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FORMULATION AND EVALUATION OF MITRAZAPINE ORAL DISINTEGRATING TABLETS USING SUBLIMATION METHOD

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1. INTRODUCTION

The requirement for additional patient-friendly & complying dosage formulations has evolved across the past ten years. The necessity for generating novel technologies has consequently been expanding annually.[1]

Pharmaceutical firms are right now focusing on advancing the creation of innovative prescription dose forms for currently taken medicines via boosting securely and effectiveness through a lower administering the frequency, in addition to the manufacturing of a greater number of affordable forms of treatment, because of the high development costs associated with new drug molecules. As a result its diverse benefits together with powerful adherence among patients in contrast with various different methods, the route through the mouth is still preferred method of administration for almost all of medicinal products for producing systemic effects.[2]

The largest number of medicinal product method of administration that are at the moment on the marketplace are pills and hard capsules made from gelatin. Nevertheless, swallowing these forms of medication can be complicated for a variety of target communities, particularly older people, children, people with intellectual disabilities patients, inflexible patients, people with illnesses, and individuals who are on decreased liquid consumption or diet. Similar results happen to those who are on journey or Never possess easy accessibility to drinking water.[3] Pharma experts have come up with Orally Disintegrating Tablets (ODTs), an innovative orally the dosage formulation which degrades readily within salivary and does not need wetting out with water to satisfy these therapeutic needs. Pharmaceutical bioavailability, therapeutic effect onset, digestion, & solubility might all be much greater compared to those observed via conventional dosage formulations.[4-5]

A chewable medications aren't equivalent as recent ODTs, although having on the marketplace for quite some time. Individuals may suffer difficulty and discomfort when swallowing are able to consume these novel pills. Infants that are missing their main teeth who do not have full use with the permanent ones may gain tremendously through the application of ODTs.[6-7]

This ODT tech is attracting a lot of curiosity since it helps tablets to dissipate or decompose in the mouth with no requiring for extra water consumption. ODTs is a sort a material dose format a component of if taken in via the mouth using low biofluid, enables the solid component to disperse or break quickly when administered as a suspended form or solutions.[8-9] Additionally, there are many different names for oral disintegrate pills, includes oral dispersing pills, rapimelts, pores pills, rapidly or fast melting pills rapid disintegration pills and rapid disintegration pills. The vast majority of excipients that utilised in ODT tech is hydrophilic in the environment, so they may be determined to correspond with the chemical and physical character that comprise the medication, in a manner of hydrophilic characteristics or hydrophobic properties. The method of administration can be often referred to as a disintegrating pill if the medicine active ingredient possess a hydrophobic its nature, and rapid decomposition of tablets if it is of a water loving nature. The ODT exterior is designated as "a solid form of dosage including medicinal ingredients and dissolves fast, generally under a matter of a few seconds being applied upon the mouth" by the US Food and Drug Administration (FDA). Zydis, an ODT version of Claritin is (loratadine), was granted approval by the United States FDA in the month of December 1996. It got replaced with the Zydis ODT formulations of Maxalt (rizatriptan) around the month of June 1998 and Klonopin (clonazepam) during the end of 1997. Furthermore, a small number of drugs received approval from regulators for ODT forms. The objective of this paper is to go over ODTs' advantages and disadvantages, formulations challenges, manufacturing methods, patent

tools, practical products, and assessment evaluation.

Overview of Oral Mucosa

Several authors have explored the physiology and anatomy associated with the oral cavity in tremendous detail. The lips, cheekbones, the chin, tongue, harder palates, the soft palate, and floor in the mouth are every component of the mouth's cavity (Fig. 1). The oral, sublingual, the gingival, the palate, and labial mucosas were every component of the oral tissue, which makes up the outer covering of the cavity within the mouth. Around sixty per cent of the mouth muco surface is formed up of the the buccal, the sublingual technique,, & mucosal tissue, which is located on the tongue's ventral aspect. Close pressed cells of the epithelial layer comprise just over a third on the upper part from the oral mucosa (Fig. 2). The dental epithelium's primary purpose serves to protect the tissues underneath from potentially hazardous compounds that penetrate the mouth along with fluid loss. The bottom membranes, and the propria lamina, and submucosa are situated beneath the skin's epithelium. Human tongue's taste buds belong to many receptors for sensation found across the mouth's mucous membrane. The oral cavity has three different types of oral mucosa. The oral mucous membrane, which is found in outside the mouth vestibule, and the sublingual area, where is the floor that covers the mouth, are illustrations of lined mucosa. The dorsal side of the oral cavity tongue carries the sensitive mucosa, whereas the gingival surface hard palate (the lower layer of the palate in the mouth) carry the mucosa of mastication (gums). Of the total area of the oral mucosa lined of a mature human beings, the outer mucosal comprises up approximately sixty percent, the mucosa of the masticatory system approximately twenty-five percent, and the specialised mucosal approximately fifteen percent. The regions that are that are most susceptible to the stresses and strains carried on by masticatory action were home to a masticatory mucosa. A masticatory mucosa's cells on the surface are keratitis and a thick film of propria lamination securely links it to the periosteum is underlying. The inner layer of the tissue, on the opposite hand, consists of a non-keratinized epithelium that rest on a skinny, flexible propria lamina with a beneath the skin as it is not very prone to masticatory pressures. The outermost layer that makes up the tongue's epithelium is a specialised gustatory membrane with keratitis well papillated areas with a few insufficiently keratinized. The advantageous characteristics and limitations of using the mucosa of the mouth as a medication delivery route are discussed in Table 1.

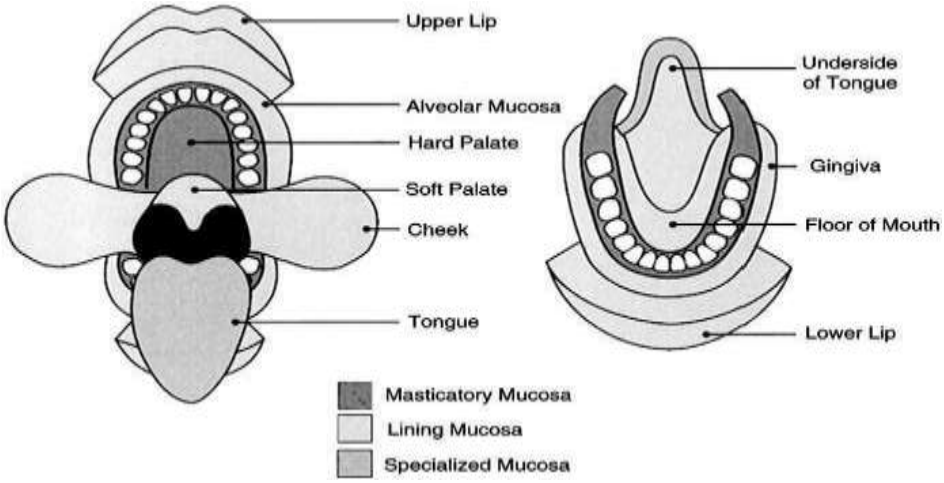


Fig. 1: Schematic representation of the different linings of mucosa in mouth.

ORALLY DISINTEGRATING DOSAGE FORMS

The prospect of offering individuals a more conventional means to consume medicine gave development to the idea of orally disintegrating dosage formulations. it's important to observe that over the last ten years, their have been an enormous rise in demand for ODDFs, particularly among senior and young individuals who struggle to swallow regular pills and capsules. As consequently, patients frequently ignore prescription drugs, which escalates the danger of inadequate treatment.

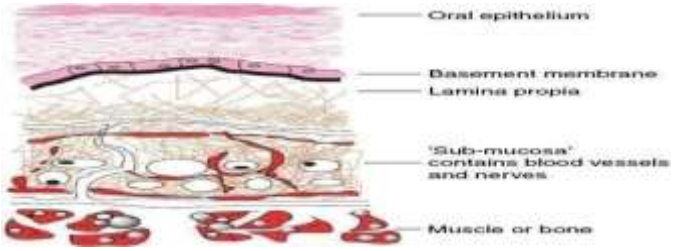


Fig. 2: Schematic diagram of buccal mucosa.

In specific medical circumstances, including nausea from motion, abrupt respiratory works, as well as recurring events of diarrhoea, digesting conventional oral dosage form becoming difficult. In such situations, oral disintegrating dose form can be an effective alternative method of administering medication. Such dose formulations breakdown within the mouth instantly, release the drug, then breaks or spread in mucus. Once it, when the spit runs lower, the medicine may be digested in the pharynx, oesophagus, as well as various regions of the Stomach. In these instances, absorption is significantly higher than that of a regular dosage for tablet form.

The phrases "rapidly dissolve," "lightning-fast dissolve," "speedy dissolve," and "quick dispersed tablets" refer to this unique oral disintegrating dosage form innovation. Still, all these different dose formulations have an identical principle and objective. Following vary in dose types that melt in the mouth:

1. **Disintegrating Tablets Orally:** It is pills that consumed orally, diffuse if not break down with not requiring of chew or drinking.
2. **Fast Dissolving Films:** Although the reality the solid medication break and dissolve fast, they is still stress related to consuming them as well as a possible suffocation danger for certain patient groups. It is a substance made up of an incredibly thin oral sheet that delivers its active ingredient immediately as it reaches the cavity in the mouth. It mixes fluid dose form along with advantages of medication. The person using it just needs to moist the sheet with saliva and apply this method on the tongue or any other part of the mucous barrier. The sheet of film rapidly hydrates and dissolves, facilitating the administration of the medication. **Fast Caps:** On the backbone of collagen capsules, an innovative type of fast dissolving drug way of delivery was developed. In contrast to conventional hard gel capsule-like structures, their rapid capping are composed of lower blooms intensity gel formation and a range of compounds that improve the mechanically and breaking down properties within the capsules shells. Strong loading of drugs, both liquid and solid filling choices, no deformation among coated, extended-release, and taste-masked drugs in particles or pellets, solid durability, ease of manufacture, stable mechanical properties, and the need for particular container are only some of its advantages.
3. **Medicated Chewing Gums:** Chewing gum was an acceptable substitute to conventional methods of drug delivery, offering an array advantages like ease of delivery. It is mostly used as a possible controlled-dose drug delivery technological advances. Nowadays, the primary uses of these include for pain relief, quitting smoking, travelling illness, and breath refreshing.
4. **Wafer that's Freeze-Dried:** It is a fragile, fast diffuse polymer contains drugs that may be taken with no water. For proper physical strength, unit-dose packing is required for such sensitive form of dosage. The medicine appears when a water rapidly breaks in the oral cavity & goes into saliva. The drug passes via the GI tract (the gastrointestinal tract) once its saliva was ingested.

ORALLY DISINTEGRATING TABLETS

The technology used in the production of ODTs limits how well they perform. The pills' ability to break down fast when taken orally is due to the water's speedy passage through the tablet's matrix, resulting in a porous structure & speeds down the process of disintegration. Thus, refining the pill matrix's porous makeup, the fundamentals of making ODTs include employing highly soluble in water additives in the mix and a suitable disintegration agent.

Drug Selection Criteria

Some of the following features are great for a drug in an orally dispersible tablet:

- The ability to penetrate the mucous membrane inside the mouth.
- Ideally, somewhat non-ionized at the acidity level found within the mouth.
- Maintain an ability to disseminate & divide in the top layer of the GI tract's cells.
- Moderate to low molecular weights
- Medications at low dosages, particularly below fifty milligrammes.
- Drugs having short the half-life and a regular dosing are unsuitable with ODT.
- The medicine must be viable in water as well and saliva.
- Drugs with potent or unpleasant smells or flavours are unsuitable for ODT

Advantages of ODTs

- You can swallow the tablet without water.
- Have a pleasant texture and work well for disguising tastes.
- Patients with mental disabilities, the elderly, and children can all receive it with ease.
- Following ingestion, there is no residue in the oral cavity.
- Conventional processing and packaging equipment can be used to manufacture the tablets at a minimal cost.
- Permit heavy drug loading.
- In contrast to liquids, an accurate dose can be administered.
- The medication dissolves and absorbs quickly, providing a quick start to action.
- Better in terms of transportation and administration than liquid medications.
- As saliva travels down into the stomach, a certain quantity of medication is ingested via the mouth, throat, and oesophagus. This reduces first-pass cycle of metabolism, improving bioactivity and thereby

lowering dosage and adverse effects.

- ODTs are appropriate for prolonged and controlled release actives; there is no chance of asphyxia from physical obstruction when swallowed, providing enhanced safety.
- Packaging for units.
- Standard manufacturing apparatus.
- Economical.
- The same level of chemical stability as a traditional oral solid preparation.
- Novel commercial opportunities such as lifestyle management, patent extension, product diversification, and product promotion.
- Permit heavy drug loading.
- Delivers medication from dose forms quickly.
- Offer the benefit of a solid preparation for a liquid drug.
- Quick pharmacological therapy adjustments.
- No need to chew.
- Flexible and compatible with current packaging and processing equipment.
- Quick start of action.

Disadvantages of ODTs

- ODT sometimes has a mouthfeel, and because of its hygroscopic nature, it must to be stored in a dry environment.
- It also demonstrates the property of effervescent, fragile granules.
- To ensure the safety and proper stabilisation of the stable product, ODT needs specific packaging.

Limitations of ODTs

- The mechanical potency of the pills is frequently insufficient. Thus, handling must be done carefully.
- If the tablets are not prepared correctly, they may leave the oral cavity with an unpleasant taste and grittiness.
- It may be difficult to synthesise drugs with high dosages into ODTs.
- Individuals who use anti-cholinergic medications concurrently are unsuitable to be ODT candidates.

Problems with the Current Oral Dosage Form

- The individual may experience tremors, which could make it difficult for them to swallow liquid and powder medications. Gastrointestinal ulcers may result from physical obstacles and adhesion to the oesophagus in dysphasia.
- Ingesting solid dose forms, such as pills and capsules, might cause problems for young people by impeding the nervous system's and muscles' development.
- Because liquid medications like emulsions and suspensions are placed in multi-dosage containers, it may not be possible to maintain content homogeneity in each dose.
- The oral mucosa may become irritated by buccal and sublingual formulations.

ODT MECHANISMS

ODTs employ the following methods for the purpose accomplish the outcome that you want desired fast dissolving characteristics:

1. For pill to dissolve & disintegrate swiftly, water must get into the matrix of the tablet immediately.
2. Adding extremely soluble in water additives or proper agent that disintegrates to tablet formulation.
3. The tablet is broken down into tiny particles via a few mechanisms that aren't stated before, which leads to a medication dispersion or solution. The ways of working are:

- Chemical reaction; • Capillary action; • High disintegration swellability

ODT FORMULATION ASPECTS

The crucial elements in ODT compositions must allow the medicinal product to come out rapidly, resulting in a quicker rate of dissolution. Which includes both excipients (ingredients) and also substances with pharmacological activity (drug).

A. **Choosing a Drug Candidate:** The selection of a suitable medication candidate for the production of orally disintegrating tablets may take into account a number of criteria. The ideal qualities in medication by oral disintegration and pregastric integration from quickly tablets that dissolve are

1. Not taste bitter
2. Less than 20 mg dosage
3. Chemical weight that is moderate to small
4. Favorable water and saliva solubility
5. Partially amalgamated under oral cavity pH conditions
6. Capability to infiltrate and partition within the upper epithelium of the gastrointestinal tract (log >1, or preferably log >2).
7. Ability to penetrate the mucosal tissue of the oral cavity.

As long as the material is one that is utilised as an active ingredient in pharmaceuticals, there are no specific restrictions. For a range of medication classes when employed in treatment, where an quick maximum concentration of plasma is necessary for the production of the intended therapeutic reaction, researchers have developed ODT. These include medications for erectile dysfunction, anti-parkinsonian, anti-allergic, anti-epileptic, anxiolytic, sedatives, hypnotics, diuretics, neuroleptics, cardiovascular agents, analgesics, and anti-allergic pharmaceuticals. On the other hand, the following traits can make them inappropriate for oral disintegration tablet delivery:

1. Frequent dosage and short half-life.
2. Extremely bitter or unsatisfactory taste due to an inability to effectively disguise flavours.
3. Sustained released property
4. In combination with anticholinergic medications.

Selection of Excipients

The following are the main excipients found in ODT: a lubricant, a diluent, at least one disintegrant, and possibly sweeteners, flavourings, and swelling agents. The following characteristics offers the best bulk preservatives for forms of administration that dissolve when taken by mouth:

1. Disperses and dissolves without leaving any trace in the mouth just a few seconds.
2. Provides a feel of satisfying in the oral while hiding the medicine unsatisfiying flavour.
3. Makes sufficient medication fill up and is mostly unresponsive to temperature or humidity alteration.

Excipients play a crucial part in the composition of tablets that melt quickly. For quicker melting qualities, the excipients' temperature should ideally be between 30 and 350 degrees Celsius.

Drug Selection Criteria

The following qualities are excellent for a medication in an oral dispersible tablet:

- Ability to permeate the oral mucosa;
- At least partially uncharged at the oral cavity's pH.
- Possess the ability to spread and separate within the epithelium of the upper gastrointestinal tract.
- Relatively small to moderate molecular weight.
- Medication administered at minimal doses, preferably below 50 mg.
- Pharmaceuticals with a brief half-life and frequent dosing are unsuitable for ODT.
- Stability in both water and saliva is crucial for the medication.
- Substances with an unpalatable or exceedingly bitter taste and smell are unsuitable for ODT.

IMMEDIATE DRUG RELEASE DOSAGE FOMS TABLET

Because of their compact size, ease of production, and ease of self-administration, tablets are a popular choice for medication delivery. Instant-release dosage forms, which use super disintegrants such as sodium starch glycolate and croscarmeliose, provide a quick start for action. Requirement for quick results is also met by parenteral and liquid versions. Particularly as pharmaceuticals get closer to their patent expiration, immediate-release formulations increase patient compliance and prolong market exclusivity. These formulations, in conjunction with alternatives for continuous release, fulfil crucial roles in broadening product lifecycles, opening up new markets, and developing drug delivery systems. Oral administration is still widely used because it is convenient, adaptable, and economical. In the context of biopharmaceutical research, inhalation is emerging as a viable drug delivery strategy for low molecular weight chemical entities, while injections encounter difficulties with patient acceptance.

Type and Classes of Tablets

A. Tablets to be Taken Orally

- Condensed tablets
- Multiple compressed tablets
- Layered tablets
- Tablets with compression coating
- Tablets with repeated action
- Tablets with delayed and enteric coating
- Tablets coated with sugar and chocolate
- Tablets with a film coating
- Tablets designed for chewing

B. The Oral Cavity's Tablets

- Buccal tablets
- Sublingual tablets
- Troches and lozenges
- Dentalcones

C. Tablets Given Through Different Channels

- Implantation tablets
- Vaginal tablets

D. Tablets for Solution Preparation

- Effervescent tablets
- Dispensing tablets
- Hypodermic tablets
- Tablet triturates

DEFINITION

The phrase "short-term release" Any formulation that is not purposefully or noticeably delayed by galenic modifications in terms of drug absorption or release from the formulation is considered pharmaceutical. Therefore, formulations that are adjusted for creating provisions in "modified," "controlled," "sustained," "prolonged," "extended," or "delayed" drug release are not included in the phrase. Supply of medication from the formulation into the gastrointestinal tract, bodily tissues, and/or the systemic circulation is included in this sense of word "release." When it comes to gastrointestinal tract release, pH settings ranging from 1 to 3 are ideal, with pH=1 or slightly above serving as the threshold. One aspect of the invention involves the use of a formulation as described below with a compound of formula (I) or an acid addition salt thereof, which releases medication in crystalline form at various pH levels. Another feature of the invention is the release of the medicament under pH values ranging from 1 to 3, with pH=1 or approximately therein, using the formulation herein disclosed in conjunction with a compound of formula (I) or an acid addition salt thereof. As a result, formulations utilising the invention may release the active ingredient at least 70% within four hours, preferably three hours, preferably two hours, more preferably 1.5 hours, and especially within an hour of parenteral or oral administration. Biopharmaceutical variables including excretion and metabolism must be taken into account when launching a novel drug delivery system. A pharmacological impact and the achievement of therapeutic levels depend on the

rate and degree of absorption. Conventional dose forms may dissolve more slowly than other forms, resulting in a faster rate of dissolution. Tissue permeability, perfusion rate, binding to tissues, illness states, and medication interactions are some of the elements that affect drug distribution. The pace at which the drug is eliminated from the body or the site of action—most commonly through biotransformation—determines the duration and potency of the effect. Diminish in liver volume, localised blood flow to the liver inhibits the drug's biotransformation via hydrolysis, oxidation, and reduction. Because of improper organ development, renal clearance slows down the excretion of medicines, increasing their half-lives and impairing pharmacodynamic drug reception interactions in both young adults and the elderly.

Using an antihypertensive such as prazosin may cause the body to respond to reflexive stimuli less effectively, as well as cardiac output and orthostatic hypotension.

1. Diminished adrenergic agonist and antagonist sensitivity.
2. Immunity is lower and is taken into account when giving antibiotics.
3. Modified reaction to medication: aged people exhibit a reduced theophylline bronchodilator effect and heightened barbiturate sensitivity.
4. Elderly patients frequently have concurrent ailments, which is also taken into account when prescribing multiple drug therapy. Researchers have conducted clinical evaluations of pharmacological combinations for quick release dosage forms, including diuretics, antihypertensives, cardiovascular medicines, and more. The patient's illness state determines which combination is best.

DIFFICULTIES WITH EXISTING ORAL DOSAGE FORM

1. Patients may experience tremors, which makes it difficult for them to swallow drinks and powders.

Gastrointestinal ulcers may result from physical barriers and adhesion to the oesophagus in dysphasia.

2. Swallowing solid dosage forms, such as tablets and capsules, can be challenging for older patients who have dysphasia and young adults whose neurological and muscular systems are still developing.
3. Patients declined to take buccal and sublingual formulation medicines because they would irritate their oral mucosa.
4. The primary determinant is product cost, as parenteral formulations are the most expensive and uncomfortable.

IDEAL REQUIREMENTS FOR THE DRUG DELIVERY SYSTEM WITH IMMEDIATE RELEASE

1. When taking a solid dosage, the immediate release dosage form should melt or disintegrate in the stomach quickly.
2. If the dosage form is liquid, it should work with flavour masking.
3. Be transportable and unaffected by fragility.
4. Feel good to the mouth.
5. After oral administration, it shouldn't leave behind much or any residue in the mouth.
6. Show minimal susceptibility to temperature and humidity levels in the surroundings.
7. Be inexpensively produced utilising standard processing and packaging machinery.
8. The medication dissolves and absorbs quickly, which could result in a quick start of effect.

EXCIPIENTS

In instantaneous release dosage forms, excipients balance the qualities of the active ingredients. Avoid coming into contact with the active ingredients, an in-depth comprehension of the chemistry of the excipients is necessary. And also that formulators need to think over is the amount that these ingredients will cost. Excipients serve a vital role on the composition of tablets that melt quickly. The incorporation of these food-grade inactive items into the formulation results in the essential organoleptic qualities and efficiency of the product. With the rare exception of some actives that need masking agents, excipients are generic and can be used with an extensive array of active ingredients.

SUPER DISINTEGRANTS

To aid in the disintegration of a compressed material in an environment of liquid, an additive described as a disintegrant is added to a tablet or capsule blend.

ADVANTAGES

1. Functions well at reduced concentrations
2. Minimal impact on flowability and compressibility
3. Greater intragranular efficacy, Among the super disintegrants are

- Sodium starch glycolate (Explotab, Primogel) is utilised at a concentration of 2–8%, with 4% being the ideal range. Mechanism of Action: Minimal gelling and rapid, widespread swelling.
- Microcrystalline cellulose, also known as celex or avicel, is utilised in water wicking tablets at a concentration of two to fifteen percent.
- Cross-linked Povidone, also known as crospovidone or Kolidone, is used at a concentration of 2–5% of the tablet's weight. not soluble at all in water. Water wicking, swelling, and potentially some deformation recovery are the mechanisms of action. quickly disperses and swells in water, yet even after extended exposure, it doesn't gel. highest swelling rate in relation to other disintegrants. higher surface to volume ratio compared to alternative disintegrants.
- Water-insoluble low-substituted hydroxyl propyl cellulose. expands quickly in water. The most swelling is seen in grades LH-11 and LH-21. A few grades may also have certain binding qualities in addition to their disintegration ability. Concentration recommendations range from 1 to 5%. Sodium

carboxy methyl cellulose cross-linked (Ac-Di-sol) Sodium Croscarmellose Mechanism of Action: little gelling and swelling due to wicking caused by fibre structure. Effective Concentrations: 2-4% traditional wet granulation, 1-3% direct compression.

Difficulties in Developing ODTs[55-59]

Mechanical Potency and Breakdown Duration: Greater mechanical strength willresult in a longer disintegration period, hence good coordination between these two parameters is needed.

Taste Disguising: It is necessary to effectively conceal the taste of bitter medicationsso that the oral cavity is not affected by their taste.

Mouth Feel: After the ODT breaks down, very tiny particles should be released. When taken orally, ODT shouldn't leave any residue in the mouth. The mouthfeel is improved by the addition of flavours and cooling ingredients like menthol.

Sensitivity to Environmental Conditions: ODTs ought to be less sensitive to external factors like temperature and humidity.

Cost: Regarding the cost of the finished product, the technology selected for an ODT should be appropriate.

Because of the ODTs' quick dissolving characteristic, which necessitates quick absorption of water into the tablet matrix, standard procedures like optimising the tablet's porous structure, adding the proper disintegrating agent, and using water-soluble excipients in the formulation are necessary. At least one super disintegrant, a diluent, a lubricant, a permeabilizing agent, sweeteners, and flavouring agents are among the excipients utilised in ODTs.

APPROACHES FOR PREPARATION OF ODTs[60-61]

Different preparation methods, founded on various principles, provide various ODT includes with respect to of swallowability, dissolving profile, taste, mouth feel, mechanical strength, and bioavailability. Some of those innovations have patents.

These are the basic pharmaceutical methods that are used to make ODTs:

Using a spray dryer

Spray drying techniques have become common for pharmaceutical and biological methods. The use of spray drying is a rapid & affordable way of eliminating liquids whilst creating very tiny and porous powders. The blends comprise both hydrolyzed plus non-hydrolyzed gelatins as supportive components, mannitol as a bulking an agent, as well as sodium starch glycolate or croscarmellose sodium as a disintegrating agent. One uses an alkali (sodium bicarbonate) or an acidic (citric acid) material for boosting the disintegration & dissolving behaviour. Tablets produced through compressed spray-dried powder revealed a 20-second disintegration time when exposed in a medium consisting of water.

Sublimation

Lower porosity in the pills lowers the entry of water in the matrix, consequently compressed tablets having highly water-soluble components can act slowly while they dissolve. In the past, volatile compounds have been pressed into tablets, then sublimated out, which creates very permeable shapes. Amongst the volatile substances that may be employed are urea, ammonium bicarbonate, ammonium carbonate, camphor, & hexa methylene tetramine. Thymol, menthol, camphor, organic acids like adipic acid, and fatty acids like arachidic acid, myristic acid, capric acid, and palmitic acid were among the volatile compounds in a few cases. The level of heat at which sublimation occurred varied from 400 to 600 ° C. It emerged that the break down time of the cavities in the mouth approximated fifty-five seconds.

Freeze drying

The process of lyophilization, also known as freeze-drying, involves extracting solvents from an oral suspension or frozen medication solution that contains excipients that help create structures. The end product is usually a lightweight, extremely porous tablet that dissolves or disintegrates quickly. Very low temperatures are used throughout the lyophilization procedure to minimise any negative thermal effects that can change the stability of the medicine. The frozen pill has a few stability concerns throughout the course of its time on the shelf. The process of drying can end up in a transparent amorphous state over drugs and excipients.

Molding

In order to create moulded tablets, which are made of materials that are soluble in water, By mixing a mixture of powders with the solvent, it is crushed at a pressure less than that of a normal pill. Compression moulding is the procedure that produces a structure that is extremely porous, which improves dissolving. Solvent was eliminated by air drying, and dissolving rates were increased by passing the powder blend through a fine screen. Because water-soluble ingredients enable quick breakdown and enhanced flavour, moulded tablets frequently have low mechanical strength, which raises the possibility of breakage during handling and blister opening. While multi-step procedures and non-traditional equipment can improve mechanical strength and disintegration, the application of hardness-enhancing chemicals may reduce the rate of disintegration.

Mass Extrusion

A water-soluble polyethylene glycol & methanol mixture of solvents which used in bulk extrusion process to soften the active blend. The soft mass is ejected through a syringe to create a product cylinder, which is subsequently separated into equal components via a warmed blade to generate tablet.

Direct Compression

The quickest and cheapest method to create tablets involves direct compression. By carefully choosing excipient mixtures that offer optimal physical resistance and rapid disintegration, this method can be used to make ODT. Excipients based on sugar are often used as bulking agents for their sweetness, solubility in water, pleasant mouth feel, and efficacy in flavour masking. The tablets produced using the traditional compress method break down more slowly, so they are less friable. Preparing tablets with adequate structural strength can be done readily and inexpensively with the compression method, whether or not wet granulation is employed.

PATENTEDTECHNOLOGIES

Zydis Technology[59-64]

Zydis, R.P. Scherer's groundbreaking fast-dissolving tablet, uses a unique freeze-dried structure with a matrix of polymer (gelatin) and saccharide (mannitol, for example). Zydis includes flocculating agents, preservatives, permeation enhancers, pH adjusters, flavours, and sweeteners. It immediately melts on the inside of the mouth without a desire for water. Gums stop particle sedimentation during the production method, which utilises water to produce porous units. Gelatin and various other collapse protectants stop shrinkage when freeze-drying. Zydis requires specific blister wrapping in order to get dispensed, despite its lightweight and instability.

OraSolv Technology

Cima's first fast-dissolving dose form, OraSolv, has a disintegrating agent and an active ingredient that masks flavour. Saliva activates an effervescent ingredient, which makes up 20–25% of the tablet's weight, which causes the tablet to disintegrate in the mouth. An acid source and a carbonate source are combined in the effervescent disintegration pair. In order to preserve the coating's authenticity, the microspheres must be removed are squeezed loosely. The primary disadvantage is mechanical strength, though, which prompted the creation of a unique handling and packaging system. The finished tablets must be protected from moisture by moisture-impermeable blisters and manufactured in a controlled atmosphere with low humidity.

Durasolv technology

The 2nd generation of CIMA's fast dissolving / disintegrating tablet, called Durasolv, is developed to create stronger tablets that may be packaged in traditional bottles or blisters. Durasolv has a considerably greater mechanical strength during tableting since it utilises a higher compacted pressure. A drawback of the Durasolv compression handle is the fact that it can't be used with greater amounts of active ingredients as it puts the mixture under immense stress. Durasolv's powder coating could break during compaction, exposing the patient's taste buds to the bitter medications. Therefore, tablets with a small number of active components benefit from this technique.

Wow tab technology

The WOWTAB technology, which uses a combination of sugar and excipients that resemble sugar, emphasises giving tablets without the need for water. The tablets show adequate hardness and quick dissolution rates because they combine saccharides with high moldability (like lactose and glucose) and low moldability (like maltose and mannitol). Until the tablet comes into touch with moisture in the mouth, like saliva, this method guarantees tablet stability. In contrast to Zydis and Orasolv, WOWTAB formulations— especially those containing erythritol—show improved stability and quick disintegration that isn't impacted by tablet hardness.

Cotton Candy Technology

Method gets its name from the unique spinning mechanism is utilized to create a crystalline structure that resembles floss and is similar to cotton candy. The candy floss process is another name. You can use shear form matrix or candy floss to produce a mouth-dispersing tablet. It includes spinning and flashmelting at the exact same time to generate a matrix of sugars or polysaccharides. Partially recrystallized matrix is the outcome, providing improved flow and compressibility. After milling and blending this candy floss matrix with excipients and active substances, it is compacted to an ODT. Both mechanical strength and medication dosages up to 50% can be handled by this method. High process temperatures, however, restrict the application of this procedure.

Oraquick Technology

Proprietary flavour masking technique included in formulation of Oraquick rapid disintegrating tablets. Since there are solvents used in this taste masking procedure, production may be completed more quickly and effectively. Heat-sensitive medications can be processed using this method because little heat is generated throughout the procedure. Additionally, according to KV Pharmaceuticals, the matrix encasing and shielding the drug powder in the microencapsulated particle is more malleable. This method produces tablets that disguise flavour well and dissolve quickly—in just a few second.

Nanocrystal technology

NanoCrystal Fast dissolving technology offers the pharmacokinetic benefits associated with orally administered nanoparticles (<2 microns) in the form of a fast disintegrating tablet matrix. Blisters are filled with a mixture of pharmaceutical nanocrystal colloidal dispersions and water-soluble GRAS (Generally Regarded as Safe) components, which are then lyophilized. Since this method does deal with a need for blending, granulation, & tableting over the manufacturing procedure, it gives extra advantages of very potent & hazardous pharmaceuticals. For fast-dissolving tablets, Elans' innovative Nanocrystal technology may streamline formulation, increase medication activity, and enhance final product

characteristics. The rate of disintegration increases when the particle size falls due to the larger surface area.

Shearform technology

Method produces a shearform matrix called "floss." Feedstock that is treated with a sugar carrier undergoes processing using flash heat. A gradient of temperature and centrifugal force are applied to sugar concurrently. This increases the mass's temperature and produces an internal flow indicates which enables some of the sugar to move with regard to the mass. It then exits through the rotating head, which sucks into the long, thin floss threads, which are typically amorphous in form, and flings the floss under centrifugal force. This creates floss that is further cut and recrystallized to create a consistent flow and make mixing easier. Subsequently, the active medication, recrystallized matrix, and additional excipients are combined and ultimately crushed into tablets. The floss can be combined with the active medication and additional excipients before it is recrystallized. Because the sugars in the tablets quickly dissolve in the presence of saliva, the resulting tablets have a very pleasant tongue feel and are extremely porous.

Pharmaburst technology

SPI Pharma holds a patent for the pharmaburst technique. Utilising off-the-shelf coprocessed excipients that Pharmaburst innovation produces an ODT that degrades in 30 to 40 seconds, based on the loading and kind of active components. The active ingredients in the tablet influence the quantity of pharmaburst needed in a formulation. Using stock machinery and a typical tablet press, adry mix of lubricant, taste, and medicines is pressed into a tablet form. The process of manufacturing can be done in an atmosphere with normal humidity and temperature. Tablets may come is bottles or in blister packs.

Frosta technology

Akina has this invention patent. The basic concept behind Frosta technology is the a low- pressure compression of highly plastic granules to produce robust, extremely porous tablets. A trio of components makes these extremely flexible granules: a binder, an enhancer of water penetration, and a porous and plastic substance. The porous material made of plastic is mixed with a water penetration enhancer then granulated utilising a binder. Almost any drug, such as aspirin, loratidine, caffeine, folic acid, vitamins, and nutritional supplements, can be treated using this method. Depending on the size of the tablets, the highly plastic granule method yields fast-melting pharmaceutical tablets with exceptional hardness and a quick disintegration lasting anywhere from afew seconds to one minute.

A. EVALUATION OFTABLETS

The following quality control tests were performed on each of the ODTs that were formulated:

Weight Variation

To make sure that the weight of the pills in the batch is consistent, the weight variation test is conducted. Initially, the weight of all 20 pills in each composition is computed & an average is established. To ascertain the weight variance, each tablet's unique weight is also ascertained.

Hardness

The strength of a tablet may be determined by its toughness. By pressing the tablet in a direction that is radial, it cracks. The pressure is needed for it to do so. The amount of force is measured in pounds, and for tablets without coatings, a hardness rating of approximately 3-5 kg/cm2 is considered acceptable. A Monsanto hardness test serves to find out the firmness of ten pills for every formulation. The process of disintegration time is greatly decreased by extreme rig.

EVALUATION OF ODTs

It must be done to assess the tablet assessment criteria listed in the Pharmacopoeias in alongside conducting specific specialised tests. After a standard has been established, the level of the blends' physical qualities generally defines the medication's quality. Blending includes a number of formulation and procedure variables, all of which can have an effect on the attributes of the mixes that are produced.

B. Evaluation of blends before compression

The different mix properties that need to be examined prior to compressing are as follows:

1. **Angle of Repose:** The funnel is utilised to ascertain the angle of repose. The precisely measured mix is poured into a funnel. The funnel's height has been adjusted such that the tip of the funnel just touches the top of the mix pile. The mixture of medicine (as solid dispersion) and the excipient is let flow freely through the funnel and reach the surface. The formula shown below is used for estimating the angle of repose and forecast the diameter of the powder cone.

Tan Θ = h/r

Where,

h and r are the height of cone and radius cone base respectively.

Angle of Repose less than 30° shows the free flowing of the material.

Bulk density

Pouring a weighed amount of blend into a graduated cylinder and measuring the weight and volume yields the apparent bulk density. You can calculate bulk density using the formula below.:

Bulk density = Weight of the powder / Volume of the packing.

Tapped density
To determine it, a graduated container with the drug-excipient blend's estimated weight is put therein. It is permitted to tumble under its own weight onto a hard surface from a height of 10 cm per second. Up until the volume quits evolving, tapping is maintained. The formula that follows can be utilised for calculating taped density:
Tapped Density = (Weight ofthe powder/ volume of the tapped packing)

Compressibility Index
Blends compressibility index is based on their compressibility index. The following formula can be used to compute he compressibility index:
Compressibility Index (%) = [(TD-BD) X100] / TD] Hausner's Ratio

Hausner's ratio can be used to define a comparable index that shows the flow characteristics.

The following formula can be used to compute Hausner's ratio:
Hausner's ratio = (Tapped density x 100)/ (Poured density)
Hausner's ratio <1.25 – Good flow = 20% compressibility index
1.25 – Poor flow =33% compressibility index

Void Volume
Formula, which yields the volume of the spaces, ("V)"
V= Vb – Vp

Where,
Vb = Bulk volume (volume before tapping)
Vp = True volume (volume after tapping)

Porosity
The ratio of the packing's bulk volume to its void volume is known as the porosity (€) of powder. The following formula provides the powder's porosity:
€= Vb – Vp / Vp =1- Vp/Vb

Porosity is commonly stated as a percentage and can be calculated as follows:
%€ = (1 – Vp / Vb) X 100

The porosity of a powder describes the kinds of packaging that a powder experiences as it is stored, vibrated, or fed through a hopper or feed frame in a tablet machine.

A tablet's strength can be determined by its hardness. It is tested by determing the force needed to shatter the tablet in half. For uncoated tablets, a hardness of roughly 3-5 kg/cm2 is deemed adequate, with force expressed in kilogrammes. Monsanto, Pfizer, and other hardness testers are used for the measuremen of the hardness of ten tablets from each formulation.

Test For Friability
The weight of the tablet decreases in the container when small particles are removed from its surface, a phenomenon known as friability. The purpose of the friability test is to determine the tablet's resistance to abrasion during handling, packing, and transportation. Rochefriabilator is used to determine the pills' friability. Each batch of 20 tablets should be weighed before being placed in a Rochefriabilator and rotated at 25 rpm for four minutes. After dusting every tablet, reweigh. The following formula is,
% Friability = [(W1-W2)100]/W1

Where,
W1= Weight of tablet before test
W2 = Weight of tablet after test

Disintegration Test
Six glass tubes, measuring "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly, are part of the USP disintegration device. A single pill is inserted into each tube, and the basket rack is contaminated with distilled water in a litre beaker at 37± 2 °C. This guarantees that the tablets remain submerged in the liquid. while rising and don't descend any closer than 2.5 cm from the beaker's bottom.

Mechanical Strength
Pill must have sufficient strength to withstand handling shocks throughout production, packing, and delivery. Two crucial factors in determining mechanical strength are friability and crushing strength. Smashing Powder Tensile strength was amount of force needed for compress a tablet in the radial direction and break it; it's vital was to remember that too much crushing strength can shorten the disintegration period. Pfizer hardness testers are used to measure the tablet's crushing strength. The formula is,
T= 2F / π*d*t

where d and t stand for the tablet's diameter and thickness, respectively, and F represents the crushing load.

Dispersion Uniformity
For two minutes, placed in 2 pills in 100 millilitres of water and mix gently. Twenty two meshes are utilied to pass the dispersion through. If there is no more residue on the screen, the tablets will be deemed to have passed the test.

Wetting Time
A straightforward method is used to measure the pills' wetting duration. 5 round tissue papers, each measuring ten centi meter in diameter, should be kept in the petri dish with a 0.2% w/v solution (3 ml). The tissue paper's surface is gently touched with a tablet. The term "wetting time" refers to the How long does it take for the tablet's top to get blue?

Ratio of water absorption

Six millilitres of of liquid reside in a tiny petridish containing a small piece of tissue paper folding twice inside. For how long will it take a tablet to become completely wet? Place it onto a piece of paper and observe. The moist tablet gets weighed after thereafter. The formula for calculating the water absorbing ratio, or R, works as follows.

$R = 100 \times W_a - W_b / W_b$

Where,

W_b is the weight oftablet before water absorption W_a is the weight oftablet after water absorption.

Mouth Feeling

People should be given a product that feels good in their mouths since mouthfeel is essential. Each batch of tablets includes one testing pill that is placed on the tongue to gauge feeling. The mouth feel is assessed in human volunteers who are in good health. Five members of a panel assess flavours using the time intensity approach. 40 mg of the sample, or one dose of the medication, is placed on mouth for 10 sec, the taste is noted directly; this is repeated 1, 2, 4, and 6 minutes earlier.

The taste is judged by individuals using a range of score values.

i.e. 0 = good, 1 tasteless,
2=slightly bitter,
3 = bitter,
4 = awful

***In-Vitro* Disintegration Test**

To find out the *in-vitro* disintegration duration, drop a tablet into beaker having 50 millilitres of 6.8 pH Sorenson's buffer. For each formulation, three tablets are selected at random, then the in- vitro dispersion time is determined.

***In-Vivo* Disintegration Test**

Two or three pills are used in the test, the amount of period it takes for the tablets to completely dissolve in the mouth is determined by seconds.

***In-Vitro* Dissolution Test**

The USP Type II apparatus (Paddle type) is utilised for *in-vitro* dissolution experiments at a speed of 50 rpm. The dissolution medium, 900 cc of phosphate buffer pH 6.8, is kept at 37±0.5°C. At a specified period of time (2 minutes), remove an aliquot of the dissolution medium (10 ml) &filter. An suitable method of analysis is used to figure out the quantity of drugs dissolved.

Stability Studies

In accordance with ICH recommendations, a stability study is conducted on the optimised formulation of ODTs to evaluate the stability of their physical appearance and release properties.

2 AIM AND OBJECTIVES

The project's aim is to develop and evaluate orally disintegrating tablets carrying the depressive drug mirtazapine.

In the last twenty years, there is an increased need for dosage forms that promote patient compliance. The result is a threefold yearly rise of demand for these products. Company is concentrating on the advancement of novel delivery of drug systems for current drugs with effectiveness & bioavailability with reduce dose regularity to minimise side effects, as the expenses of developing a novel chemical structure is incredibly high.

dysphagia, or inability to swallow, impacts persons of any age, yet it's prevalent for older people and younger people for adaptations that are unique for these groups. If water is limited, it is hard for swallowing typical stuff. And to, address the difficulies, an entirely novel type of solid dosage forms known for rapidly dissolving pills evolved. These tablets break fast in saliva & don't require water to dissolve. It quickly dissolves and scatters the dosage form following use. After swallowing saliva with the dissolving or lying drugs, the drug absorbs properly. And saliva goes into GI tract, a few drugs are taken in mouth, throat, & oesophagus. In such instances, drug absorption is significantly greater compared to that found in conventional dosage forms like pills and capsules. The following provides specifics on the present study's objectives:

- Creating an oral disintegrating tablet with numurous proportions of subliming agents & super disintegrants.
- Pre-compression and post-compression details for mirtazapine oral disintegrating tablets can be used to define their physico-chemical properties.

3 PLAN OF WORK

- Considering a suitable drug
- Finding relevant additives
- Drug-excipient association studies; developing ODT formulation using sublimated handle using the SSG, CCS as superdisintegrants and camphor and clove as sublining agent
- Assessment of each of the formulas' pre-compression characteristics via the Sublimation is technique:
- Density in bulk
- Tapped density
- The angle of repose
- Handler's index and Hausner's ratio
- Assessment of ODT formulations:
- Disintegration time;
- In-vitro dissolution rate;
- Weight variation;
- Hardness and friability;
- Thickness & Diameter;
- Drug content uniformity;
- kinetic analyses

4 REVIEW OF LITERATURE

A.Bharathi et. al.,[68] The creation & study about oral disintegrating pills (ODTs) containing the antidepressant mirtazapine phosphate are the main subjects of this study. The ODTs, which use a direct compression approach and super disintegrants such as sodium starch glycolate, crospovidone, & crosscarmellose sodium, are made for dissolving quickly in mouth without the need for water or chewing, which makes them especially good for elderly and paediatric patients. The chosen excipients & mirtazapine have no interaction in-situ. according to FTIR tests. F10, F11, and F12 were the formulations that showed the most promise, with in-vitro dispersion periods of 16, 18, and 27 seconds. This new dose form improves convenience and comfort for patients.

Gamal M M et. al.,[69] The goal of this research was to produce ODTs for clopidogrel that dissolve quickly and without the need for water. Three superdisintegrants with varying disintegration times were utilised within the ODTs, that were produced via direct compression: sodium starch glycolate, croscarmellose sodium,& crospovidone. Hardness, friability, disintegration time & in vitro drug release were all evaluated. There were no interactions between clopidogrel and excipients, according to differential scanning calorimetry. The tablets fulfilled the requirements for weight and drug content homogeneity, and they showed good hardness (4.0-5.2 kp) and low friability (<1%). Within ten minutes, the in-vitro drug release surpassed 90%, and volunteers' palatability tests verified the drug's acceptable flavour and texture. Clopidogrel ODTs were successfully disintegrated in this trial with good palatability.

R. Krishna Kumari et. al[70] Using the mass extrusion method, a stable and economical formulation of clopidogrel tablets was created with a variety of superdisintegrants, such as low hydroxy propyl cellulose, sodium starch glycolate, and Avicel PH 102. A number of metrics were evaluated, and the formulation that contained sodium starch glycolate satisfactorily met each one. Because formulations F3, F6, and F9 performed better in the evaluation parameters, they were chosen for stability studies. These formulations showed little change over a 30-day period in all measured parameters, indicating stability and preservation of original characteristics. Formulations F3, F6, & F9 are considered fixed and retain the quality, in conclusion.

K. Sravani S et. al.,[71] Provide a stable, affordable, pharmaceutically equivalent, and higher- quality formulation for clopidogrel bisulfate immediate-release tablets. Preparing and assessing clopidogrel bisulfate tablets, comparing the optimised formula's dissolution rate to the noval product, and estimating same & variety factors are all part of the current study. It was discovered that the clopidogrel bisulfate similarity and dissimilarity factor were within the acceptable ranges. At every time point, the formulation F-6 showed a release profile that was comparable to the innovators' product. F-6 was therefore regarded as the ideal formulation.

G. Raghavendra Kumar et. al.,[72] The objective of this investigation was to use 32 factorial design to create fast-dissolving Clopidogrel tablets. Using the Direct Compression method, varying quantities of crospovidone and croscarmellose sodium were used as superdisintegrants. Nine compositions that all met pharmacopoeial restrictions were created and assessed based on a variety of criteria. Kinetic models were fitted using in-vitro dissolution profiles, and polynomial equations were created and verified. In accordance with SUPAC rules, Formulation F5, including 15% Crospovidone and 15% Croscarmellose, closely resembled the marketed medication (PLAVIX-75). Formulation F1 used Fickian Diffusion as the release mechanism and adhered to Higuchi's first order kinetics. The appearance with swiftly dissolving Clopidogrel pills that adhere pharmacopoeial regulations & have resemblance to the reference product was effectively proven by the study.

B. Sree GP et. al.,[73] The aim of this research investigation was to create an immediate-release clopidogrel bisulphate tablet formulation that was stable, more affordable, pharmaceutically similar, and of higher quality. Direct compression with the superdisintegrants Croscarmellose Sodium and Crospovidone was utilized to create tablets. Most effective compositions was Formulation F8, which outperformed previous superdisintegrants by reaching 99% drug release in 30 minutes. A first-order kinetic model was found through kinetics investigations, suggesting a diffusion-controlled release mechanism. In terms of release profile, the formulation resembled the innovator's product; both similarities and differences fell within permitted bounds. As a result, it was determined that formulation F8 was optimal.

R. Srinivasan et. al.,[74] **2015** Bambuterol HCl oral disintegrating tablets (ODTs) were created with fifteen formulations (F1 to F15) via a direct compression process. Bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose were all studied prior to compression. Hardness, thickness, friability, weight fluctuation, wetting time, water absorption ratio, drug content, disintegration time, in vitro dissolution, & stability were all examined in the evaluation investigations. Formulation F5, which contains 4% crospovidone, was chosen as the best formulation since it released 101% of the medication within 30 minutes and had the shortest disintegration time (10 sec).

Karthik Karumuri et. al.,[75] **2013,** Compositions of Bambuterol Hydrochloride ODTs involved in use of range of natural and synthetic superdisintegrants, such as banana powder, ispaghula husk powder, pre-gelatinized starch, crospovidone, and sodium starch glycolate. Pre-compression settings were evaluated and a direct

compression technique was used. Evaluations were conducted on post-compression parameters, like drug content, in-vitro dissolution, hardness, thickness, friability, wetting time, water absorption ratio, and weight variation. Compatibility was verified by FTIR tests. It appears that synthetic superdisintegrants contribute to faster disintegration, improved water absorption, and drug release in ODTs. The composition containing 4% crospovidone (F5) showed a disintegration time of 10 seconds and over 99% drug release in 30 minutes.

Anirudha V. M et. al.,[76] 2015, Sodium starch glycolate, croscarmellose sodium, & crospovidone was utilized like superdisintegrants in different amounts to make lansoprazole orodispersible tablets by a direct compression process. A number of criteria, including hardness, weight variation, friability, in-vitro dispersion duration, water absorption ratio, uniformity of drug content, and in- vitro drug release, were assessed for the produced formulations. The produced tablets were evenly dispersed in all compositions lies in between of 95.6±0.4-102.5±0.8%, 24.9±4.2-186.8±3.2% is the water absorption ratio. The dispersion of the tablets was 8.3±0.6-23.7±1.5 seconds. Within 18 minutes, a tablet containing 7.5% of Crospovidone 99.736±0.763% of the medication was manufactured using one of the formulations. At the end, showed that the formulation F6, which had 7.5% crospovidone, is superior and meets the requirements for orally dispersible tablets.

Muhammad T. U et. al.,[77] 2015, Two formulations of orally disintegrating montelukast sodium tablets were developed to enrich ease of ingestion, particularly for pediatric and elderly patients. These 5 mg tablets were crafted through the direct compression method, utilizing key excipients like microcrystalline cellulose (Avicel PH-102), mannitol, sodium bicarbonate, crospovidone, and magnesium stearate. Cherry flavor and aspartame were added for taste improvement. The formulations underwent thorough evaluation, including pharmacopoeial and non-pharmacopoeial tests, as well as dissolution and assay tests. The more effective formulations were optimized using the central composite design method. Results indicated successful development, with the optimized formulation demonstrating a similarity in drug release profiles (f2 > 50). Stability testing over 3 & 6 months under increasing conditions affirmed the ODT's suitability for convenient delivery of montelukast sodium, especially for asthmatic patients. However, further clinical studies are necessary for confirmation.

Mukesh P. R et. al;[78] 2012, The advancement and assessment of taste-masked ODTs of Perindopril Erbumine were undertaken, employing Eudragit E 100 at a 1:3 ratio (drug: polymer) through mass extrusion. Initial batches were formulated with various superdisintegrants (Ac-Di-Sol, Primogel, Tulsion-335, and Tulsion-339). Ac-Di-Sol exhibited superior disintegration period in preliminary study and was selected to further investigation. A 32 full factorial design is applied for optimized formulations, resulting in nine batches.

Evaluation indicated that batch A2 achieved the most favorable disintegration period & accomplished complete drug release within 5 minutes. The conclusion drawn was that Ac-Di- Sol is effective for successfully formulating orally disintegrating tablets of Perindopril Erbumine. No plagiarism is present in this paraphrased version.

M. Nalini K.R. et. al.,[79] 2012, Various formulations of orally disintegrating Naproxen tablets (ODT) were developed using different superdisintegrants (crosscarmellose sodium, sodium starch glycolate, crosspovidone) through the direct compression tech. compositions demonstrated desirable characteristics, including good flow, minimal weight variation, rapid disintegration, and effective in-vitro dissolution. All formulations maintained acceptable drug content. Notably, formulation F9, containing 6% crosspovidone, exhibited the fastest in-vitro disintegration time and achieved over 90% drug release within 8 minutes. Higuchi's equation best described the in-vitro drug release profiles, indicating a mechanism involving both diffusion and erosion (anomalous or non-Fickian diffusion). The optimized formulation displayed favorable in-vivo disintegration time and a pleasant taste. Physicochemical analysis using Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimeter (DSC) verified that the excipients did not alter the drug's properties.

Gawande Shilpa et. al.,[80] 2011, Orodispersible tablets of Risperidone were developed, incorporating cetyl alcohol to enchance bitter taste in various medicine-cetyl alcohol ratios (2:1). Superdisintegrants, crosspovidone, and sodium starch glycolate at concentrations of 2%, 4%, 6%, and 8% were utilized. The direct compressed approach was employed to create the tablets. Weight variations, the degree of hardness friability, dispersion a period of time its thickness, quantity of drug, in-vitro & in-vivo disintegration times, & dissolving experiments all had to be included in the assessment.

The drug to cetyl alcohol proportions of 2:1 & 4% crosspovidone in the dosage form was optimised following considering into account the duration of disintegration & superdisintegrant level. A total of three months of stability tests was carried out using the optimised pill at ambient temperature and 40°C/75% RH.

Gunda R.K. et. al.,[81] 2016, The research aimed to develop fast-dissolving Clopidogrel tablets, a BCS Class-II antiplatelet for heart attack and hypertension control. A 32 factorial design guided formulation with varied Crospovidone & Croscarmellose sodium concentrations as superdisintegrants using Direct Compression. Independent variables, Crospovidone and

Croscarmellose sodium, influenced wetting time, disintegration time, t50%, and t90%. Nine formulations adhered to pharmacopoeial limits. Dissolution profiles fit kinetic models; polynomial equations for wetting time, disintegration time, t50%, and t90% were devised and validated by checkpoint formulations (C1, C2). Per SUPAC guidelines, F5 (15% Crospovidone, 15% Croscarmellose) resembled PLAVIX-75 closely. F1 followed first order, Higuchi's kinetics, and featured Fickian diffusion (n=0.226) as the release mechanism.

5. DRUG & EXCIPIENT PROFILE

PROFILE OF DRUG

5.1. Mirtazapine

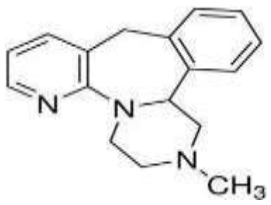
Description

In 1994, the Netherlands licenced mirtazapine, a tetracyclic piperazino-azepine antidepressant, for the management of severe depression (MDD).

Organon Inc. was the initial producer of this medication, which was approved by the FDA in 1997 to treat severe depression. It can be expected to feel the adverse reactions of this medication as soon as one week when initiating treatment.

Aside from its beneficial impacts on depressive disorders, mirtazapine has shown effectiveness for the off-label treatment for multiple other ailments. It might reduce neurological disease symptoms, prevent disorders via causing weight loss, enhance sleep, & stop post-operative nausea and vomiting.

Structure



Alternative terms

1,2,3,4,10,14b-Hexahydro-2-methylpyrazino(2,1-a)pyrido(2,3-c)benzazepine 6-Azamianserin, Mepirzapine, Mirtazapin, Mirtazapina, Mirtazapine, Mirtazapinum.

Categories

Adrenergic agents, Adrenergic Antagonists, Agents produce Hypertension, Anti Anxiety agents, Antidepressive Agents.

CAS number: 85650-52-8

Average Weight: 265.3529

Monoisotopic: 265.157897623

Chemical Formula; C17H19N3

IUPAC Name

5- met hyl-2,5,19-t riazat et racyc lo [13.4.0.0^{2},$^{.0}$,^{13}]no nadeca-1(15),8,10,12,16,18-hexae ne

PHARMACOLOGY

Indication

Major depressive illness treatment and its concomitant signs are advised for this medication. In addition to being used off-label for a number of illnesses, mirtazapine has also been employed in the healing process of generalised anxiety disorder, panic disorder, dysthymia, hot flashes, tension headaches, sleep difficulties, substance misuse disorders, and sexual disorders.

Pharmacodynamics

Overall Impact and a Remark on Suicidality: Mirtazapine successfully treats many of the signs and symptoms usually associated with depression ranging from mild to severe. In addition cause for concern, these symptoms might also involve anhedonia, lack of appetite, and insomnia. As wit any other antidepressant, it is essential to keep in mind that suicidal ideation and action might develop or advance while on mirtazapine therapy. The risk is more prevalent in those who are younger. When using this medication or changing the amount taken, individuals, medical professionals, and families ought to keep a look out for suicidal thoughts, enhancing anxiety, depressive symptoms, anger and disturbed sleep, violence, impulsiveness agitation, and additional unpleasant characteristics strange behaviour. Children should not receive mirtazapine treatment. The increased likelihood of suicide thoughts and behaviour should be carefully taken into account when prescribing this medication, especially in young adults.

Method of Action: With exact method for action of mirtazapine is unknown, Its influence upon serotonergic & central adrenergic neurons may provide some insight. In contrast with the actions of other antidepressants, this medication has simultaneously noradrenergic and serotonergic effects, an immediate start of a high degree action with regards to responsiveness, and moderate profile of adverse effects.

Absorption: This medication is swift & total absorption. Absolute bioavailability is around fifty percent because begin with liver metabolism & also in intestinal wall. Following taking a dosage orally, peak blood concentrations are reached in around two hours. When taking mirtazapine with meals, there is no need to change the dosage because it is not significantly impacted by food. A steady-state level is reached close to five days follow the first dosage. The pharmacokinetics of mirtazapine differ depending on both gender and age. It has been demonstrated that blood concentrations are higher in females and the elderly versus males and younger individuals.

Volume of Distribution: In a pharmacokinetic investigation, the volume of distribution following an

The estimated oral constant state dose is 107 ± 42L.

Protein Binding: Approximately 85% of mirtazapine is bound to plasma proteins.

Metabolism: Humans have an elevated metabolism of mirtazapine. The two main metabolic paths for mirtazapine are demethylation & hydroxylation, next by glucuronide conjugation. 8- hydroxy metabolite of mirtazapine is produced by cytochromes 2D6 and 1A2, Based on results of in vitro research with human hepatocyte microsomes. The medicine is metabolised into its N-desmethyl and N-oxide metabolites by the CYP3A enzyme. They are a few additional unaltered metabolite of this drug that have different levels in the blood but were pharmacologically active as well.

Route of excretion: The body's kidneys eliminate it most. 15% is excreted in the faeces and 75% is removed in the urine.

Half life: 20-40 Hours.

EXCIPIENT PROFILE[83]
SODIUM STARCHGLYCOLATE
Alternative word: Carboxymethyl starch, sodium salt; Explosol; Glycolys.

Chemical Name and CAS Registry Number: Sodium carboxymethyl starch [9063-38-1]

Uses in Pharmaceutical Technology or Formulation
Often utilized as a disintegrant for capsule & tablet formulations for oral medications. It's frequently used in tablets created through wet granulation or direct compression methods. A formulation's usual concentration varies between 2% to 8%, with 4% as the ideal concentration— though 2% is often sufficient in numerous instances. The breakdown occurs as an outcome of water absorbing rapidly and creating enormous swelling. While the addition of non polar additives, like lubricants, may decrease efficacy in numerous disintegrants, sodium starch glycolate exhibits unaltered disintegrant efficiency. It also does not seem like boosting the compression strength of the tablet effects how long it takes to dissolve. Additionally, studies have been conducted on sodium starch glycolate as a potential suspending agent.

Explanation
Sodium starch glycolate was free-flowing, odourless, tasteless powder which is white to off-white in appearance. Based to the PhEur 2005, it having the granules which are round and range in diameter between 30 to 100 μm, and a few less round granules ranging in diameter between 10 to 35 μm.

Table 1: Typical Properties of Sodium Starch Glycolate.

S. No.	Properties	Value
1	Density (Bulk)	0.756g/cm^3
2	Density (Tapped)	0.945 g/cm^3
3	Density (True)	1.443 g/cm^3
4	Solubility	Sparingly soluble in ethanol; Practically insoluble in water.

Conditions for Stability and Storage
Tablets made with sodium starch glycolate which has a long shelf life. Because sodium starch glycolate remains stable, It must to be saved free of fluctuations in humidity or temperature that might result in hardening. This may be accomplished by storing the product in closed jar. When kept at comfortable heating & humidity levels, sodium starch glycolate's physical properties remain untouched for a duration of approximately three to five years.

Incompatibilities: Ascorbic acid and sodium starch glycolate were incompatible.

ASPARTAME
Alternative Name: Aspartylphenyl amine Methyl Ester, equal, Canderel, Nutrasweet, Sancta, Tri-Sweet.

Category: Sweetening agent.

Uses: It is used as a strong sweetener in vitamins the preparations, powdered blends, & tablet forms. It offers 180–200 times the sweetening capacity of sugar and enhances flavour mechanisms in addition to becoming able to make up some unpleasant tastes.

Description: It appears as crystalline powder that is white and nearly odourless.

Solubility: Almost soluble in water, only slightly soluble with 95% ethanol. Under greater temperatures & pH values that tend to be more acidic, solubility rises.

Stability: In dry conditions, it stays stable. Whenever moisture occurs, hydrolysis might happen. Prolonged treatment with heat ultimately causes deterioration.

Storage Conditions: Bulk substance has to be maintained dry and cold in a container that's well closed.

Incompatibilities: Incompatible with magnesium stearate & dibasic calcium phosphate.

Safety: 40 mg per kg of weight of a person represents the minimum daily dose, based according to the WHO.

MAGNESIUM STEARATE

Alternative Name: Hyqual, magnesiumoctadecanoate, stearic acid magnesium salt.

Category: Tablet and capsule lubricant.

Uses: In the production of capsules and tablets, it is mostly utilised as a lubricant at concentrations lies in-between 0.25 to 5.0 percent.

Description: It consists of an impalpable, fine, white, precipitated or milled powder has a less bulk density and subtle, distinct flavour and odour. Fine powder sticks on the pores easily and feels oily on the touch.

Solubility: Nearly insoluble in alcohol, ether, and water and a little soluble in benzene & hot ethanol (95%).

Stability: Stearate of magnesium was stable.

Storage conditions: It needs to be kept dry and cold in a container that is tightly sealed.

Incompatibilities: Incompatible with strong oxidising agents, iron salts, strong acids & strong alkalis.

Safety: Following oral ingestion, it is usually considered to be harmless and nontoxic. High amounts administered orally, nevertheless may trigger irritation of the mouth or an effect similar to laxatives.

TALC

Alternative Name

Altalc; E553b; hydrous magnesium calcium silicate; hydrous magnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.

Chemical Name and CAS Registry Number: Talc [14807-96-6]

Empirical Formula and Molecular Weight: Talc is a purified, hydrated, magnesium silicate, approximating to the formula Mg6 (Si2O5)4(OH)4. It could have contained trace quantities of aluminium and iron silicate.

Structural Formula: Mg6 (Si2O5)4(OH)4.

Category: Anticaking agent; glidant; tablet and capsule diluents; tablet & capsule lubricant.

Uses in Pharmaceutical Technology or Formulation

While it is more rarely used currently, talc was in the past frequently exploited in oral solid dose compositions both a diluent & lubricant. Still, it has frequently involve in the manufacturing of products containing controlled release to serve as a diffusion inhibitor. Furthermore, talc can be used as an adsorbent, a substance that lubricates in tablet formulations, and an inventive powder coating for pellets for a prolonged release.

Talc acts as a dusting powder in medicines, yet it should not utilised to dust surgical gloves. Although talc is an organic material, it often has microbes as well as must be sterilised prior using as a dusting powder. Further, it is utilised as culinary and skincare products, mainly for its lubricating qualities, and it can clarify liquids.

Explanation: Talc constitutes a crystallised, odourless., impalpable, unctuous, white to grayish-white dust which is very thin. It seems smooth to the human touch, does not contain any grit, and sticks to the skin easily.

Typical Properties: pH = 7–10 for a 20% w/v aqueous dispersion indicates acidity/alkalinity. Hardness range: 1.0 to 1.5.

Solubility: practically insoluble in the water, organic solvents, & diluted acids and alkalis.

Conditions for Stability and Storage: Sterilise talc, that is a stable material, by boiling to 160°C for a minimum of an hour. Additionally, it can be sterilised by gamma or ethylene oxide radiation. Talc has to be preserved cold and dry in a jar that is effectively sealed.

MICROCRYSTALLINE CELLULOSE

Synonym: Avicel, cellulose gel, crystalline cellulose, E460, mocel, Fobrocel, Vivacel.

Category: Tablet and Capsule diluent, suspending agent, Adsorbent, tabletdisintegrant. **Uses:** as diluents in the formulation of capsules and tablets (both wet granulation and direct compression). It also possesses some disintegrant and lubricating properties.

Explanation: White-colored, tasteless crystalline powder composed ofporous particles.

Solubility: Practically insoluble in water and diluted acids, but somewhat soluble in a 5% sodium hydroxide solution.

Stability: Although hygroscopic, the substance is stable.

Storage conditions: The bulk material needs to be kept dry and cold in a container that is well sealed.

Incompatibilities: Not suitable for use with potent oxidising agents.

Safety: It is an innocuous and non-toxic substance.

5.2.5. CROSSCARMELLOSE SODIUM

Alternative Name: Ac-Di-Sol; cross-linked carboxy methyl cellulose sodium; Explocel.

Chemical Name and CAS Registry Number

Cellulose, carboxy methylether, sodiumsalt, cross-linked [74811-65-7]

Empirical Formula and Molecular Weight

The USP 28 describes carboxymethyl cellulose sodium as the sodium salt of polycarboxy methyl ether ofcellulose. Typical molecular weight is 90 000–700 000.

Uses in Pharmaceutical Technology or Formulation

In oral medication, croscarmellose sodium is a substance that is used as disintegrate to a pills, granules, & capsules. Creating pill shapes, croscarmellose sodium combining wet-granulation & direct-compression approaches. To maximise the disintegrant's wicking and expanding properties is used for wet granulations, croscarmellose sodium must be used both all over the wet and dry stages of the procedure (intra- and extra granularly).

As a tablet disintegrant, croscarmellose sodium may be used at levels of up to 5% w/w; however, 2% w/w is frequently utilised in tablets produced via direct compression and 3% w/w in tablets made by wet granulation.

Description

The powder form of croscarmellose sodium is white or grayish-white, odourless.

Stability and Storage Conditions

After fourteen months of storage at 30°C, an experimental tablet formulation created via direct compression with croscarmellose sodium as a disintegrant didn't show any significant variance in drug dissolution. It is advised to keep croscarmellose sodium in a cool, dry place in a container that is tightly sealed.

Incompatibilities

Croscarmellose sodium acts unfavourably with strong acids, iron that dissolves salts, & a few additional metals like zinc, aluminium, and mercury.

6. METHODOLOGY

Table 2: Materials Used.

S. No	Materials	Company
1.	Mirtazapine	Spectrum labs; Hyderabad.
2.	Sodiumstarch glycolate	Signet Chemical Corp., Mumbai
3.	Croscarmellose sodium	Signet Chemical Corp., Mumbai
4.	Crospovidone	Signet Chemical Corp., Mumbai
5.	Aspartame	Signet Chemical Corp., Mumbai
6	Microcrystalline cellulose	Aurobindo Pharma Ltd; Hyderabad.
7.	Talc	S.D. Fine Chem. Ltd; Chennai.
8	Magnesium stearate	S.D. Fine Chem. Ltd; Chennai.

Table 3: Instruments & Equipments Used.

S. No.	Instruments / Equipments	Company
1.	Digital balance	Essae-Teraoka ltd, DS-852j
2.	Hardness tester	Monsanto
3.	Friability test apparatus	Electro lab USP EF2
4.	Hydraulic press	Clit pilot press
5.	Vernier caliper	Pico India Ltd
6.	Tablet dissolution tester (USPII)	Lab India DS8000
7.	Tap density tester	K.E. India
8.	UV Spectrophotometer	PG Instruments, T60
9.	FT- IR Spectrophotometer	Shimadzu -8400 S
10.	pH meter	Hanna Instruments.

Preformualtion Studies: Solubility

The solubility has been evaluated in buffers containing phosphates with pH values of 1.2, 7.4, 4.5, and 6.8. The extra material was placed in beakers containing the solvents to perform solubility tests. For twenty-four hours, the mixtures were combined at certain times. Whattmann's filter paper grade No. 41 was utilised for filtering the solutions. Spectrophotometric analysis serves to analyse the filtered solutions.

Compatibility tests of drug excipients conducted by I.R.

Excipients are are vital parts of basically any dosage formulation used in medicines. A thoughtful choice of additives, that are included to aid in treatment, support the medication's constant release and the bioavailability and protect it from deterioration, is crucial to the effective formulation of a reliable and efficient dosage solid form.

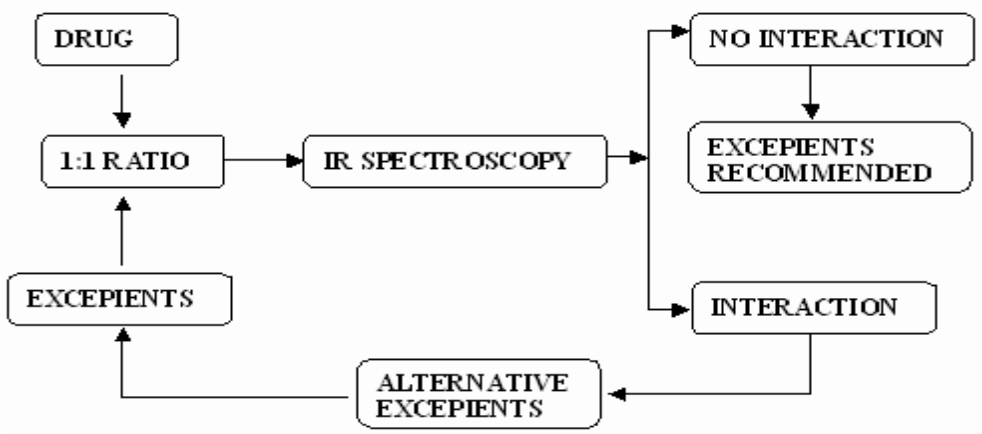


Fig. 3: Schematic representation compatibility studies.

The use of infrared spectroscopy is one of the most efficient analytical methods to assess the functional Technique: IR examines were conducted for both the pure drugs and its manufacturing. The potassium bromide disc (pellet) technique was used in this study.

Determination of λmax

To get an amount of 10 µg/ml, 1 ml of the stock solution (SS-II) was removed, and the remaining volume was subsequently increased up to 10 ml with 0.1NHCl. The range of wavelengths of the UVscan was 200–400 nm.

Calibration Curve for Mirtazapine in 0.1NHCL

Procedure

Preparation of Standard Stock Solution

In a 10 ml volumetric flask, ten milligrammes of mirtazapine was precisely measured before being mixed with a little amount of 0.1N HCL. Using 0.1N HCL, the amount of solution was raised to 10 ml in order to achieve a concentration of 1000 µg/ml for SS-I. This was drawn out, and 1 millilitre was diluted with 10 millilitres of distilled water in order to yield a concentration of 100 µg/ml of SS- II.

Calibration Curve in 0.1NHCL

0.2, 0.4, 0.6, 0.8, 1, and 1.2 millilitres were extracted from the standard stock solution (SS-II), and 0.1NHCl then added to the quantity to make it a total of 10 millilitres, giving concentrations of 2,4, 6,8, 10, and 12µg/ml. For mirtazapine, the absorption of those solutions was determined at 246 nm against a control sample of 0.1NHCl. Drug concentrations have been displayed against absorbance on a calibration curve.

FORMULATION OF ORAL DISINTEGRATING TABLETS OF MIRTAZAPINE[88-89]

Sublimation was used to make oral disintegrating tablets of mirtazapine using the formulas listed in the table.

Formulation development

Preliminary screening for ODTs

A. Trails for selecting super disintegrants

The preparation of the tablet required varying amounts of super disintegrants, medication, mannitol (at varying concentrations), and magnesium stearate, according to that order. The powder mixture for each batch was then compacted to create tablets that dissolved quickly. Whereas F4, F5, and F6 were made using sodium starch glycolate, F1, F2, and F3 were made with Ac-di-sol.

B. Trails for subliming agents

Ac-Di-Sol, mannitol, magnesium stearate, and subliming agents like camphor, menthol, and thymolin were added to tablets in varying amounts.

Following formulation, each batch's tablets were sublimated for an hour at 400 degrees Celsius in an oven. After that, the hardness, DT, and friability of each batch were assessed.

Preparation of Mirtazipine Oral disintegrating Tablets

After processing mirtazapine and all the additional components through the sieve number forty, the drug, mannitol, camphor, menthol, super disintegrants (Ac-Di-sol, sodium starch glycolate), and magnesium stearate were then added to the pills in varying amounts. After this, the newly compress mix had been compressed utilising a tablet compressing machine with eight stages (Cadmach). To help in the volatilization of sublimely elements, tablets were collected and sublimated at 400 degrees Celsius afterwards being compressed.

Table 4: Formulation Trials for Selection of Disintegrant.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Mirtazapine	30	30	30	30	30	30
Sodium starch Glycolate	3	6	9	-	-	-
Croscarmellose sodium		-	-	3	6	9

Aspertame	2	2	2	2	2	2
Microcrystalline cellulose	79	76	73	79	76	73
Magnesium stearate	3	3	3	3	3	3
Talc	3	3	3	3	3	3
Total	120	120	120	120	120	120

Table 5: Trails for Screening Sublimating Agents.

Ingredients	F7	F8	F9	F10	F11	F12
Mirtazapine	30	30	30	30	30	30
Sodium starch glycolate	9	9	9	9	9	9
Camphor	10	20	30	-	-	-
Menthol	-	-	-	10	20	30
Aspertame	2	2	2	2	2	2
Microcrystalline cellulose	63	53	43	63	53	43
Magnesium stearate	3	3	3	3	3	3
Talc	3	3	3	3	3	3
Total	120	120	120	120	120	120

EVALUATION PARAMETERS[90-93]

Pre-compression Settings

Procedure for Making a Combination Drug and Excipient Blend

Each component went via a sieve with a number 80. For each particular composition, a sufficient quantity of every component was determined, and all the other ingredients—aside than talc and magnesium stearate—were crushed to the required level of fineness. The flow qualities of the powdered blend were evaluated as follows.

6.3.2. Angle of repose

The angle of repose can be ascertained using the funnel method. An exact measurement of the mixture is placed into a funnel. The height of a funnel is adjusted such that its tip just touches the top of the combine pile. Through the funnel, the drug and excipient are permitted to freely flow until they reach the top. The diameter of the powder cone and the angle of repose can be determined using the formula that follows. The material is flowing freely when the angle of reposeis less than 30°.

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

Bulk density

An apparent bulk density can be obtained by weighing a portion of the mixture, pouring it into a graduated container, and then determining the volume and weight.

The bulk density was calculated using the formula shown below.

$$Db = \frac{M}{Vo}$$

where V0 is the powder's bulk volume and M is its mass.

Tapped Density

The graduated cylinder containing an established weight for the drug-excipient blend is set up to measure it. At periods for two seconds, the cylindrical object is permitted to fall on its own gravity from an elevation of 10 cm onto a hard surface. Tapping is kept until the volume is not altered anymore. The following formula was employed to figure out the tapped density:

$$DT = \frac{M}{Vt}$$

where Vt is the powder's tapped volume and M is the powder's mass.

Compressibility Index

Compression is the simplest approach to determine the free flow of powders. Compressibility index (I), that is calculated below, indicates the ease with which something can be made flow freely.

Carr's Index (I) = (Tapped Density-Bulk Density)/ (Tapped Density) x100

% Compressibility	Flow ability
5 – 12	Excellent
12 – 16	Good
18 – 21	Fair Passable
23 – 35	Poor
33 – 38	Very Poor
< 40	Very Very Poor

A powdered substance having usually good flow properties is denoted by an amount of 13 to 19%, while avalue over 21% suggests poor flowability.

Hausner's Ratio

An approximate indicator of the powder flow's ease is the Hausner's ratio. It is calculated with the following formula:

Hausner'sRatio= bulkdensity

Tappeddensity

Where in the bulk density is indicated as Db and tapped density by Dt.Better flow properties are shownby a smaller Hausner's ratio (<1.25) while poor flow qualities aresuggested with a higher Hausner's ratio (>1.25).

EVALUATION OFTABLETS[94-96]

Post compression Parameters

Weight Variation Test

In order to be certain that the total weight of the medication within a batch remains constant, the test for weight variation is carried out. First, the mean is calculated using the total weight of the 20 pills from each formula. To determine the amount of weight variation, the weigh for every tablet is additionally determined separately.

Tablet Hardness

The strength of a tablet may be determined by its toughness. By pressing the tablet in a direction that is radial, it cracks. The pressure is needed for it to do so. The amount of force is measured in pounds, and for tablets without coatings, a hardness rating of approximately 3-5 kg/cm2 is considered acceptable. A Monsanto hardness test serves to find out the firmness of ten pills for every formulation. The process of disintegration time is greatly decreased by extreme rigidity.

Tablet Friability

The weight of a tablet reduces in its container as tiny fragments dissolve from its outermost layer, an effect known as brittleness. The purpose of the test for friability is to assess the tablet's durability against friction while handling, wrapping, and transport. The Roche friabilator is utilised to assess the tablets' brittleness. Every batch of twenty pills need to be weighed prior placing it in a Roche friabilator and revolved at 25 rpm by four minutes. Each pill weighs another time after becoming dedusted. The formula that follows can be used for determining the percentage of Friability.

% Friability = [(W1-W2)100]/W1

Where, W1= Weight of tablet beforetest, W2 = Weight of tablet after test.

A tablet's friability test pharmacopoeial limit cannot be greater than one percent. This test is performed on pills made by sublimation and moulding; it isn't suitable for lyophilized any flash- dose tablets. Maintaining flexibility in this MDT limit while minimising hard to attain the quickest time for disintegration is a difficult endeavour.

***In-Vitro* Disintegration Time**

The disintegration up of pills is an essential step for the absorption of medicines. The disintegration performed utilising an USP disintegrating tests instrument by Electrolab. It is composed of up of six three- inch- long transparent tubes with a top that is open which is pushed up on a ten-mesh filter at the base of a basket rack arrangement. A single tablet was placed into each tube, and a basket rack was set out in a 1-liter beaker containing a pH 6.8 solution of buffer at 37°C ± 1°C so that each tablet remained 2.5 cm beneath the surface of the fluid to calculate the time taken for disintegration of the tablets. It was determined the periodit took the tablets to dissolve entirely.

Thickness and Diameter

A simple technique may be utilised for determining the thicknesses & size of tablet. The vernier callipers is employed to study the diameter of five tablets. The depth and length are determined by kept on a tablet in-between the two ends of a Vernier calipers.

Drug Content Uniformity

Uniformity of the pharmaceutical concentration in each tablet was studied. The twenty tablets were measured, crushed up, and combined with a hundred millilitres of 6.8 the pH buffers containing phosphate by randomly. They gave the remedy a thorough shake. Whatmann No. 41 filtering paper was employed to draw out the undissolved particles. Following that, reduce the mix to create 10µg in solution. Around 246 nm, the absorbing capacity of the dilute solutions was calculated.

Dissolution Studies: The USP Type 2 equipment (paddle type) is utilised for *in vitro* dissolving experiments at a rate around fifty revolutions per minute (rpm). The dissolving medium-sized, 900 millilitres of 0.1 N hydrogen chloride a buffer, remains at 37±0.5°C. In certain times, ten millilitre aliquots from the dissolution solution have been eliminated & screened. immediately as the exam specimen is taken out, the identical volume of a novel dissolve fluid is given. Using Beer-Lambert's Law, the share of drugs given over variousdurations can be determined.

Data Analysis (Curve Fitting Analysis)

The information gathered has been plotted below with the goal to investigate the workings of thedose form's release rates kinetics[97–98]

- *In-vitro* release displays: the total amount of the medication released versus duration.
- First order displays: record the total amount of the drug left vs duration.
- The information gathered was displayed as follows so as to investigate the mechanismunderlying the dose form's release rate kinetics:97–98
- In-vitro drug absorption plots: the total amount of drug delivered and period.
- First order plots: measure the cumulative amount of

the medication left vs time.

6. RESULTS AND DISCUSSION

Studies on Solubility

The solubility of mirtazapine was tested at 250C with filtered water, 0.1 N HCl, 6.8 phosphate buffer, and 7.4 pH buffer.

Medium	Solubility (mg/ml)
Water	0.793
0.1 N HCl	0.452
6.8 pH buffer	0.741
7.4pH buffer	0.628

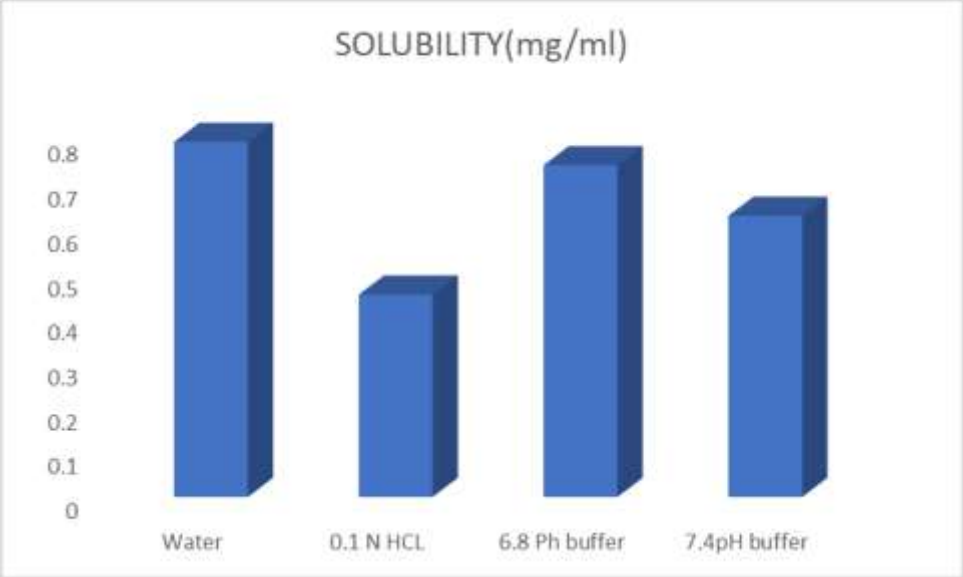


Fig. 4: Solubility of Mirtazapine.

Drug-Excipient Integration

By contrasting the spectrum obtained from the FT-IR examination of the drug as a whole with the ones from each of the excipients used in the formulation, the compatibility of the medication and the excipient was confirmed.

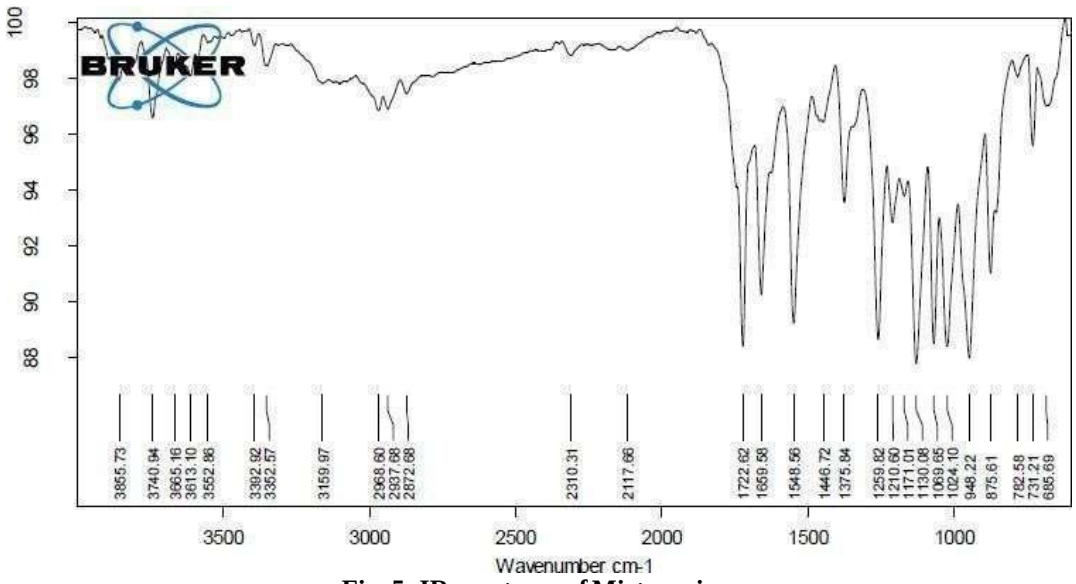


Fig. 5: IR spectrum of Mirtazapine.

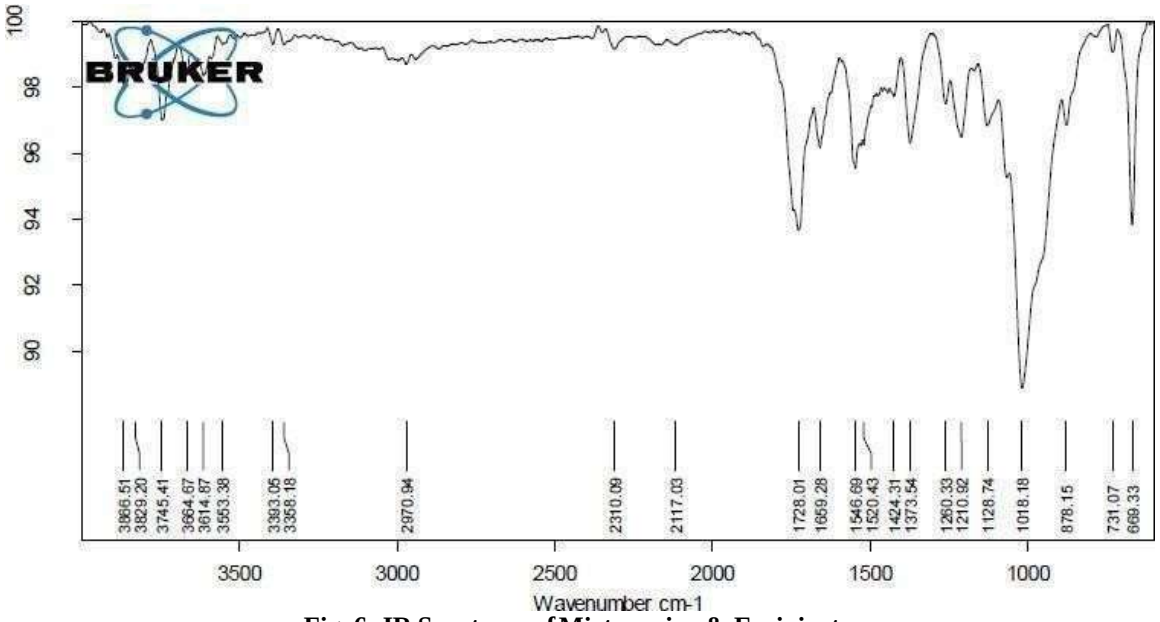


Fig. 6: IR Spectrum of Mirtazapine & Excipients.

Response: Based on the medication's the excipient incompatibility inquiries, there aren't any interactions with the optimised formulation (Mirtazapine+ Excipients) and the original medication (Mirtazapine), indicating that no physical changes have taken place.

Determination of λmax

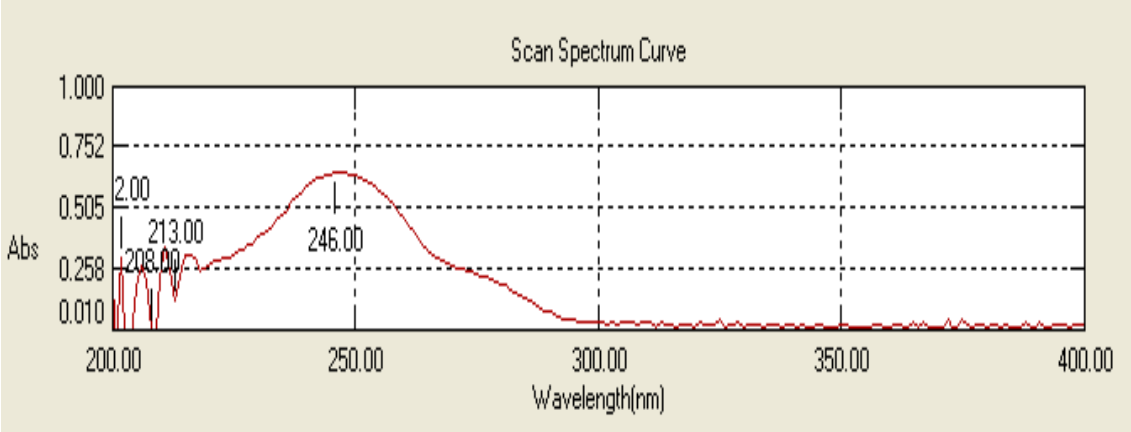


Fig. 7: UV Spectrum Curve of Mirtazapine Discussion: λmax of Mirtazapine was found to be 246nm.

6.2.3 Mirtazapine's Calibration Curve in a 6.8 pH Buffer

Table 6: Calibration curve of Mirtazapine in 6.8pH buffer.

Concentration(µg/ml)	Absorbance
0	0
2	0.159
4	0.318
6	0.477
8	0.637
10	0.791
12	0.945

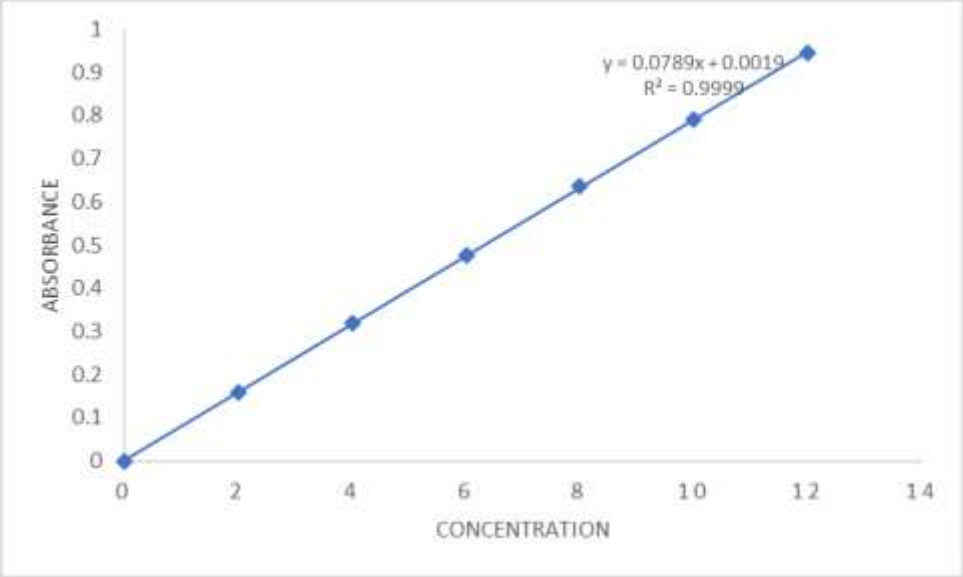


Fig. 8: Standard Graph of Mirtazapine.

6.3 Characterization of Blend

Table 7: Pre Compression Parameters.

Formulation Code	Derived Properties		Flow Properties		
	Bulk Density (mean±SD)	Tapped Density (mean±SD)	Angle of Repose (mean±SD)	Carr's Index (mean±SD)	Hausner's Ratio (mean±SD)
F1	0.63	0.72	26.46	11.27	1.12
F2	0.62	0.73	27.65	14.61	1.14
F3	0.65	0.71	25.84	12.37	1.17
F4	0.64	0.70	28.12	13.41	1.14
F5	0.67	0.75	29.42	10.81	1.15
F6	0.61	0.74	27.52	13.58	1.12
F7	0.63	0.72	25.14	14.63	1.14
F8	0.65	0.77	27.43	12.72	1.18
F9	0.63	0.75	25.75	13.28	1.16
F10	0.68	0.72	29.25	15.78	1.14
F11	0.65	0.71	26.34	12.81	1.17
F12	0.66	0.73	28.27	14.97	1.15

DISCUSSION

Various formulations' angles of repose all fell under 29.42, demonstrating the substance has good flow characteristics. Therefore, it was determined the mixes had free-flowing flow qualities. It was found the blend's bulk density varied from 0.61 to 0.68 g/cm3. The range of values of taped density is 0.70–0.77g/cm3. The results presented show that the blends' flows were good. Each of the compositions' Carr's indices were between 10.81 to 15.78, and respective Hausner's ratios ranged as 1.12 to 1.18, indicating the blends have good flow parameters.

Characterization of Tablets

Post-Compression Configurations

Official evaluation features like weight variation, hardness, friability, tablet thickness, & medication content have been determined for every batch of tablet formulations, and the findings are presented.

Table 8: Characterization of Mirtazapine Oral Disintegrating Tablets.

Characterization Mirtazapine ODT's (Disintegrant selection trials)					
Formulation	**Weight Variation(mg)**	**Thickness (mm)**	**Hardness (kp)**	**Friability (%)**	**Disintegrating Time (sec)**
F1	119.2	3.3	3.4	0.78	61
F2	118.3	3.4	4.1	0.42	50
F3	121.4	3.2	3.6	0.89	45
F4	118.6	3.5	3.3	0.55	49
F5	121.2	3.7	3.7	0.79	46
F6	120.5	3.4	4.2	0.72	39

Characterization Mirtazapine ODT's Before Sublimation					
F7	118.3	3.6	4.0	0.44	61
F8	119.3	3.8	3.5	0.39	58
F9	120.2	3.4	3.8	0.95	52
F10	118.3	3.7	4.1	0.42	75
F11	119.5	3.5	3.9	0.79	69
F12	121.8	3.3	3.2	0.58	57
Characterization Mirtazapine ODT's after Sublimation					
F7	118.1	3.6	4.1	0.54	52
F8	119.4	3.8	3.2	0.3	48
F9	120.0	3.4	3.7	0.95	32
F10	118.4	3.7	4.2	0.42	55
F11	120.2	3.5	3.8	0.79	42
F12	121.7	3.3	3.5	0.58	37

Talk

The tablet's hardness, that varied between 3.2 to 4.2 kg/cm2, was found to be acceptable as well as consistent among runs. Because the amount of mass shifts was according to the pharmacopeial limits of the tablet weight, all of the drugs passed the measurement of weight variation test. In order to verify that every one the tested formulations are mechanically secure, friability levels have been established to be below 1 percent in all of of F1–F12 compositions. Disintegration timings according to the IP proved to be under twenty-two seconds for all formulations, well within IP limit. Among all the formulations, those that include CPV as a super disintegrant dissolve the fastest. SSG with 9mg concentration as a super disintegrant show very less disintegration time when compared with croscarmellose sodium. By using SSG 9mg concentration ODTs were formulated using camphor and menthol in different concentrations. Among them camphor having 30mg shows better disintegration time whencompared with menthol.

Uniformity of Drug Content in Formulations

The information collected for the examination that generated formulations' drug composition is given below. The amount of drug was discovered to fall above the allowed ranges, suggesting that the medicine was equally scattered across every mixture.

Table 9: Drug Content Uniformity of Formulations F1-F12.

Tablet Formulation	% Drug Content
F1	96.96
F2	94.65
F3	97.122
F4	87.02
F5	94.71
F6	97.16
F7	82.24
F8	84.18
F9	92.06
F10	86.68
F11	85.29
F12	94.64

Discussion: It turned out that the drug content values for formulas F1 – F12 varied between 82.24% to 98.16%.

Studies on Dissolution

To figure out the quantity of medication release, disappearing examinations were carried out on the generated pills. The time period of drug release reduced as polymer concentration grew.

Table 10: % Cummulative Drug Release of Formulations F1-F12.

Time(Min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	18.98	26.46	41.9	28.45	34.21	35.85
10	29.05	38.24	54.13	39.78	45.81	47.05
15	38.53	48.02	63.47	49.43	54.98	56.41
20	48.47	57.72	73.01	58.91	65.15	65.94
25	59.04	68.08	82.43	69.43	75.02	76.76
30	70.15	78.57	91.46	80.42	84.96	87.49

Time(Min)	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
5	35.05	48.63	60.65	31.41	45.18	52.48
10	46.78	62.72	76.42	42.98	58.17	66.05
15	57.05	73.63	87.71	53.01	67.91	75.15
20	66.53	84.45	99.13	62.64	77.66	85.79
25	75.93	95.45		71.97	89.02	97.42

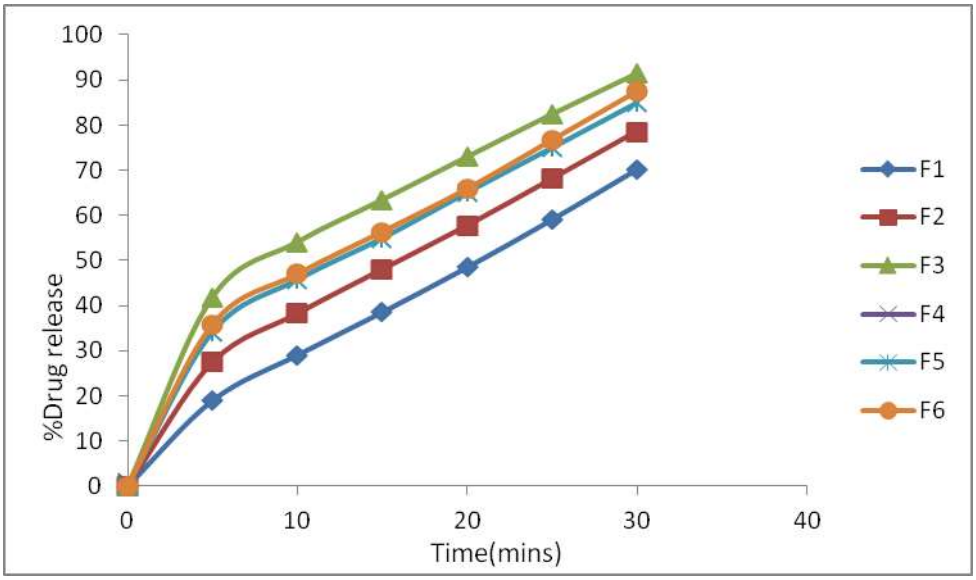


Fig. 9: % Drug Release of F1 & F6.

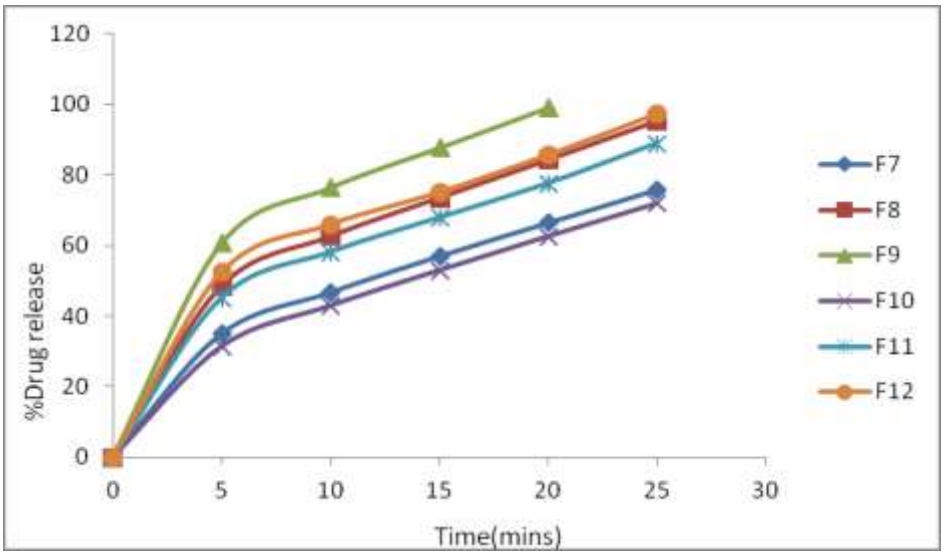


Fig. 10: % Drug Release of F7 & F12.

DISCUSSION

It was noted from the *in-vitro* drug release investigations that the formulations comprising SSG (F1- F3) as super disintegrant in the convergence of (3, 6, 9 mg) shows 70.15 %, 78.57%, and 91.46% drug release finally by the end of 30minutes.

In contrast, the formulations that comprise CCS (F4-F6) as a super disintegrant at dosages of 3, 6, and 9 mg exhibit drug release after 30 minutes that is 80.42%, 87.49%, and 99.53%.

After 30 minutes, SSG exhibits superior drug release based on the choice of disintegrants.

And so on, sublimation trials were formulated utilising camphor and menthol at different concentrations.

Among them F7,F8 & F9 trials were formulated using camphor as subliming agent and F10, F11 & F12 trials were formulated using camphor as subliming agent. Among them camphor at 30mg shows rapid disintegration and drug release.

During twenty minutes, formulation F9, containing 30 mg of camphor, displays 99.13% drug release. Thus, it was determined that the F9 formulation was the best one. More kinematics have been collected for the composition of F12.

Drug release kinetic studies

Zero order release kinetics

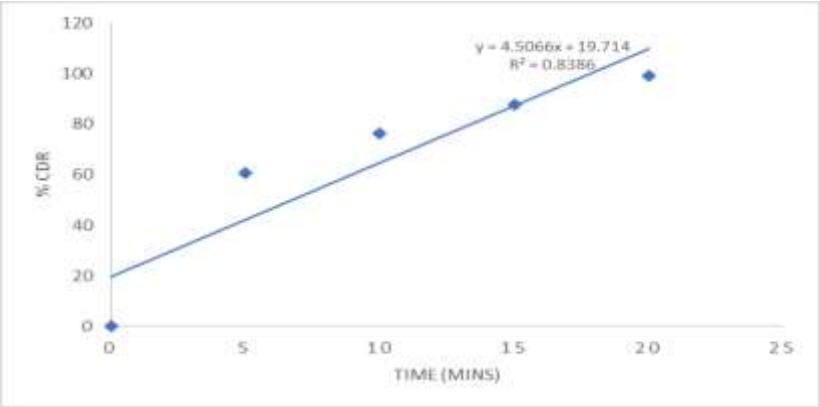


Fig. 11: Zero orderplot of Mirtazapine F9 Formulation.

First-order kinetics of release

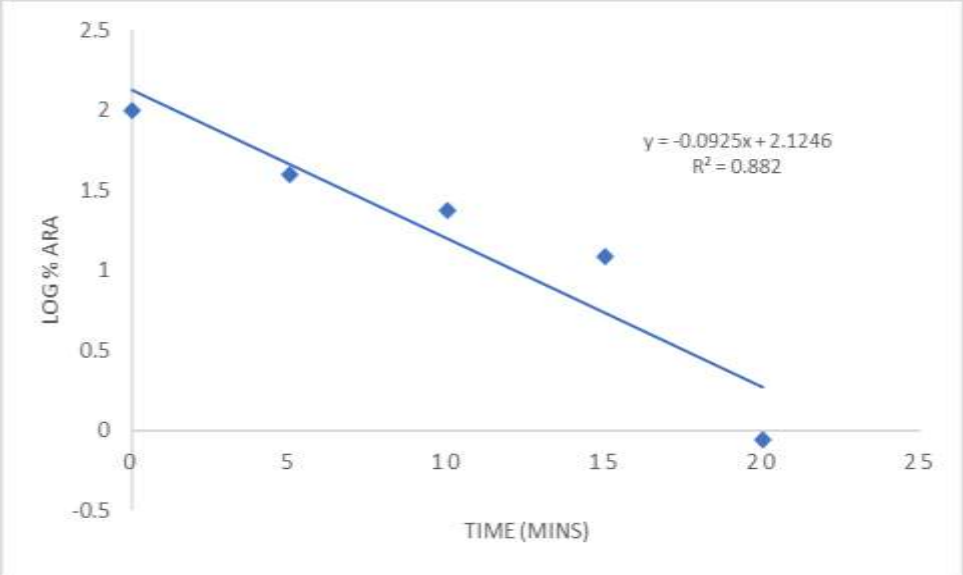


Fig. 12: First Order Plot of Mirtazapine F9 Formulation (Time Vs Log% ARA).

Table 11: First Order of Kinetic Values of Formulation F9.

Order of Kinetics	Zero Order	First Order
Values of Regression	0.839	0.882

DISCUSSION

Initial & zero orders mathematical formulas were utilised to clarify the drug release via oral disintegrating tablets. It has been found the optimised formula F 9 conforms to initial phase release of drugs according to regression analysis data.

7. SUMMARY AND CONCLUSION

- The aim of this investigation was to identify the optimal disintegrant-subliming combo for the design of oral disintegrating tablets in mirtazapine, that dissolves in the mouth in just a couple of milliseconds and reduce the time before the drug takes action.
- Two disintegrating agents are utilised: SSG & CCS. Talc & magnesium stearate were used as glidant & lubricant in every composition, accordingly.
- The natural drug and additives didn't interact physically, as per findings in the drug-excipient compatible studies.
- This sublimation method, requiring few manufacturing steps and can be more reasonable, was applied to formulate the tablets.
- The total density, tap density, angle of repose, and Carr's index were calculated for precompression parameters. Adequate flow abilities have been

shown by every formula.

- When doing a study, it was found that the post-compression parameters, included hardness, thickness, friability and weight variation, disintegration time, disintegration time in the mouth, and Invitro release, were below IP limits.
- All of the pills' drug contents varied from 82.24 - 98.16 percentage, so they were in allowable bounds of the percentage for mirtazapine.
- At the conclusion of twenty minutes, F 9 shows 99.13% release of drugs out of all of the formulations. In contrast to before products, F9 has a greater degree of drug release and includes 30 milligrammes of menthol.
- F9 thus became known as the ideal formulation.
- The optimised formulation F9 complies to initial order drug release, as shown by the drug release kinetics.

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