starch as disintegerants. Immediate release tablet of Metoclopramide hydrochloride was prepared by wet granulation method. The tablet disintegrated rapidly and has an acceptable friability and hardness. *In vitro* drug release from the tablets shows significantly improved drug dissolution. Hence it could be concluded that the superdisintegrant based on immediate release tablet of Metoclopramide hydrochloride would be quite effective in emesis, providing quick onset of action on administration.

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