

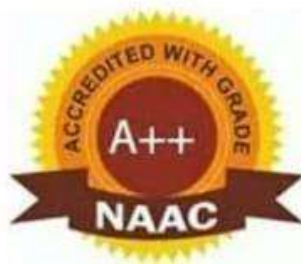
**FORMULATION AND *In vitro* CHARACTERIZATION OF
DAPSONE FAST DISINTEGRATING TABLETS USING
CO-PROCESSED EXCIPIENTS**

Submitted in partial fulfillment of the requirements for the award of

BACHELOR OF PHARMACY

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DECLARATION

We hereby declare that the work presented in the thesis entitled "FORMULATION AND *IN VITRO* CHARACTERIZATION OF DAPSONE FAST DISINTEGRATING TABLETS USING CO-PROCESSED EXCIPIENTS" submitted by us to the Sathyabama Institute of Science and Technology (Deemed to be University), Chennai - 600119, for the award of Bachelor of Pharmacy (2020-2024) by research is an original record of research work carried out by us under the supervision of "Mr. Voleti Vijaya kumar , Assistant Professor, School of Pharmacy". The contents of this dissertation, in full or in parts, have not been submitted to any other institute or university for the award of any degree, diploma, membership, fellowship, associate-ship etc.. In keeping with the general practicing reporting scientific observation, due acknowledgement has been made whenever the work described is based on the findings of other investigators.

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ABSTRACT

OBJECTIVE: The primary objective of this study is to formulate and evaluate Dapsone Fast Disintegrating Tablets by Direct compression method using co-processed superdisintegrants such as Sodium Starch Glycolate, and Crospovidone. Additionally this study aims to improve the solubility of Dapsone by converting it into Solid Dispersions.

METHODS: Dapsone solubility enhanced by converting pure Dapsone into solid dispersions. The formulation of solid Dispersion was confirmed by XRD studies. Co-processed excipients of Sodium Starch Glycolate and Crospovidone was prepared by Solvent evaporation method. A total of 11 formulations was prepared and characterized for Pre-compression and post compression parameters

RESULTS: Dissolution studies of Pure drug, Solid dispersions and Physical mixture of Dapsone has been compared. Solid dispersions of Dapsone confirmed by XRD studies. All the Pre/Post compressional parameters showed the better results

CONCLUSION: In summary, our study successfully enhanced the solubility of Dapsone by transforming it into solid dispersions. Notably, among the 11 formulations tested, those incorporating co-processed excipients demonstrated the most significant improvement in drug release compared to physical mixtures. This highlights the effectiveness of our approach in optimizing the formulation for better drug delivery.

Keywords: Fast disintegrating tablets, Solid dispersions, Co-processed excipients, Physical mixture .

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LIST OF ABBREVIATIONS

FDT - Fast Disintegrating Tablets

ODT - Orally Disintegrating Tablets

USP - United States of Pharmacopoeia

FDA- Food and Drug administration

WOW- Without Water

IPEC- International Pharmaceutical Excipients Council

SSG- Sodium Starch Glycolate

CP - Crospovidone

MCC- Microcrystalline Cellulose

XRD - X-RAY Diffraction

FTIR- Fourier-Transform Infrared Spectroscopy

BCS - Biopharmaceutical Classification System

CNS- Central Nervous System

API - Active Pharmaceutical Ingredient

PM - Physical Mixtures

CP- Co-Processed excipients

RPM- Revolutions per minute

SD - Solid Dispersions

IP - Indian Pharmacopoeia

g - Gram

IR - Infrared Spectrum

UV - Ultraviolet

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CHAPTER - 1

INTRODUCTION

INTRODUCTION TO FAST DISSOLVING TABLETS

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates) and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and therefore, less expensive to manufacture. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance^[1].

The most desirable formulation for use by the elderly is one that is easy to swallow and easy to handle. Taking these requirements into consideration, attempts have been made to develop a rapid dissolving tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place. For example, it can be taken anywhere at any time by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules. Recently, many companies have researched and developed various types of fast-disintegrating dosage form technologies with the potential to accommodate various physicochemical, pharmacokinetic and pharmacodynamic characteristics of drugs^[2, 3]. These tablets are also called as Oro dispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelts. However, of all the above terms, United States of pharmacopoeia (USP) approved these dosage forms as ODTs (orally disintegrating tablets). Recently, European Pharmacopoeia has used the term Oro dispersible tablet for tablets that disperses readily within 3 min in mouth before swallowing. United States of Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute¹

CHARACTERISTICS OF FAST DISSOLVING TABLETS

- Be compatible with other excipients used.
- Not require water to swallow, but it should be dissolved or disintegrated in the mouth in a matter of seconds
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipment's at low cost.
- Ease of administration to the patient who cannot swallow, such as the elderly, stroke victims, bedridden patients, patient affected by renal failure and patient whorefuse to swallow such as pediatric, geriatric and psychiatric patients.
- No need of water to swallow the dosage form, which is highly convenient feature for patients who are traveling and do not have immediate access to water.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases bioavailability of drug is increased.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patient.^[4,5]

BENEFITS OF FAST DISSOLVING TABLETS

- Convenience of administration and accurate dosing as compared to liquids.
- No need of water to swallow the dosage form, which is highly convenient especially for patients who are traveling and do not have immediate access to water.
- Good mouth feel property of these tablets helps to change the basic view of medication as “bitter pill”, particularly for pediatric patients.
- Rapid dissolution and absorption of drug, which may produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach; in such cases bioavailability of drugs is increased.
- Ability to provide advantages of liquid medication in the form of solid form.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of tablets.
- Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, it combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.^[6,7]

LIMITATIONS OF FAST DISSOLVING TABLETS ¹⁰

- The tablets may leave unpleasant taste or grittiness in mouth if not formulated properly.
- The tablets usually have low hardness. So, they are friable and/or brittle and are difficult to handle. They often require specialized peel-off blister packaging and careful handling required.
- Delivery of drug from the fast-dissolving formulation would not expect to avoid first pass metabolism since the unit disintegration rapidly and the drug would be swallowed.^[7,8]

CHALLENGES IN FORMULATING FAST DISSOLVING TABLETS

Palatability

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance. ^[9]

Mechanical strength

In order to allow FDTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles, such as Wowtab® by Yamanouchi-Shaklee and DuraSolv® by CIMA labs. ^[10]

Hygroscopicity

Several fast-dissolving dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging. ^[11]

Amount of drug

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films. ^[12]

Aqueous solubility

Soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite. ^[13]

Size of tablet

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size is both easy to take and easy to handle. ^[14,15]

METHODS OF PREPARING FAST DISSOLVING TABLETS

Tablet Molding

Tablet produced by moulding are solid dispersion. Moulded tablets disintegrate more rapidly and offer improved taste because the dispersion matrix is in general made from water soluble sugars. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. Moulding process is of two types i.e. solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in moulded plates to form a wetted mass (compressing moulding). ^[16,17] The solvent is then removed by air drying. Such tablets are less compact than compressed tablets and possess a porous structure that hastens dissolution.

The heat-moulding process involves setting the molten mass that contains a dispersed drug. The heat-molding process uses an agar solution as a binder and a blister packaging well as a mould to manufacture a tablet. The process involves preparing a suspension that contains a drug, agar and sugar (e.g., mannitol or lactose) pouring the suspension into the blister packaging; well, solidifying the agar solution at room temperature to form a jelly and drying at 30°C under vacuum. ^[18,19]

Spray drying

Spray drying is used in pharmaceutical industries to produce highly porous powders. The processing solvent is evaporated rapidly by spray drying, which renders the product highly porous and fine powders can be produced. In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate, croscarmellose, crospovidone are used as a super disintegrants. Disintegration and dissolution were further enhanced by adding an acid (e.g. citric acid) or an alkali (e.g. sodium bicarbonate). The formulation was spray dried to yield a porous powder. Tablets manufactured from this powder have been reported to disintegrate in less than 20 seconds in an aqueous medium. ^[20,21]

Mass-Extrusion

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste. ^[22,23]

Freeze-Drying or Lyophilization^{3,13}

Freeze drying is the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. A typical procedure involved in the manufacturing of ODT using this technique is mentioned here. The active drug is dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture is done by weight and poured in the walls of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminum foil backing is applied on a blister-sealing machine. Finally, the blisters are packaged and shipped. ^[23,24] The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophilization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions ^[25]

Sublimation

The slow dissolution of the compressed tablet containing even highly water-soluble ingredients is due to the low porosity of the tablets. Inert solid ingredients that volatilize readily (e.g. urea, ammonium carbonate, ammonium bicarbonate, hexamethylene tetramine, camphor, etc.) are added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials are then removed via sublimation, which generates porous structures. Tablets manufactured by this technique have reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane, benzene can be used as pore forming agents. ^[26,27,28]

Direct Compression

From the pharmaceutical manufacturer's point of view, direct compression is the simplest most cost-effective tablet manufacturing procedure. Pharmaceutical companies can use conventional manufacturing equipment and commonly available ingredients. This method can be applied to manufacturing FDTs by choosing appropriate combinations of excipients, which can provide fast disintegration and good physical resistance. Sugar-based excipients have been widely used as bulking agents because of their high aqueous solubility, pleasing mouth-feel and good taste masking. Nearly all formulations for FDTs incorporate some sugar materials in their formulations. ^[29,30]

SUPERDISINTEGRANT ADDITION

A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. Super disintegrants are used at a low level in the solid dosage form, typically 1-10% by weight relative to the total weight of the dosage unit. Examples of super disintegrants are croscarmellose, crospovidone and sodium starch glycolate, which are a cross linked cellulose, cross-linked polymer and a cross linked starch respectively. The proper choice of disintegrant and its consistency of performance are critical to formulation development of such tablets. ^[30,31]

Microcrystalline cellulose and low substituted hydroxypropyl cellulose were used as disintegrating agents in the range of 8:2 – 9:1 to prepare fast dissolving tablet. Agarpowder is used as disintegrant for the development of rapidly disintegration

tablets by enhancing the porosity of agar by water treatment. Sodium starch glycolate, croscovidone and croscarmellose are some of the popular super disintegrants.^[31,32] The list of commonly used super disintegrants with their description is shown in Table 1.1

Mechanism of Super disintegrants

There are four major mechanisms for tablet disintegration as follows:

1. 7.1.1 Swelling

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

1.7.1.2 Porosity and capillary action (Wicking)

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles.[33,34]. Water uptake by tablet depends upon hydrophilicity of the drug /excipients and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating ^[35,36]. A hydrophilic network around the drug particles. The wicking and swelling process of disintegration is shown in Fig. 1.

WICKING

SWELLING

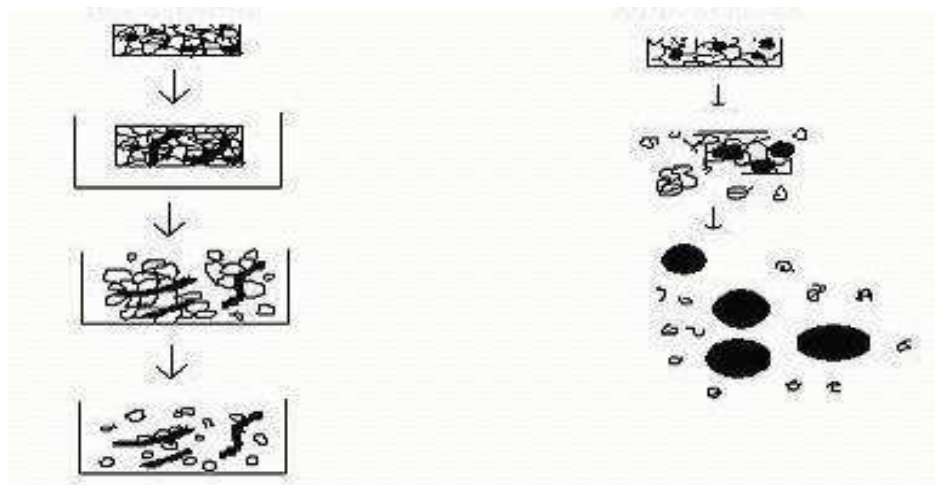


Fig. 1.1 Disintegration by wicking and swelling process

Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegrants attempts to explain the swelling of tablet made with 'non-swelling' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets. The repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.^[37,38]

Due to deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.^[39,40] Disintegration of tablets by deformation and repulsion is shown in Fig. 1.2

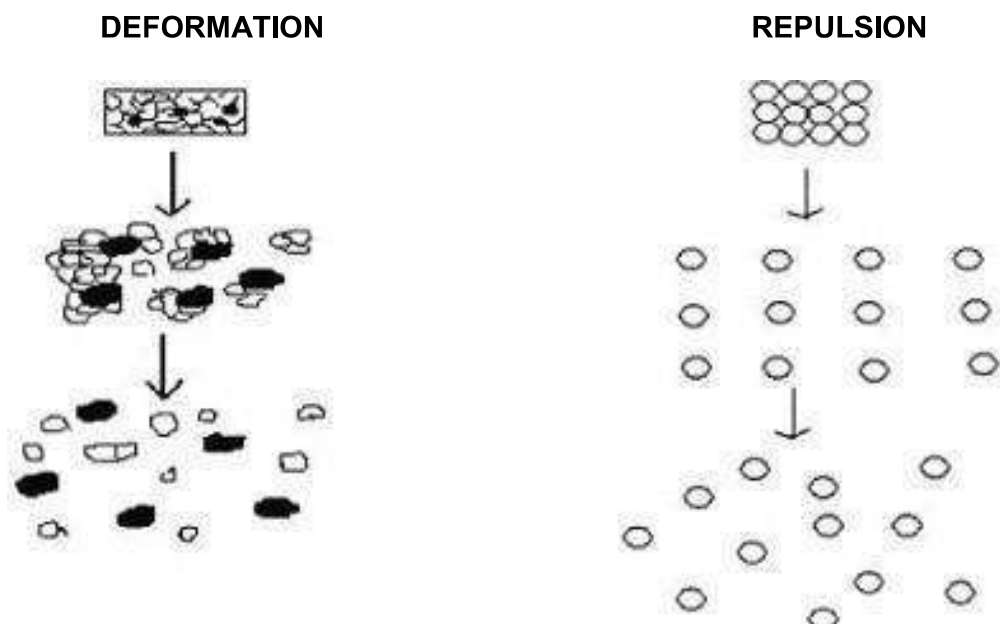


Fig 1.2 Disintegration by deformation and repulsion process

Table 1.1 List of super disintegrants

Super disintegrants	Example	Mechanism of action	Special comment
Croscarmellose ® Ac-Di-Sol® Nymce ZSX® Primellose®Solutab ® Vivasol®L-HPC	Crosslinked Cellulose	Swells 4-8 folds in < 10 seconds, acts by swelling and wicking both	Swells in two dimensions, used for direct compression or granulation [40]
Crospovidone Crospovidone M® Kollidon® Polyplasdone	Crosslinked PVP	Swells very little and returns to original size after compression but act by capillary action	Water insoluble and spongy in nature so get porous tablet [41]

Sodium starch glycolate Explotab® Primogel	Crosslinked Starch ^[43]	Swells 7-12 folds in < 30 seconds	Swells in three dimensions and high level serve as sustain release matrix
Alginic acid NF	Crosslinked	Rapid swelling in aqueous medium ^[45]	Promote disintegration
Satialgine®	alginic acid ^[46]	or wicking action	in both dry or Wet granulation
Soy polysaccharides Emcosoy®	Natural super disintegrant]		Does not contain any starch or sugar, used in nutritional products ^[44]
Calcium silicate		Wicking action	Highly porous, 20-40% ^[45]

PATENTED TECHNOLOGIES FOR FAST DISSOLVING TABLETS

Zydis technology

Zydis, the best known of the fast dissolving/disintegrating tablet preparations, was the first marketed new technology tablet. The tablet dissolves in the mouth within seconds after placement on the tongue. Thirteen products are currently available using Zydis technology. In the U.S., they include: Claritin Reditab, Dimetapp Quick Dissolve, Feldene Melt, Maxalt- MLT, Pepcid RPD, Zofran ODT and Zyprexa Zydis. On the worldwide market, other Zydis formulations are available for oxazepam, lorazepam, loperamide and enalapril. ^[46]

A Zydis tablet is produced by lyophilizing or freeze drying the drug in a matrix usually consisting of gelatin. The product is very lightweight and fragile, and must be dispensed in a special blister pack. Patients should be advised not to push the tablets through the foil film, but instead peel the film back to release the tablet. The Zydis product is made to dissolve on the tongue in 2 to 3 seconds.³ The Zydis formulation is also self-preserving because the final water concentration in the freeze-dried product is too low to allow for microbial growth. The Zydis formulation utilizes flavors and sweeteners to optimize the taste of the dosage form. In addition, it utilizes microencapsulation with specialized polymers or complexation with ion exchange resins to mask the bitter tasting drug. The combination of lyophilization and taste masking creates a product that is both pleasing to the eye and also to the senses of taste and touch^[47]

DuraSolv technology 4, 22

DuraSolv is Cima's second-generation fast dissolving tablet formulation. DuraSolv product is thus produced in a fashion similar to OraSolv; DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tableting. The DuraSolv product is thus produced in a faster and more cost-effective manner. DuraSolv is so durable that it can be packaged in either traditional blister packaging or vials. The newest DuraSolv formulation, NuLev, is actually dispensed in a conventional stock bottle. Pharmacists are advised to take care when dispensing such DuraSolv formulations from stock bottles to ensure they are not exposed to high levels of moisture or humidity^[48]

OraSolv technology

OraSolv was Cima's first fast-dissolving/disintegrating dosage form. The OraSolv technology, unlike Zydis, disperses in the saliva with the aid of almost imperceptible effervescence. The OraSolv technology is best described as a fast-disintegrating tablet; the tablet matrix dissolves in less than one minute, leaving coated drug powder. The taste-masking associated with the OraSolv formulation is two-fold.

The unpleasant flavor of a drug is not merely counteracted by sweeteners or flavors; both coating the drug powder and effervescence are means of taste-masking in OraSolv. This technology is frequently used to develop over-the-counter formulations. An advantage that goes along with the low degree of compaction of OraSolv is that the particle coating used for taste masking is not compromised by fracture during processing. The major disadvantage of the OraSolv formulations, its mechanical strength. The OraSolv tablet has the appearance of a traditional compressed tablet. However, the OraSolv tablets are only lightly compressed, yielding a weaker and more brittle tablet in comparison with conventional tablets.^[49]

Flash dose technology

Flash dose tablets consist of self-binding shear form matrix termed as “floss”. In flash heat process, the feed stock (carbohydrates including sugars and polysaccharides) is simultaneously subjected to centrifugal force and to a temperature gradient, resulting in discrete fibers.^[51] The preformed matrices obtained are partially crystallized and have good self-binding and flow properties. The so formed matrices are complex crystalline structures with high specific surface area and result in rapid dissolution rate of the drug. Flash dose tablets are soft, friable and hygroscopic dosage forms, which require specialized packaging.

WOW tab technology 22

WOW tab technology is patented by Yamanouchi Pharmaceutical. WOW means “without water”. This process uses a combination of low mouldability saccharide (rapid dissolution) and high mouldability saccharide (good binding property) to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (e.g. lactose, mannitol) and granulated with a high mouldability saccharide (e.g. maltose, sorbitol) and compressed into tablets. The WOWTAB product dissolves quickly in 15 seconds or less. The WOW in WOWTAB signifies the tablet is to be given without Water. Two WOWTAB formulations currently on the U.S. market are Benadryl Allergy & Sinus FASTMELT and Children's Benadryl Allergy & Cold FASTMELT.^[52]

CO-PROCESSED EXCIPIENTS⁶⁵

The pharmaceutical industry first started to use co-processed excipients from the late 1980s, with early examples including co-processed microcrystalline cellulose and calcium carbonate, introduced in 1988, MEGGLE's co-processed cellulose and lactose (1990), and co-processed glucomannan and galactomannan (1996). The International Pharmaceutical Excipients Council (IPEC) defines excipient as "substances other than the API which have been appropriately evaluated for safety and are intentionally included in a drug delivery system". An excipient that has undergone co-processing is a combination of two or more compendial or non-compendial excipients with the goal of physically changing their properties without altering chemical properties^[52]

Advantages of co-processed excipients

- One excipient can serve many purposes.
- Overcome the excipients limitations.
- Improved organoleptic qualities.
- Displays constructive interaction.
- Improved physiochemical characteristics.
- Minimizes modifications to the profile of dissolution.
- Enhanced palatability and increased tongue feel.
- Reduce unfavorable characteristics.^[53]

Disadvantages of co-processed excipients

- Elevated temperature enprocessing and specialized filling equipment are needed.
- Pre-clinical species do not always tolerate some lipidic excipients well.
- Cost of process is high due to labour costs, space costs, time, energy, and specialized equipment needs.
- Material loss throughout different processing phases.
- Drugs that are thermolabile or moisture sensitive are not good candidates.
- Long duration^[54]

Methods of co-processing⁶⁵

- Spray drying
- Wet granulation
- Melt extrusion
- Granulation
- Solvent evaporation
- Hot melt extrusion
- Co-transformation
- Milling

Spray drying

This spray drying technique allows the conversion of feed from a fluid state into dried particle. The feed can be a solution, suspension, dispersion, or emulsion. The dried product can be formed in the powders, granules, or agglomerates and these are depending upon the physical and chemical properties of feed and the dryer design final powder properties needed. It is a continuous particle processing drying operation. The spray drying process parameters like inlet air temperature, atomization air pressure, feed rate, liquid viscosity, solid content in feed, disc speed can be helped in design particle with desire characteristics^[55]. hence spray drying process can be desire as consisting of four steps:

- Atomization of the liquid into droplets.
- Contact of the droplet with the warm drying gas.
- Fast evaporation of the droplets to form dry particles.
- Recovery of the dry particles from the drying gas, using a cyclone

1.9.3.2. Wet granulation

Wet granulation is a conventional and simple method for co- processed adjuvant production. Fluid bed granulators and high shear mixers are two commonly used equipment used for the same. In fluid bed granulation, the powder mix is subjected to fluidization by a flow of air injected upwards through the bottom screen of the granulator. The binding solution is sprayed in the opposite direction to the air flow on the powder bed. The solid particles are mixed with the liquid droplets and hit the bed

which results in adhesion and eventually the formation of granules. Partial drying by the fluidizing air occurs continuously during granulation. In high-shear granulation, an impeller keeps the powder in agitation in a closed vessel. The binder solution is sprayed from the top. With the new single-pot technology, drying occurs in the same system. The granules formed are understandably denser than those obtained in fluid bed granulation^[56]

Melt extrusion

Melt extrusion is a process of formation of small beads, pellets from the molten mass which extruded through extruder. Extruders consist of four distinct parts:

- An opening through which material enters the barrel that may have a hopper that is filled with the materials to be extruded.
- A conveying section (process section), which forms the barrel and the screws that transport, and where applicable, mix the material.
- An orifice (die) for shaping the material as it leaves the extruder.
- Downstream auxiliary equipment for cooling, cutting and/or collecting the finished Product^[55]

Granulation

Granulation is the act or process of forming or crystallizing into grains. Granules typically have a size range between 0.2 to 4.0 mm depending on their use. In pharmaceutical industry, two types of granulation technologies are employed, namely, Wet granulation and Dry Granulation. Wet granulation is the most preferred method for coprocessing.^[56]

Solvent evaporation

This process is carried out in a liquid manufacturing vehicle. The coating excipient is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core excipient material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the proper size microcapsule. The mixture is then heated (if necessary) to evaporate the solvent.^[57] Once all the solvent is evaporated, the liquid vehicle temperature is reduced to ambient temperature (if needed) with continued agitation. At this stage, the microcapsules can be used in suspension form, coated on to

substrates or isolated as powders. The core materials may be either water -soluble or water- insoluble material

Hot melt extrusion

Hot melt extrusion uses heat with a temperature greater than 80°C. This method is not suitable for thermos labile materials. The excipients are melted and then pressurized through the die and solidify into a variety of shapes. The solvent is not needed in the process as the molten polymer can function as a thermal binder. ^[57]

Co-transformation

Co-transformation technique involves the application of heat or solvent effect to “open-up” that is for swelling the particle of one excipient. The other excipients are incorporated into the “opened-up” structure of the forementioned excipient.^[58] The augmented excipient strengthens the functionality of the end product.

Milling

A roller mill, ball mill, bead mill, millstone mill, jet mill or a hammer mill can be used to perform milling or dry grinding. The excipients are premixed and passed through a high-speed milling machine. During the process of milling, the particles meet each other and form bonds when they are subjected to force to mill or pass through the screen. Rao et al. (2012) applied this technique to co-process cross-linked polyvinylpyrrolidone and calcium silicate.^[59]

Table 1.2 Commercially available Co-processed Excipients Used in Direct Compression

Co-processed excipients	Trade name	Manufacturer	Advantages
Mannitol, hydroxypropyl methylcellulose	Pearlitol	Roquette	Used in direct compression of controlled oral tablets, binder ^[60]
Microcrystalline cellulose,colloidal silicon dioxide	Dicomsanaq ® sp206	Pharma trans sanaq	Used in direct compression of hygroscopic and moisture sensitive apis and has excellent flow properties ^[60]
Lactose monohydrate, cellulosemicro crystalline	Dicom sanaqml011	Pharma trans sanaq	Enhance the stability and effectiveness during Manufacturing product process and high compressibility, superior dilution properties and rapid disintegrating ^[61]
Spray granulated d-mannitoland croscarmellose sodium	Parteck® odt	Merck kga	Directly compressible excipient designed for orally disintegrating tablets and provided rapid disintegration and exceptional strength as well as a pleasant taste and mouthfeel ^[61,62]
Hypromellose and lactose	Retalac®	Meggle	Improved flow and bendability,enhancing compatibility in direct compression

70% alpha-lactose monohydrate, 20 % microcrystalline cellulose(mcc) and 10 % white, native corn starch	Combilac®	Meggle	Improved compaction properties compared to an equivalent admixture of individual ingredients, providing robust tablets with minimal friability, and assuring rapid,hardness independent tablet disintegration for effective API release ^[62]
Microcrystalline cellulose, colloidal silicon dioxide, mannitol, fructose,crospovidone	Prosolv® odtg2	Rs pharma	Smooth and creamy mouthfeel,Excellent flowability, excelle blending ntcharacteristicsfor improved content uniformity, High patient compliance ^[63]
Microcrystalline cellulose, colloidal silicon dioxide, mannitol,fructose, crospovidone	Prosolv® odtg2	Rs pharma	Smooth and creamy mouthfeel,Excellent flowability,excellent blending characteristics for improvedcontent uniformity, High patient compliance ^[64,65]
Crospovidone, monohydratemannitol, monohydrate lactose	Disintequik™odt	Kerry	Direct tableting operations for use in orally disintegrating tablets. It can be blended with a flavor, active, suitable lubricant, additional sweetener if desired ^[65]

Microcrystalline cellulose, monohydrate lactose	Disintegrants	Kerry	Direct tableting operations where hard tablets and fast disintegration are required. [64,65]
Carmellose, croscopovidone, mannitol, microcrystalline cellulose	Granfiller-d	Daicel group and nichirin-chem	Direct compression tablets, high tablet hardness and rapid disintegration [62,63]
Sucrose 3%, Dextrin microcrystalline Cellulose, silicon dioxide	Dipac	Penwest pharmaceuticals company	Directly compressible, better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability [65,66]
Lactose and cellulose	Cellactose	Meggle	High compressibility, good mouth feels, better tableting At low cost [66]
Sucrose and dextrin	Dipac	Penwest pharm	Directly compressible grade
Microcrystalline cellulose and silicon dioxide	Prosolv	Penwest pharmaceuticals	Better flow, reduced sensitivity to wet granulation, better hardness of tablet, reduced friability [67]
Microcrystalline cellulose and guar gum	Avicel ce-15	Fmc corp.	Less grittiness and minimal chalkiness

Calcium carbonate and sorbitol	Formaxx	Merck	High compressibility, excellent taste masking, free flow, superior content uniformity, controlled particle size distribution ^[68]
Microcrystalline cellulose and lactose	Microcelac	Meggle	Capable of formulating high dose, small tablets with Poorly flowable active ingredients ^[69]
Lactose and maize starch	Starlac	Meggle	Good flowability due to spray drying, the acceptable crushing force due to lactose content and rapid disintegration ^[70]
Lactose,3.2%kallidone kallidone cl	Ludipress	Basfag, ludwigsha fen , Germany	Low degree of hygroscopicity, good flowability, tablet hardness independent of machine speed ^[69,70]
Lactose,25% cellulose	Cellactose	Meggleg mbh&co. Kg, Germany	Highly compressible, good Mouthfeel, better tableting at low cost ^[71]

CHAPTER - 2

AIM AND OBJECTIVE

According to BCS Classification, Dapsone is a Class-II (Low solubility and High Permeability) drug have low oral bioavailability due to Low Solubility. To minimize such problems Dapsone is formulated in the form of fast dissolving tablets where the drug is rapidly disintegrated in mouth within fraction of seconds and improves the oral drug bioavailability.

Hence, in the present study an attempt has been made to formulate and evaluate fast dissolving tablets of Dapsone by direct compression method using co-processed super disintegrants such as sodium starch glycolate, (SSG) croscarmellose sodium(CCS) and crospovidone (CP), microcrystalline cellulose (MCC) as direct compressible vehicle with other excipients like sweetener and flavor with a view to develop a convenient means of administration to those patients suffering from difficulties in swallowing.

OBJECTIVES OF THE PRESENT WORK

- ✓ To study the preformulation factors of *Dapsone* such as, solubility, melting point, pH, λ_{max} and standard calibration curve of drug in phosphate buffer pH 6.8.
- ✓ To study the drug-polymers compatibility by FT-IR spectroscopy.
- ✓ To formulate fast dissolving tablets of Dapsone using co processed super disintegrants
- ✓ To study the pre-compression parameters like bulk density, tapped density, angle of repose, Carr's index and Hauser's ratio for prepared tablet formulations
- ✓ To evaluate prepared tablets by different post-compression parameters such as thickness, hardness, friability, in vitro dispersion time, content uniformity, weight uniformity, wetting time, water absorption ratio and in vitro dissolution study.
- ✓ To study *in vitro* dissolution of fast dissolving tablets Dapsone in phosphate buffer pH 6.8 solution.

PLAN OF WORK

- Literature survey
- Selection of drug and its Charecterization
- Selection of Excipients
- Preformulation studies
 - Solubility
 - Melting point
 - Determination of $\lambda_{\max}$
 - Preparation of standard calibration curve of Dapsone
- Preparation of Dapsone solid dispersions
- Charecterization of prepared Dapsone solid dispersions
 - Solubility
 - Dissolution studies
 - XRD Charecterization
- Preparation of co-processed excipients
- Pre-compression parameters
 - Angle of repose
 - Bulk density
 - Carr's index
 - Hauser's ratio
 - Drug- Excipients Compatibility by FT-IR studies.
- Formulation of Dapsone fast disintegrating tablets by use of co-processed excipients by direct compression.
- Charecterization of Prepared Dapsone FDT (Post-compression parameters)
 - Friability
 - Hardness
 - Weight Variation
 - Thickness

- Drug Content
- Water absorption ratio
- Wetting time
- In vitro Dispersion time
- In vitro dissolution time

CHAPTER - 3

REVIEW OF LITERATURE

3.1. Vineet bharadwaj *et al.*, has formulated mouth dissolving tablet of the mouth dissolving tablet of Amlodipine using different super disintegrants by sublimation method. Different concentrations (2%, 4% and 6%) of super disintegrants such as Ac-Di-Sol, sodium starch glycolate, Kollidon-CL were used respectively. Camphor was used as a sublimating agent. Tablets are prepared by direct compression and evaluated for hardness, friability, weight variation, wetting time, thickness, water absorption ratio disintegrating time, uniformity of content and in-vitro drug release. All the tablets had hardness 2.3-3.7 kg/cm² and friability of all formulations was less than 1%, weight variation and drug content were within official limit. Amongst all formulations, formulation F9 prepared by 6% Ac-Di-Sol showed least disintegrating time of 11sec. and faster dissolution. Formulation F9 was then studied for accelerated stability studies as per ICH guidelines for 60 days that shows no remarkable change in the formulation^[66]

Margret Chandira *et al.*, developed fast dissolving tablets of Rupatadine fumarate is H1 and PAF antagonist used primarily in treatment of allergic rhinitis symptoms, seasonal or perennial. Fast dissolving tablets of Rupatadine fumarate were prepared by direct compression method. The tablets were prepared by using mannitol, microcrystalline cellulose as filler, croscopovidone, croscarmellose, SSG as super disintegrants in different concentration (2-5%). Total twelve formulations and one control tablet were prepared and evaluated for Hardness, friability, weight variation, content uniformity, wetting time, water absorption ratio, disintegration time and invitro drug release. Optimized formulation F4 was compared with control formulation for disintegration time and % drug release. The stability studies were performed as per ICH guidelines. The Optimized formulation (F4) showed no significant variations for the tablets parameters and it was stable for the specified time period. It was

concluded the FDT for Rupatadine fumarate can be formulated for emergency treatment of allergic rhinitis. ^[67]

C.P. Jain et al has formulated fast dissolving tablets of valsartan using different super disintegrants by direct compression method. FDTs were evaluated for physicochemical properties and in vitro dissolution. Effect of disintegrant on disintegration behavior of tablet in artificial saliva, pH 5.8 was evaluated. Wetting time of formulations containing Crospovidone was least and tablets showed fastest disintegration. The drug release from FDTs increased with increasing concentration of super disintegrants and was found to be highest with formulations containing Crospovidone. The release of valsartan from FDTs was found to follow non-Fickian Diffusion kinetics. ^[68]

Raval s.b et al., developed mouth dissolving tablets of Tramadol hydrochloride using ion exchange resin Indion 294 as a taste masking agent. Ion exchange resins and tasteless granules were prepared with Indion 294 in weight ratio of 1:2. Prepared complex was further examined through U.V. Visible Spectroscopy. The mouth dissolving tablets of both resins and granules were prepared with different super disintegrants e.g. cross carmellose sodium, crospovidone & Indion 234 in different concentration. The blend was examined for their flow properties. The tablets were evaluated for physicochemical properties. The tasteless blends having good flow properties. The prepared zero-defect mouth dissolving tablets were passed all the official and non-official parameters. The disintegration time was also tested and was found to be less than one minute. A tablet having resins shows less time for onset of action of drug due to enhanced and fast release of Tramadol hydrochloride. It was concluded that tablets prepared by addition of super disintegrant Indion 234 has less disintegration time, fast and more drug release than those prepared by crospovidone. ^[69]

Mohini k et al. developed fast dissolving tablet of amlodipine besylate for rapid action. Sublimation method was adapted to prepare the tablets by using a 2 full factorial design. FT- IR and D.T.A studies revealed that there was no physio-chemical interaction between amlodipine besylate and other excipients. All formulations are evaluated for pre-compression and post-compression parameters, wetting time, water absorption ratio. The results obtained showed that the quantity of starch potato, sodium starch glycolate, camphor significantly affect response variables. The results indicate that the optimized tablet formulation provides a short DT of 8 sec with sufficient crushing strength and acceptable friability. Stability studies of optimized formulation revealed that formulation is stable. ^[70]

Rashmi Dahima et al. developed fast dissolving tablets of amlodipine besylate by the preparation of its solid dispersion with cross povidone using solvent evaporation method. Drug polymer interactions were investigated using differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR). Surface morphology of solid dispersion particle determined by SEM study. Dissolution rate of solid dispersion was determined in 0.01 N HCl at 75 rpm. The obtained results showed that dispersion of the drug in the polymer considerably enhanced the dissolution rate. The drug-to-carrier ratio was the controlling factor for dissolution improvement. FTIR spectra revealed no chemical incompatibility between the drug and cross povidone. As indicated from DSC data, amlodipine besylate was in the amorphous form, which explains the better dissolution rate of the drug from its solid dispersions. For the preparation of amlodipine besylate mouth dissolving tablets, solid dispersion in the ratio of 1:4 with cross povidone was used with various disintegrants. In conclusion, this investigation demonstrated the potential of experimental design in understanding the effect of the formulation variables on the quality of mouth dissolving tablets containing solid dispersion of a hydrophobic drug. ^[71]

Margret Chandira *et al.*, formulated mouth dissolving tablets of Etoricoxib by variety of super disintegrants like primogel, kollidone, Ac-Di-sol, L-HPMC, L-HPC, were selected and tablets were prepared by direct compression method in different concentration like 4% and 8%. The prepared tablets were evaluated for weight variation, hardness, friability, *in vitro* disintegration time, wetting time, *in vitro* dissolution study, etc. formulation f-9 shows the lowest disintegration time (44sec) and wetting time (52sec). *In vitro* dissolution studies revealed that formulation F-9 containing 8% L-HPC showed 97% drug release at the end of 20 min.^[72]

Rajesh S. Jadon *et al.* developed a bitterless oral disintegrating tablet of Lornoxicam. Taste masking was done by complexing Lornoxicam with amino alkyl methacrylate copolymer (Eudragit EPO) in different ratios. In vitro release profile obtained at pH 6.2 indicate that perceivable amount of drug will not be released in saliva while high percentage release (more than 80 % in 30 mins.) would be obtained at acidic pH 1.2 of the stomach. Three super disintegrants were used while preparing the tablets e.g. sodium starch glycolate, crospovidone and croscarmellose sodium. The tablets were evaluated for different properties like drug content, hardness, friability and disintegration time. The tablets shown good taste and disintegration in oral cavity.^[73]

Bhupendra G. Prajapati *et al.*, formulated taste masked orally disintegrating tablets of piroxicam, out of twelve formulations (F-1 to F-12), F-11 formulation containing crospovidone XL 10 %, drug: polymer 1:0.35, aspartame 6% and sodium lauryl sulphate 0.5%, showed optimum characteristics of Oro dispersible tablet (ODT) of piroxicam with sufficient crushing strength (5.5 to 6.5 kp), friability (0.18%), wetting time (28 sec) and disintegration time (22 sec). In-vitro dissolution profile studies revealed that 82.3% drug was released within 5 min. The study concluded that crospovidone XL and Eudragit EPO can successfully be used as super disintegrant and taste masking excipient respectively.^[74]

Gopal.V et al., formulated orally disintegrating tablets containing antihistamines like Loratadine using different pharmaceutical compositions with simple manufacturing procedures to enhance patient compliance. Loratadine was formulated into orally disintegrating tablets by direct compression method using suitable excipients like Maltodextrin, Mannitol, Micro crystalline cellulose, combination of Mannitol with Starch, Croscarmellose sodium, Citric acid, Sodium bicarbonate along with Mint flavor, which were evaluated by using simple analytical techniques. The taste of the formulation was enhanced using artificial sweetener Aspartame and Mint flavor. The tablets were evaluated for weight variation, hardness, friability, drug content, wetting time and disintegration time along with *invitro* dissolution. It was observed that the direct compression process using commercial grades of excipients like combination of Mannitol with Starch and Micro crystalline cellulose as directly compressible diluents along with super disintegrants like Croscarmellose Sodium was found to be more promising to prepare orally disintegrating tablets.^[75]

Reeta Rani Thakur et al., prepared oral disintegrating tablets of salbutamol sulphate using various super disintegrates crospovidone, sodium starch glycolate, croscarmellose sodium following by direct compression technique. Nine formulations having different super disintegrants at different concentration levels were prepared to assess their efficiency and critical concentration level. The tablets were evaluated for hardness, friability, weight variation, disintegration time, diameter, thickness and wetting time, in vitro dissolution studies. All the formulation showed disintegration time in range of 8-20 min. These disintegrants were used in three different concentration 7.5%, 10%, 12.5% by using three different disintegrants. Then study the effect of disintegration behavior by comparative study in between them by using same disintegrants and different disintegrants at different concentration. We found that croscarmellose and sodium starch glycolate at 12.5% were optimum and in crosspovidone formulations in different concentration was no significant effect in comparison of all formulations we found that formulation of sodium starch glycolate was best at 12.5%, because it releases app. 100% in 8 minutes.^[76]

Bhupendra G. Prajapati *et al.*, formulated directly compressible orally disintegrating tablets of Cinnarizine with different super disintegrants such as crospovidone, croscarmellose sodium, and sodium starch glycolate on disintegration time was studied. The disintegration time of the optimized CP5 batch was 25 sec. good correlation was observed between disintegration time and water absorption ratio (R) for each of three super disintegrants at concentrations studied. Considering the 'R' values and disintegration time, crospovidone was significantly superior compared to other two super disintegrants tested. Release of drug was faster from formulations containing 6% crospovidone (CP5) compared to the marketed conventional Cinnarizine tablet. Differential scanning calorimetric studies did not indicate any excipient incompatibility, either during mixing or after compression. Finally concluded that directly compressible orally disintegrating tablets of cinnarizine with lower friability, acceptable taste, and shorter disintegration times were obtained using crospovidone at optimized concentrations.^[77]

Nitin Bansal *et al.*, formulated orally disintegrating tablets of ondansetron HCl using natural Super disintegrants by dry granulation method using different concentrations of super disintegrants such as modified gum karaya, modified natural agar, croscarmellose sodium and sodium starch glycollate. The formulations were evaluated for weight variation, hardness, friability, drug content, wetting time, in vitro disintegration time and in vitro dissolution study. gum karaya and modified natural agar produce rapid disintegration of tablets. The optimized formulation showed acceptable physical characteristics. The optimized batch produced complete drug release within 6 minutes. The incorporation of clove oil provided additional properties such as symptomatic relief from nausea and vomiting, good mouth feels and taste masking. Kinetic analysis showed that drug release from optimized formulation was adequately described by first order release kinetics.: Modified gum karaya and modified natural agar can be used as an alternative super disintegrants to commonly available synthetic and semisynthetic super disintegrants due to their low cost, biocompatibility as well as easy availability.^[78]

Shayeda *et al.*, formulated Oral Disintegrating Tablets (ODT) of metoprolol Tartrate using super disintegrants- sodium starch glycolate, cross carmellose sodium and cross povidone and to observe the effect of various diluents on the release profile of tablets. Formulations from F1 to F12 were prepared with various super disintegrants by using mannitol as diluent. From these formulations tablets prepared with cross povidone showed good release profiles. Formulations F13 to F16 were prepared by using cross povidone as super disintegrant and spray-dried lactose as diluent and formulations F17 to F20 were prepared by using cross povidone as super disintegrant and dibasic calcium phosphate as diluent. Based on disintegration time and in vitro drug release profile F14 was selected as optimized formulation. Formulating as an ODT will also aid in rapid onset of action as the tablets disintegrate in less than a minute. Taste masking which is an important aspect of ODT formulation is achieved by using the sweetener aspartame. No chemical interaction between drug and excipients was confirmed by FTIR studies.^[79]

CHAPTER - 4

DRUG PROFILE

DAPSONE

Structure of the Compound

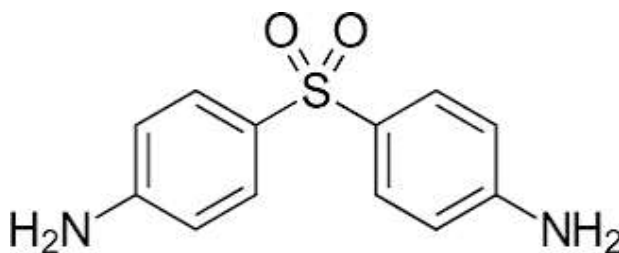


Fig 4.1 Structure of Dapsone

Chemical Name: 4-(4-aminophenyl) sulfonyl aniline

Molecular weight: 248.301

BCS Classification: Class II (Low solubility and high permeability)

Molecular formula: C₁₂H₁₂N₂O₂S

Description: White or slightly yellowish crystalline powder. Slight odor and tasteless.

Solubility: Practically insoluble in ether and water, freely soluble in chloroform, in pyridine and in acid alcohol water mixture, slightly soluble in dilute acids and in alcohol.

Storage: It should be protected from moisture.

Melting point: 217°-224°C,

Category: Antiacne, Leprostatic

Pharmacokinetic properties:

- Bioavailability: **70-80 %**
- Protein Binding: **70-90 %**
- Metabolism: **Liver (CYP2E1 mediated)**

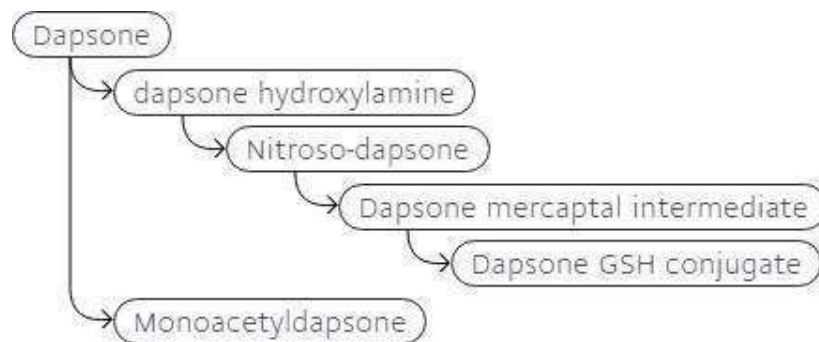


Fig 4.2 Mechanism of Dapsone

- Elimination Half Life: **20-30 hours**
- Excretion: **Kidney**

Mechanism of action:

Dapsone acts against bacteria and protozoa in the same way as sulphonamides, that is by inhibiting the synthesis of dihydrofolic acid through competition with para-amino-benzoate for the active site of dihydropteroate synthetase. The anti-inflammatory action of the drug is unrelated to its antibacterial action and is still not fully understood.

Available forms: Available with or without a prescription

- Dapsone is available in 25 mg and 100 mg tablets
- Topical dapsone is available in 5% and 7.5% gel formulations

Dose: 25-100 mg

Contraindications: Hypersensitivity to cyclizine; asthma; glaucoma; emphysema; chronic pulmonary disease; shortness of breath; difficulty breathing; urinary retention caused by enlarged prostate.

Adverse Effects:

- **Cardiovascular:** Hypotension; tachycardia; palpitations.
- **CNS:** Drowsiness; excitation; nervousness; restlessness; insomnia; euphoria; vertigo; hallucinations.
- **Dermatologic:** Rash; urticaria.

- **ENT:** Dry nose and throat; visual disturbances; tinnitus.
- **GI:** Nausea; vomiting; dry mouth; diarrhea; constipation; anorexia.
- **Genitourinary:** Urinary frequency; urinary retention; difficulty urinating.

EXCIPIENT PROFILE

SODIUM STARCH GLYCOLATE

Structural formula:

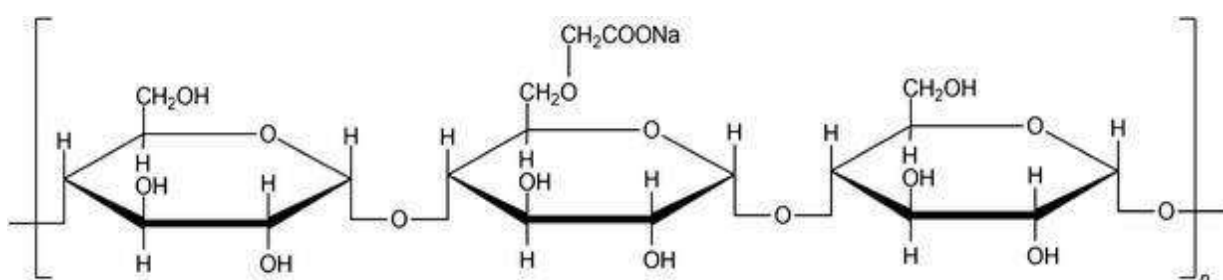


Fig 4.3 Sodium Starch Glycolate

Synonyms : Explotab, Primogel.

Non-proprietary Name: BP-Sodium starch glycolate, USPNF-Sodium starch glycolate.

Functional category: Tablet and capsule disintegrant.

Chemical names : Sodium carboxymethyl starch.

Solubility : Practically insoluble in water, sparingly soluble in ethanol

Incompatibilities : Incompatible with ascorbic acid.

Description: Sodium starch glycolate is a white to off-white, odorless, tasteless, free flowing powder. It consists of oval or spherical granules, 30-100 μm in diameter with some less spherical granules ranging from 10-35 μm in diameter.

Stability and storage conditions: It is a stable material. It should be stored in a well closed container to protect from wide variations in humidity and temperature that may cause cracking

Applications: As a disintegrant in tablet (wet granulation and direct compression) and Capsule formulation in 2-8% concentration

CROSPVIDOE

Structural formula:

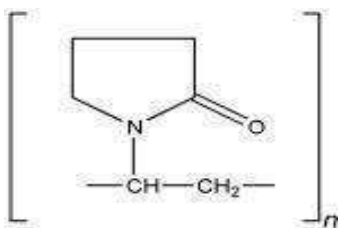


Fig 4.4 Structure of Crospovidone

Synonyms : Crosslinked povidone, E1202, Kollidon CL, Polyplasdone XL, Polyplasdone XL-10, PVPP and 1-vinyl-2-pyrrolidinone homopolymer.

Non-proprietary Names: BP-Crospovidone, PhEur-Crospovidonum, USPNF: Crospovidone.

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

Molecular weight : $(C_6H_9NO)_n$ $n > 1\,000\,000$.

Functional category : Tablet disintegrant.

Description: Crospovidone is a white to creamy-white, finely divided, Free flowing, practically tasteless, odorless and hygroscopic powder

Stability and storage conditions: Since crospovidone is hygroscopic, it should be Stored in an airtight container in cool, dry place

Applications in pharmaceutical formulation or technology: Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2-5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets.

MICROCRYSTALLINE CELLULOSE

Structural formula:

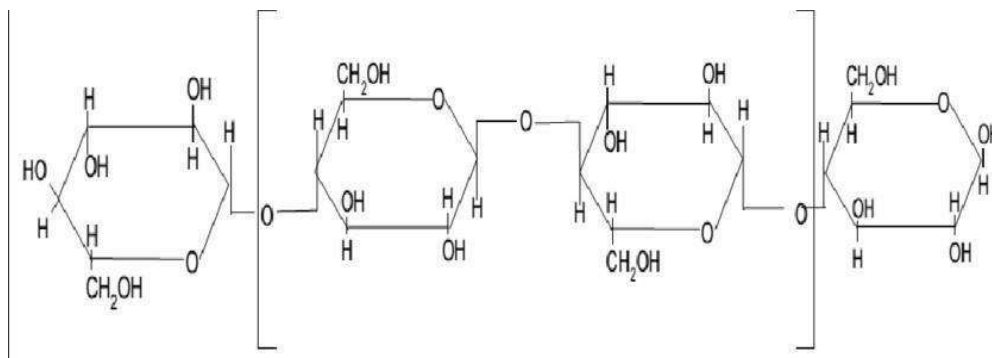


Fig 4.5 Structure of Microcrystalline cellulose

Synonyms : Cellulose gel: Crystalline cellulose: Avicel PH101, 102.

Non-proprietary name: NF-Microcrystalline cellulose, USP- Microcrystalline cellulose

Chemical name: Cellulose

Empirical formula: (C₆H₁₀O₅)_n = 220.

Molecular weight : 36,000(approx.).

Density : Apparent density - 0.28g/cm³; Tap density - 0.43g/cm³.

Functional category : Tablet and capsule diluent, tablet disintegrant

Description: Purified, partially depolymerized cellulose occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

Solubility: Insoluble in water, dilute acids and most organic solvents, slightly soluble in 5% w/v NaOH solution.

Storage conditions: Stable, hygroscopic. Store in a well closed container.

Applications: Tablet binder/diluent, tablet disintegrant, tablet glidant.

ASPARTAME

Synonyms : APM, Sanecta, Aspartyl phenylamine methyl ester,
Nutrasweet, Tri-sweet.

Non-proprietary name: USP - Aspartame, IP - Aspartame, BP - Aspartame.

Chemical name : L-aspartic acid, L-phenylalanine.

Functional category : Sweetening agent.

Description: It occurs as white and almost odourless crystalline powder.

Solubility: Slightly soluble in ethanol (95%), sparingly soluble in water, solubility increases at higher temperature and at more acidic pH.

Stability and Storage Conditions: It is stable in dry conditions. In presence of moisture, hydrolysis occurs. Degradation also occurs during prolonged heat treatment. Bulk material should be stored in a well-closed container, in a cool, dry place.

Safety: The WHO has set an acceptable daily intake of 40 mg/kg body weight. Reported adverse effects are headache, grandmal seizures, memory loss, gastrointestinal and dermatological symptoms.

Applications: It is used as an intense sweetening agent in tablets, powder mixes and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste and has sweetening power of 180-200 times that of sucrose.

MAGNESIUM STEARATE

4.2.6

Synonyms : Metallic stearic; magnesium salt.

Non-proprietary name: NF- Magnesium stearate; BP/EP- Magnesium stearate.

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

Chemical names : Octadecanoic acid; magnesium salt; magnesium stearate

Molecular weight : 591.3.

Density (He) : 1.03-1.08 g/cm³

Bulk volume : 3.0-8.4 ml/g

Tapped volume : 2.5-6.2 ml/g

Functional category : Tablet and capsule lubricant.

Description: It is a fine, white, precipitated or milled, impalpable powder of low bulk density having a faint characteristic odour and taste

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

Stability and storage conditions: Stable, non-self-polymerizable. Store in a cool, dry place in a well closed container.

Incompatibilities: Incompatible with strong acids, alkalis, iron salts and with strong oxidizing materials.

Safety: Described as inert or nuisance dust. OSHA has adopted limits of 15mg/m³ for the total dust and 5mg/m³ for the respirable fraction. Dust clouds of magnesium stearate may be explosive. However, oral consumption of large quantities may result in some laxative effect or mucosal irritation.

Applications: Tablet and capsule lubricant, glidant and anti-adherent in the concentration range of 0.25 to 2.0%.

CHAPTER - 5

MATERIALS AND METHODS

MATERIALS

The following materials of Pharma grade or the best possible Laboratory Reagent (LR) were used as supplied by the manufacturer. The double distilled water was used in all experiments.

Table 5.1 List of chemicals used with grade and supplier

SINO.	Materials used	Grade	Manufacturer
1.	Dapsone	API	Invitron Labs, Hyderabad
2.	Microcrystalline cellulose	LR	S D fine chemical Ltd, Mumbai
3.	Sodium starch glycolate	LR	Shreeji chemicals, Mumbai
4.	Crosscarmellose sodium	LR	Shreeji chemicals, Mumbai
5.	Crospovidone	LR	Shreeji chemicals, Mumbai
6.	Mannitol	LR	S D fine chemical Ltd, Mumbai
7.	Magnesium sterate	LR	S D fine chemical Ltd, Mumbai
8.	Aspartame	LR	Shreeji Chemicals, Mumbai
9	Potassium dihydrogen orthophosphate	LR	S D fine chemical Ltd, Mumbai
10	Sodium hydroxide	LR	S D fine chemical Ltd, Mumbai

Table 5.2 List of instruments used

SI NO	Instrument	Manufacturer
1.	UV visible spectrophotometer	Shimadzu Corporation, Japan.
2.	FTIR spectrophotometer	IR-Affinity-1, Shimadzu, Japan.
3.	Electronic balance	Citizen scales Pvt. Ltd
4.	Digital pH meter	Digisun Electronics, Hyderabad
5.	Bulk density apparatus	Biological museum, Agra
6.	Tablet punching machine	Cadmach, Ahmedabad
7.	Roche friabilator	Biological museum, Agra
8.	Tablet hardness tester	Pfizer
9.	USP dissolution XXIII apparatus	Electrolab TDL-08L
10.	Disintegration apparatus	Electrolab

PREFORMULATION STUDIES

Organoleptic Characteristics

The color, odor, and taste of the drug were characterized and recorded using descriptive terminology

Melting Point

Melting point of pure Dapsone was determined by open capillary method. The capillary tube was closed at one end by fusion and was filled with Dapsone by repeated tapings. The capillary tube was placed in a digital melting point apparatus. The instrument was set to automatically at the rate of 100°C rise of temperature per minute. The rise in temperature was viewed through magnifying lens. The temperature at which the drug started melting was recorded. This was performed thrice and the average value was calculated.

Solubility:

Solubility of the Dapsone was determined in different solvents like water, 0.1 N HCl, phosphate buffer pH 6.4, alcohol, acetone etc.

UV absorption maxima of Dapsone

UV scanning was done in Shimadzu double beam UV/Visible spectrophotometer using 10 µg/ml drug solutions in the wave length range of (200-400nm). Phosphate buffer 6.4 used as a blank.

Preparation of Calibration Curve:

Preparation of stock solution

- Dapsone (100mg) was accurately weighed and transferred into the 100 ml standard volumetric flask.
- It was dissolved in phosphate buffer (P^H 6.4) and volume was made up to the mark (to get a 1000 µg/ml solution).
- From this 10 ml was pipette out and then diluted up to 100 ml with phosphate buffer the (P^H 6.4) From that solution again 10 ml pipetted out and diluted up to 100 ml in volumetric flask with phosphate buffer the (P^H 6.4) to get a stock solution of 10µg/ml

Preparation of Standard Curve:

From the stock solution 2, 4, 6, 8 and 10 ml were transferred to 10 ml standard volumetric flasks and diluted with phosphate buffer the (PH 6.4) up to the mark to obtain Dapsone concentration of 2, 4, 6, 8 and 10 µg/ml respectively. Absorbance of each solution was measured at 260 nm.

PREPARATION OF SOLID DISPERSIONS

Solid dispersions of Dapsone were prepared by solvent evaporation method. Accurate amount of dapsone was weighed and taken in a China dish, dissolved in methanol and then carrier was added (Urea in ratio of 1:1, 1:2 & 1:3). The solvent was evaporated at room temperature and dried in hot air oven at 500 C for 4 hours. The resultant mass was passed through sieve no. 60 and stored in desiccator.

Physical mixtures:

Physical mixtures (PMs) having the same weight ratio were prepared by thoroughly mixing appropriate amounts of Dapsone and urea in a mortar until a homogenous mixture was obtained. the result was sieved through a 60# sieve and denoted as PM.

Characterization of solid dispersions of Dapsone with Urea:

b) Drug content:

An accurately weighed quantity of solid dispersion equivalent to 25mg Dapsone was taken into 100 ml of volumetric flask. Dissolved in phosphate buffer pH 6.4 and the volume were made up with the same. An aliquot of the filtrate was diluted and analyzed spectrophotometrically (UV-1700, Shimadzu Corporation) at 260 nm.

c) Dissolution study

- Apparatus: **USP type-II (Paddle)**
- Dissolution Medium: **pH 6.8 Buffer**
- Volume of Dissolution medium: **900 ml**
- RPM: **50**
- Sample with drawn: **5 ml**
- Sample replaced: **5 ml**
- Sampling time: **every 2 minutes**
- Wavelength: **260 nm**

d) Powder X- Ray Diffraction (PXRD)

PXRD patterns were recorded using Philips PW 1729 X- ray generator, USA fitted with a copper target, a voltage of 40 kV, and a current of 30 mA. The scanning rate was 1°/min over a 2 θ range of 1-50°. Powder X- ray diffraction patterns were traced for carvedilol, physical mixture and solid dispersions. The samples were slightly ground and packed into the aluminum sample container.

PREPARATION OF CO-PROCESSED SUPERDISINTEGRANTS

The co-processed super disintegrants were prepared by solvent evaporation method. Crospovidone and sodium starch glycolate (in the ratio of 1:1, 1:2, 1:3, 2:1, 3:1) were mixed together with 10 ml of isopropyl alcohol. The contents of beaker (250 ml capacity) were mixed thoroughly and stirring continue till most of isopropyl alcohol evaporated. The wet coherent mass was granulated through # 44 mesh sieve. The wet granules were dried in a hot air oven at 60°C for 20 minutes. The dried granules were sifted through # 44 mesh sieves and stored in airtight container till further use.

Table 5.3 Preparation of Co-processed excipients

Code of mixture	PM1	PM2	PM3	PM4	PM5	CP1	CP2	CP3	CP4	CP5
Crospovidone	1	1	1	2	3	1	1	1	2	3
SSG	1	2	3	1	1	1	2	3	1	1

PM - Physical Mixture

CP - Co-processed Super disintegrants of CP and SSG in different ratios (1:1,1:2, 1:3, 2:1,3:1),

Cp - Crospovidone,

SSG - Sodium Starch Glycolate

DRUG & EXCIPIENT COMPATIBILITY

In the preparation of tablets formulation, drug and excipients may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate excipients. FT-IR spectroscopy was employed to ascertain the compatibility between dapsone and the selected polymers. Potassium bromide, pure drug and the polymers were heated to 105°C for one hour to remove the moisture content if present in a hot air oven. Then in presence of IR lamp, potassium bromide was mixed with drug and/or polymer in 9:1 ratio and the spectra were taken. FT-IR spectrum of Dapsone was compared with FT-IR spectra of polymers.

PRE-COMPRESSION PARAMETERS

Bulk Density:

Bulk and tapped density determination were carried according to USP 'Bulk density' and 'Tapped density' method-1 respectively. 50 gm of active ingredient was in 250ml graduated cylinder for bulk density. For tapped density the cylinder was tapped 100 times. Bulk density, tapped density and Carr's index were calculated by the following equation (1) & (2):

Tapped Density:

After measuring the bulk volume, the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to 300 taps drop per minute and operated for 500 taps. Volume was noted as (Va) and again tapped for 750 times and volume was noted as (Vb). If the difference between Va and Vb not greater than 2% then Vb is consider as final tapped volume. The tapped density is calculated by the following formula,

$$\text{Bulk density} = \frac{\text{Mass of the powder (M)}}{\text{Tapped volume (VT)}} \quad (1)$$

$$\text{Tapped density (Dt)} = \frac{\text{Mass of the powder (M)}}{\text{Tapped volume (VT)}} \quad (2)$$

Compressibility Index (Carr's Index)

The compressibility index of the granules was determined by Carr's compressibility index. Grading of the powders for their flow properties according to Carr's Index is shown in below table

Hausner's ratio

The Hausner ratio of the powder was determined by the following equation.

$$\text{Hausner 's ratio} = \text{TBD} / \text{LBD}$$

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

5.5.3 Angle of Repose (θ)

The frictional force in a loose powder or granules can be measured by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane.

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

Where,

Θ is the angle of repose

h is height of pile

r is radius of the base of pile

Different ranges of flowability in terms of angle of repose are given in below table.

Method: A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile, thereby evaluating the flowability of the granules. Height of the pile was also measured.

Table 5.4: Limits and their interpretation of flow properties:

S NO.	FLOW PROPERTIES	ANGLE OF REPOSE (°)	COMPRESSIBILITY INDEX (%)	HAUSNER'S RATIO
1	Excellent	25-30	<10	1.0-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Possible	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.59
7	Very very poor	>66	>38	>1.60

FORMULATION OF DAPSONE FAST DISSOLVING TABLETS

Preparation of tablets containing solid dispersions of Dapsone

Dapsone mouth dissolving tablets were prepared according to the proportion given in table. The raw materials were passed through a screen (Sieve No.# 40) prior to mixing. Powdered 1:3 ratio solid dispersion (Best proportion), containing amount equivalent to 50 mg Dapsone, was mixed with the other excipients and compressed on a rotator tablet punching machine equipped with flat-faced 10-mm punches. The tablet weight was adjusted to ~200 mg.

Preparation of Mixed blends of drug and excipients:

All the ingredients were weighed accordingly specified in the formulation and mixed well except magnesium stearate. Then the blend was passed through sieve no 60 which was used for the evaluation of flow properties.

Formulation of Tablets:

- To the mixed blend of powder and excipients finally add magnesium stearate
- The mixed blend was compressed with sixteen (16) station tablet punching machine using 7 mm flat punches with break line.
- Four punches in the sixteen-station compressor are fixed with die cavity and remaining is fixed with dummy punches.
- A minimum of 200 mg tablets for each batch were prepared.

Table 5.5 Formulation of Dapsone Fast dissolving Tablets

INGREDIENTS	CP0	PM1	PM2	PM3	PM4	PM5	CP1	CP2	CP3	CP4	CP5
	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)	(mg)
Dapsone	50	50	50	50	50	50	50	50	50	50	50
Crospovidone + Sodium Starch Glycolate	-	6	6	6	6	6	6	6	6	6	6
Aspartame	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3
Flavor	3	3	3	3	3	3	3	3	3	3	3
Microcrystalline cellulose (Avicel PH-102)	30	30	30	30	30	30	30	30	30	30	30
Mannitol (Pearlitol SD 200)	108	102	102	102	102	102	102	102	102	102	102
Total Weight	200	200	200	200	200	200	200	200	200	200	200

POST COMPRESSION PARAMETERS

The tablets after punching of every batch were evaluated for in-process and finished product quality control tests i.e. thickness, weight uniformity test, hardness, friability, drug content, in vitro dispersion time, water absorption ratio, wetting time and in vitro drug release studies. The results were tabulated in table no 6.10

Thickness

Thickness of tablets indicates the strength to withstand compression force applied during manufacturing process. Thickness of tablets was measured by digital caliper. The results were tabulated in table no 6.10

Hardness Test

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. The hardness was tested using Monsanto tester. "Hardness factor", the average of the six determinations, was determined and reported. The force was measured in kilograms per centimeter square. The results were tabulated in table no 6.10

Friability Test

It is not an official method but required for the shipment of the product. It is carried out by using Friabilator. The 10 or 20 tablets were weighed initially and transferred into a Friabilator and allowed to rotate 100 rotations. After the completion tablets were weighed

The % friability was calculated using the equation,

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

The results were tabulated in table no 6.10

Weight Uniformity Test

Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits ($\pm 7.5\%$). The total weight of tablets formulated was 150mg. The percentage deviation for weight uniformity of tablets as per IP limits is shown in below table.

Table 5.6 Weight Uniformity Test

Average weight of tablet	Percentage deviation
80 mg or less	± 10
More than 80 mg and less than 250 mg	± 7.5
250 mg or more	± 5

Any variation in the weight of tablet (for any reason) leads to either under medication or over medication. So, every tablet in each batch should have a uniform weight. Deviation within the IP permissible limit of 7.5% is allowed as the tablet weighs 200 mg. The results were tabulated in table no 6.10

In vitro dispersion Time

In vitro dispersion time was measured by dropping a tablet into a petridish containing 10 ml of phosphate buffer pH 6.8 solution (simulated saliva fluid). Three tablets from each formulation were randomly selected and tested. In vitro dispersion time was found and expressed in seconds. The results were tabulated in table no 6.11

Wetting time and Water absorption ratio

Wetting time of dosage form is related with the contact angle. Wetting time of the mouth dissolving tablets is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablet can be measured using a simple procedure. Two circular tissue papers of 10 cm diameter are placed in a petri dish having the same inner diameter. Ten ml of phosphate buffer solution, 6.8 pH containing Eosin, a water- soluble dye, is added to petri dish. A tablet is carefully placed on the surface of the tissue paper so that complete tablet was not immersed in the solution. Then, the time required for buffer to reach upper surface of the tablet is noted as wetting time. The results were tabulated in table no 6.11

Drug content determination

Procedure of determining drug content

Three uncoated tablets were selected randomly and average weight was calculated. Tablets were crushed in a mortar and accurately weighed amount of tablet powder was taken from the crushed blend. Then the samples were transferred to three 100 ml volumetric flasks and were diluted up to the mark with phosphate buffer (pH 6.8) solution. The contents were shaken periodically and kept for 24 hours for solvation of drug completely. The mixtures were filtered, appropriately diluted, and absorbances were measured at λ_{max} 229.50 nm against blank reference. The drug content in each tablet was calculated using the standard calibration curve of Dapsone in phosphate buffer pH 6.8 solution. The results were tabulated in table no 6.10

Drug Release Kinetics

To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models:

a. Zero order kinetics: Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation

$$Q_t = Q_o + K_o t$$

Where, Q_t = amount of drug dissolved in time t , Q_o = initial amount of drug in the solution K_o = zero order release constant.

b. First order kinetics: To study the first order release rate kinetics the release rate data were fitted to the following equation.

$$\text{Log } Q_t = \text{log } Q_o + K_1 t / 2.303$$

Where,

Q_t is the amount of drug released in time t ,

Q_o is the initial amount of drug in the solution,

K_1 is the first order release constant

c. Higuchi model: Higuchi developed several theoretical models to study the release of water- soluble and low soluble drugs incorporated in semisolids and or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media, the equation is

$$Q_t = K_H \cdot t^{1/2}$$

Where, Q_t = Amount of drug released in time t ,

K_H = Higuchi dissolution constant.

d. Korsmeyer - Peppas release model: Korsmeyer et al. derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas model.

$$M_t / M_\infty = K t^n$$

Where, M_t / M_∞ is a fraction of drug released at time t

k is the release rate constant and

n is the release exponent.

The n value is used to characterize different release for cylindrical shaped matrices.

Table 5.7: Interpretation of diffusional release mechanisms

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
$0.45 < n < 0.89$	Non-Fickian transport	t^{n-1}
0.89	Case II transport	Zero order release
Higher than 0.89	Super case II transport	t^{n-1}

CHAPTER - 6

RESULTS & DISCUSSIONS

Table 6.1 Organoleptic Characteristics of the Dapsone

S. No	Physical Property	Result
1	Colour	White
2	Odour	Odourless
3	Taste	Tasteless

Table No.6.2 Melting Point of the Dapsone

S. No	Method	Result
1	Capillary tube Method	178 ⁰ C

Table No.6.3 Solubility of the Dapsone

S. No	Type of Solvent	Result
1	Water	Insoluble
2	Acetone	Slightly soluble
3	Ethanol	Soluble
4	Methanol	Soluble
5	pH 6.8 Buffer	Soluble

PREPARATION OF CALIBRATION CURVE OF DAPSONE

Table 6.4: Standard curve of Dapsone in phosphate buffer pH 6.4

Concentration($\mu\text{g/ml}$)	Absorbance
0	0.000
2	0.108
4	0.221
6	0.316
8	0.423
10	0.536

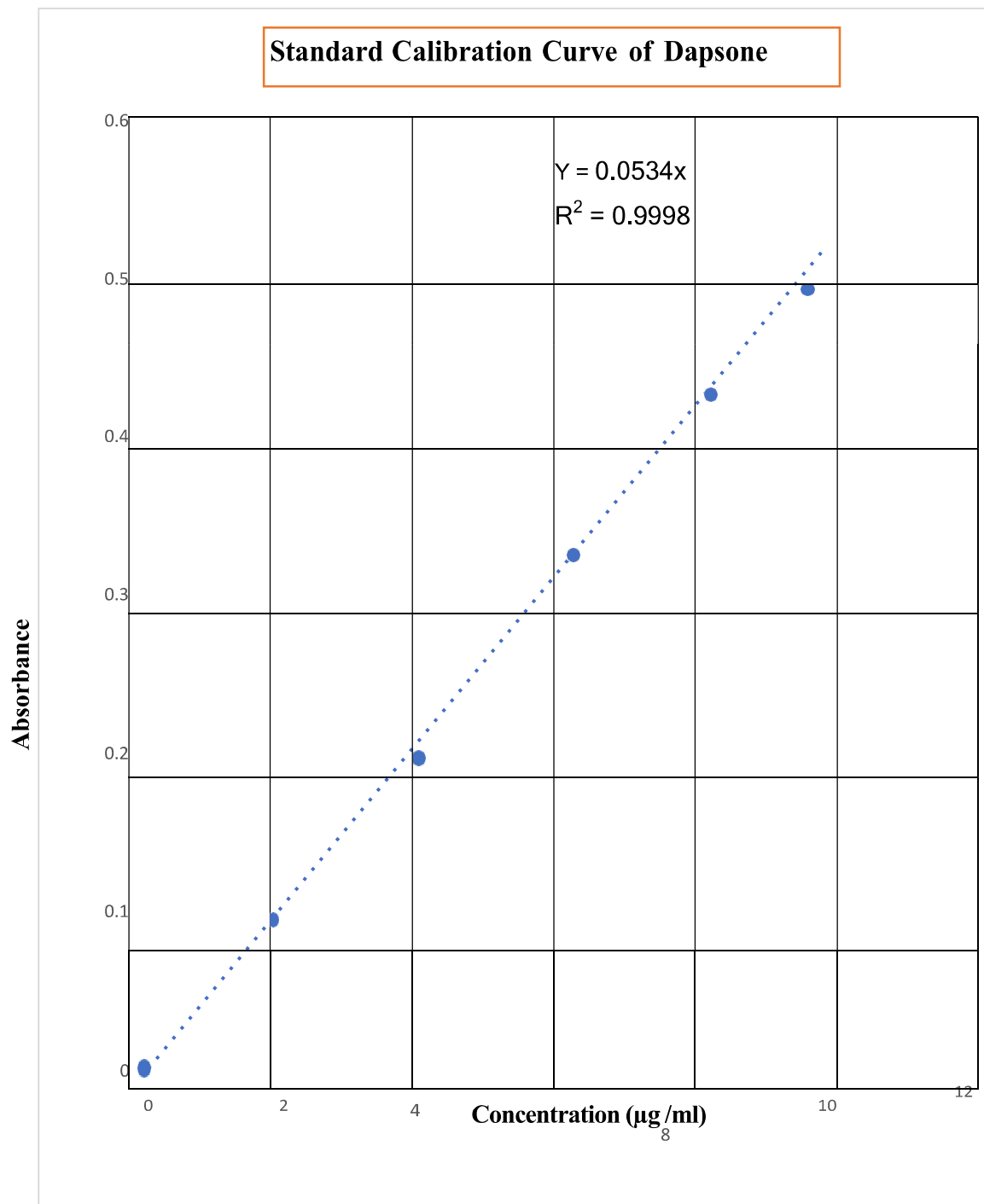


Fig 6.1 standard calibration curve of Dapsone

CHARACTERIZATION OF SOLID DISPERSIONS OF DAPSONE

Drug content

Table 6.5: Drug content in physical mixture and solid dispersions.

Solid dispersion (Dapsone to Urea ratio)	Drug content (%)	Physical mixture (Dapsone to Urea ratio)	Drug content (%)
DSD 1:1	93.11	DPM 1:1	91.13
DSD 1:2	97.18	DPM 1:2	92.41
DSD 1:3	99.04	DPM 1:3	98.21

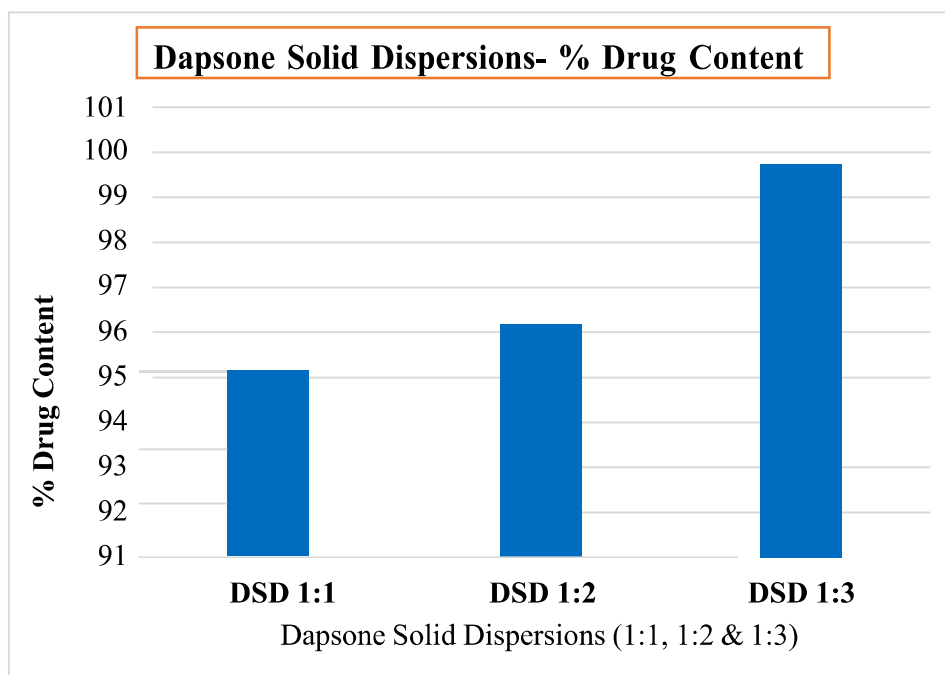


Fig 6.2 % Drug content - Dapsone Solid Dispersions

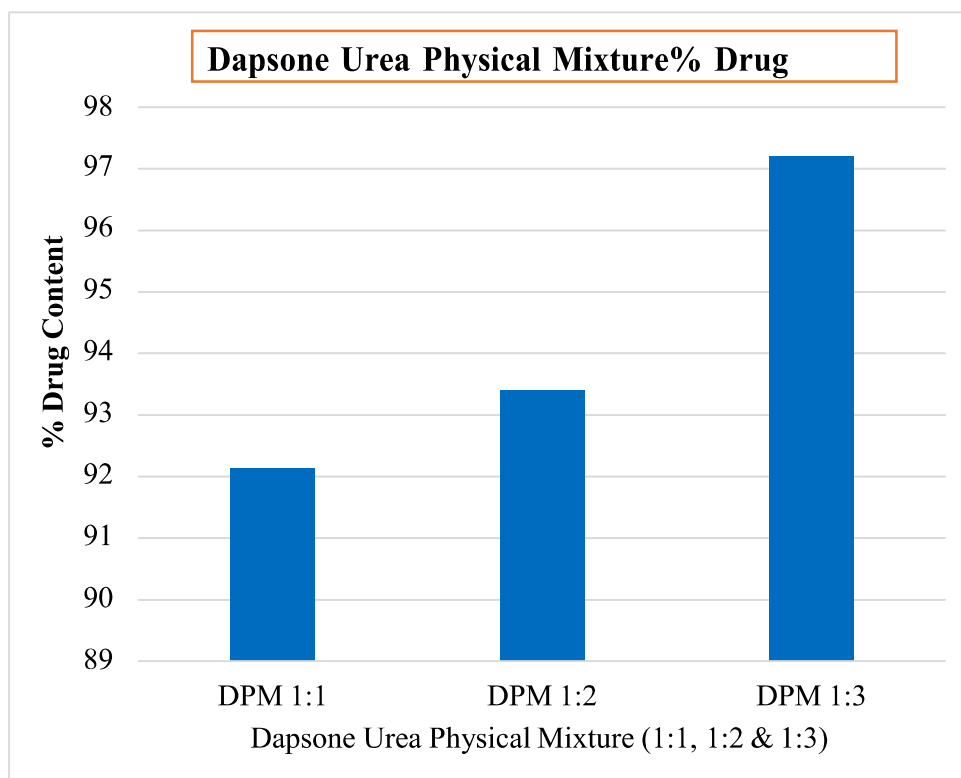


Fig.6.3 % Drug content -Dapsone -Urea Physical Mixture

Dissolution studies of solid dispersions and physical mixtures:

Table 6.6: Comparative In vitro Dissolution profiles of the Pure drug, Solid dispersions and Physical Mixture of the Dapsone in pH 6.4 phosphate Buffer.

S. No	Formulation	Cumulative % drug release after 20 min.
1	DRUG	29.16 ± 1.22%
2	DPM 1:1	45.45 ± 2.11 %
3	DPM 1:2	62.24 ± 1.07 %
4	DPM 1:3	74.33 ± 1.81 %
5	DSD 1:1	94.21 ± 1.34 %
6	DSD 1:2	98.02 ± 1.24 %
7	DSD 1:3	***99.82 ± 1.23 %

At the Different time intervals, the percentage of drug release from the physical mixture and solid dispersions was calculated. It is an evident that dissolution of pure dapsone is very low, about 29.16% being dissolved in 20 min. At the end of 20 min, Dapsone Solid Dispersions DSD containing 1:3 of drug and Urea showed better drug release 99.84% than other ratios of SD's. Likewise at the end of 20 min, Dapsone Physical Mixture DPM containing 1:3 of drug and Urea showed highest drug release 74.33% than other ratios of. From the results, it was observed that Dapsone Solid Dispersions (1:3) showed better results with other samples.

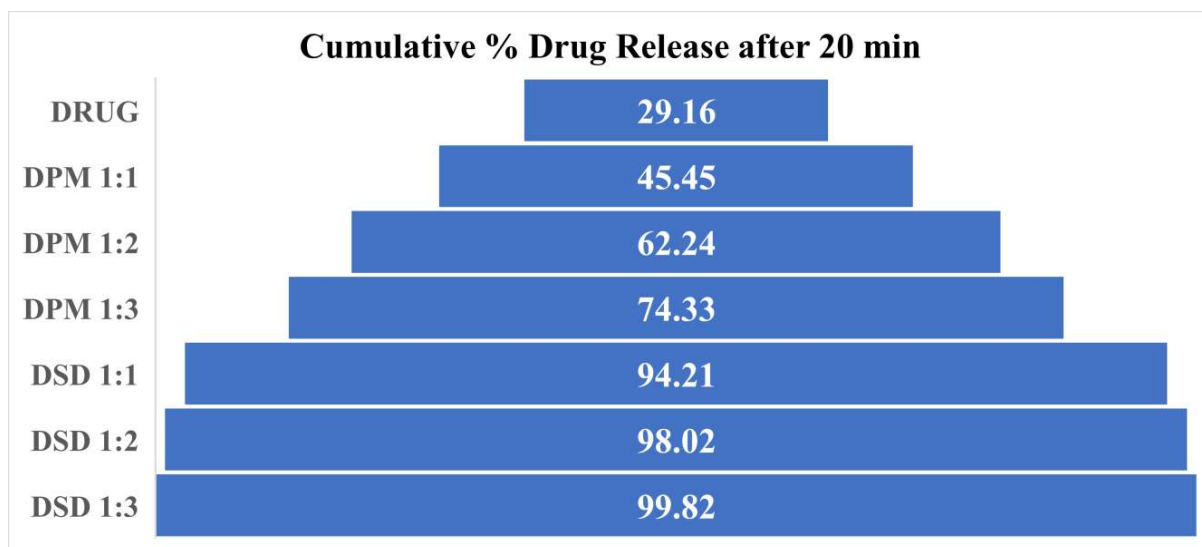


Fig.6.4 % Drug Release for the Pure Dapsone, Solid Dispersions & Physical Mixture

X- RAY DIFFRACTION STUDIES

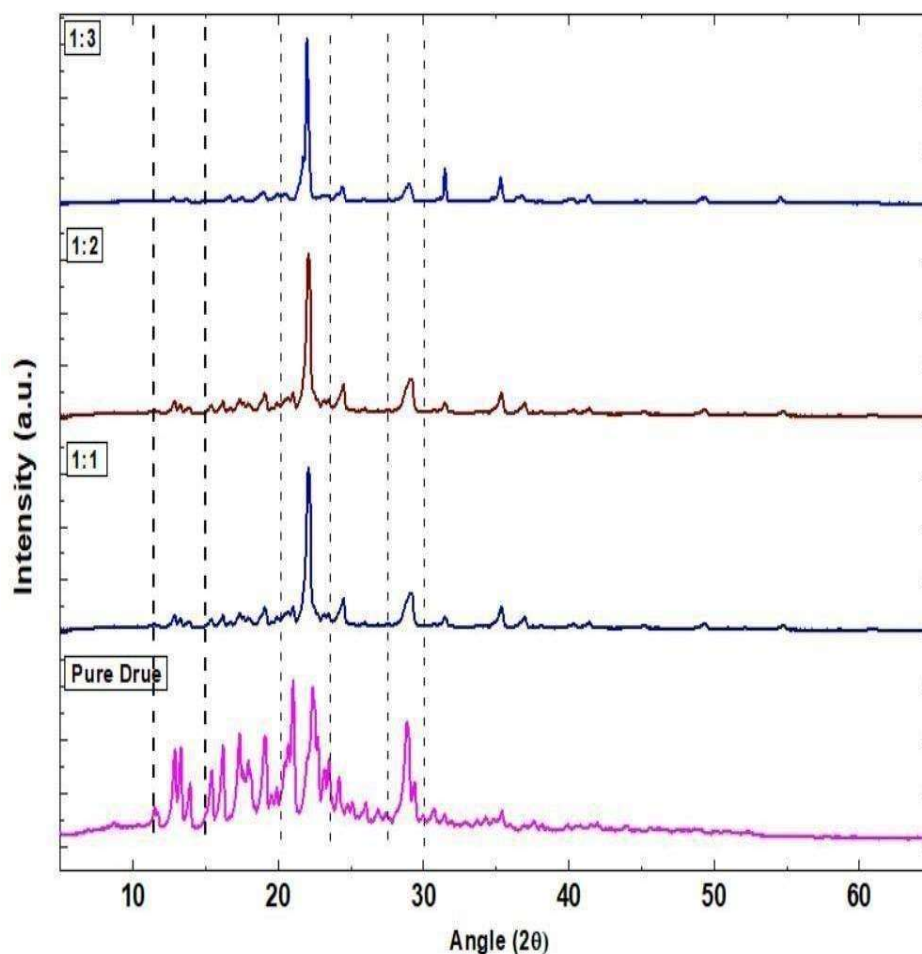


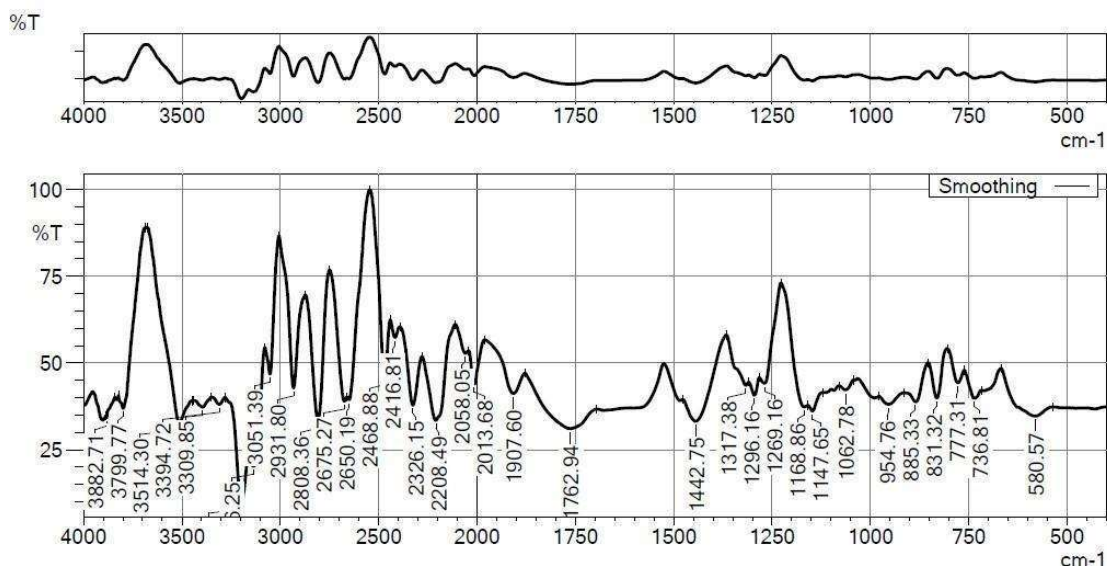
Fig.6.5 XRD studies of the Pure Dapsone and formulated Solid Dispersions (1:1,1:2 & 1:3)

XRD studies were also performed for the formulated SDs to know the crystallinity of the formulation. XRD was performed for both the pure Dapsone and the prepared DSDs. The XRD spectrum of Dapsone API was found to have the sharp, high intense peaks, which indicating the crystal nature of API, whereas the XRD spectrum formulated DSDs was found to have the broad, less intense peaks, which is confirming the form conversion of API from crystalline to amorphous after solid dispersion formation. The XRD spectrum is displayed in figure 6.5

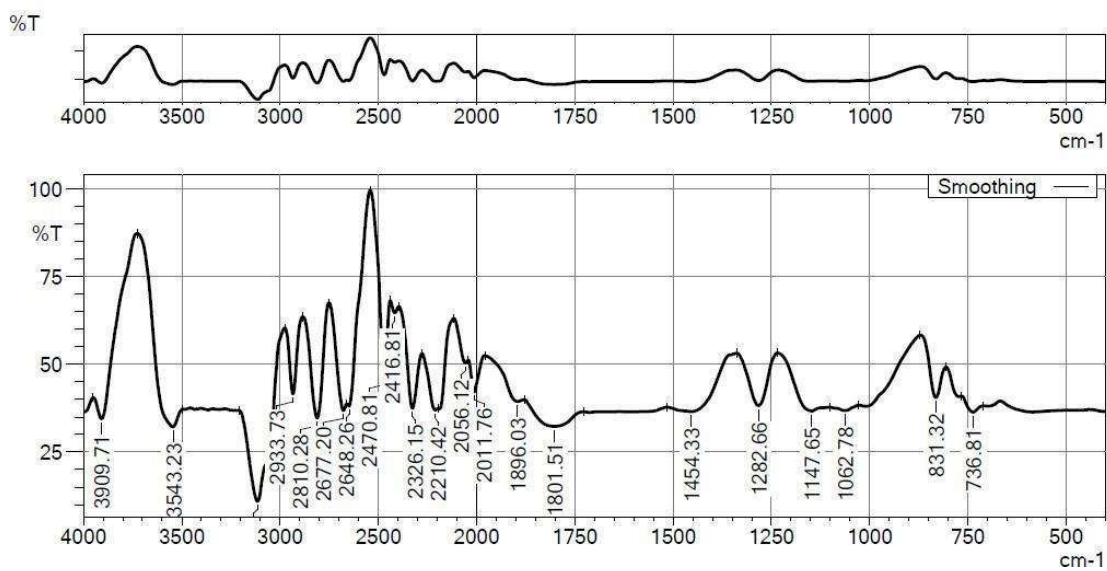
09-01-2024 16:45:41



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**Fig 6.8 FTIR of the Dapsone Solid dispersions (1:2)**

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**Fig 6.9 FTIR of the Dapsone Solid dispersions (1:3)**

From the FTIR data it is proves that there is no significant interaction between pure Dapsone with urea used for manufacturing of Solid dispersions

Table 6.7 Interpretation of FTIR data

Sl. No.	IR Spectrum	Peaks $\text{cm}^{\pm 1}$	Groups	Stretching / Deformation
1	Dapsone	3034.13	C-H Aromatic	Stretching
		2945.40	C-H Alkane	Stretching
		2364.81	O-H Carboxylic acid	Stretching
		759.98	C-Cl	Stretching
2	FTIR of the Dapsone Solid Dispersions (1:1)	3421.83	C-H Aromatic	Stretching
		2953.76	C-H Alkane	Stretching
		2376.38	O-H Carboxylic acid	Stretching
		761.91	C-Cl	Stretching
3	FTIR of the Dapsone Solid Dispersions (1:2)	3034.13	C-H Aromatic	Stretching
		2947.33	C-H Alkane	Stretching
		2368.66	O-H Carboxylic acid	Stretching
		758.05	C-Cl	Stretching
4	FTIR of the Dapsone Solid Dispersions (1:2)	3049.56	C-H Aromatic	Stretching
		2943.47	C-H Alkane	Stretching
		2374.45	O-H Carboxylic acid	Stretching
		758.05	C-Cl	Stretching

PHYSICAL PARAMETERS OF DRUG AND SUPER DISINTEGRANTS

Table 6.8 Physical Parameters of Drug and Super disintegrants

Drug/Polymer	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index	Hauser's ratio
Dapsone	0.54	0.44	19.54	1.27
Physical Mixture	0.53	0.42	18.33	1.26
Co processed Excipients	0.51	0.45	16.66	1.18
Crospovidone	0.55	0.44	19.22	1.25

EVALUATION OF DAPSONE TABLETS

Table 6.9 Precompression parameters of Dapsone FDT

Formulation Code	*Angle of Repose(θ)	*Bulk Density(g/cc)	*Tapped Density(g/cc)	*Carr's index	*Hauser's ratio
CP0	21.43±0.202	0.65±0.005	0.724±0.001	10.22±0.01	1.11±0.001
PM1	20.55±0.476	0.65±0.001	0.735±0.001	11.56±0.06	1.13±0.001
PM2	21.30±0.561	0.65±0.001	0.725±0.001	10.34±0.05	1.11±0.001
PM3	22.29±0.206	0.64±0.001	0.734±0.007	12.80±0.07	1.14±0.002
PM4	21.43±0.109	0.65±0.005	0.732±0.005	11.20±0.07	1.12±0.001
PM5	20.82±0.117	0.64±0.005	0.722±0.007	11.35±0.01	1.12±0.001
CP1	20.45±0.220	0.65±0.005	0.734±0.007	11.44±0.01	1.12±0.005
CP2	21.45±0.476	0.64±0.001	0.734±0.001	12.80±0.22	1.14±0.005
CP3	20.67±0.502	0.65±0.001	0.732±0.005	11.20±0.07	1.12±0.005

CP4	20.84±0.782	0.64±0.001	0.734±0.001	12.80±0.02	1.14±0.005
CP5	21.25±0.543	0.65±0.005	0.722±0.005	9.97±0.01	1.11±0.005

Table 6.10 Results of thickness, hardness, friability and weight variation of Dapsone tablets

Formulation	*Thickness	% Drug	*Hardness	Friability	Weight
Code	(mm)	Content	(kg/cm²)	(%)	Variation
CP0	2.496±0.02	100.21±0.39	3.14±0.25	0.234±0.07	199.10±0.20
PM1	2.487±0.02	99.83±0.42	3.69±0.25	0.296±0.07	201.09±0.33
PM2	2.483±0.01	98.53±0.41	3.12±0.27	0.348±0.04	200.19±0.21
PM3	2.476±0.01	99.40±0.45	3.20±0.25	0.376±0.04	200.33±0.76
PM4	2.444±0.01	100.61±0.42	3.47±0.27	0.336±0.13	198.80±0.34
PM5	2.438±0.01	99.32±0.37	3.51±0.25	0.376±0.04	200.33±0.12
CP1	2.436±0.01	100.01±0.25	3.12±0.27	0.336±0.14	199.60±0.28
CP2	2.452±0.01	98.56±0.87	3.20±0.25	0.227±0.03	200.43±0.71
CP3	2.451±0.01	100.17±0.38	3.50±0.27	0.309±0.05	201.67±1.27
CP4	2.448±0.01	99.40±0.55	3.34±0.25	0.339±0.07	199.26±0.20
CP5	2.459±0.01	100.52±0.43	3.66±0.25	0.321±0.01	200.34±0.48

**Table 6.11 Results of in vitro dispersion time, wetting time and water
Absorption ratio of Dapsone tablets**

Formulation code	*In vitro dispersion Time(sec)	*Wetting time (sec)	*Water Absorption Ratio
CP0	19	22	109
PM1	22	24	100
PM2	24	28	96.38
PM3	34	36	87.44
PM4	26	30	98.12
PM5	32	38	93.1
CP1	36	44	92.01
CP2	50	61	89.65
CP3	12	14	120.11
CP4	13	21	118.19
CP5	12	25	109.11



Fig 6.10 WETTING TIME of Dapsone FDT FORMULATION

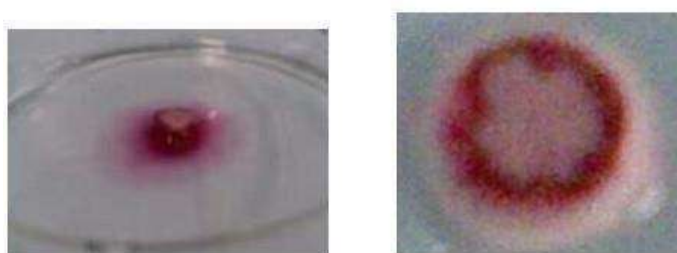


Fig 6.11 IN VITRO DISPERSION TIME(SECONDS)OF DAPSONE FDT

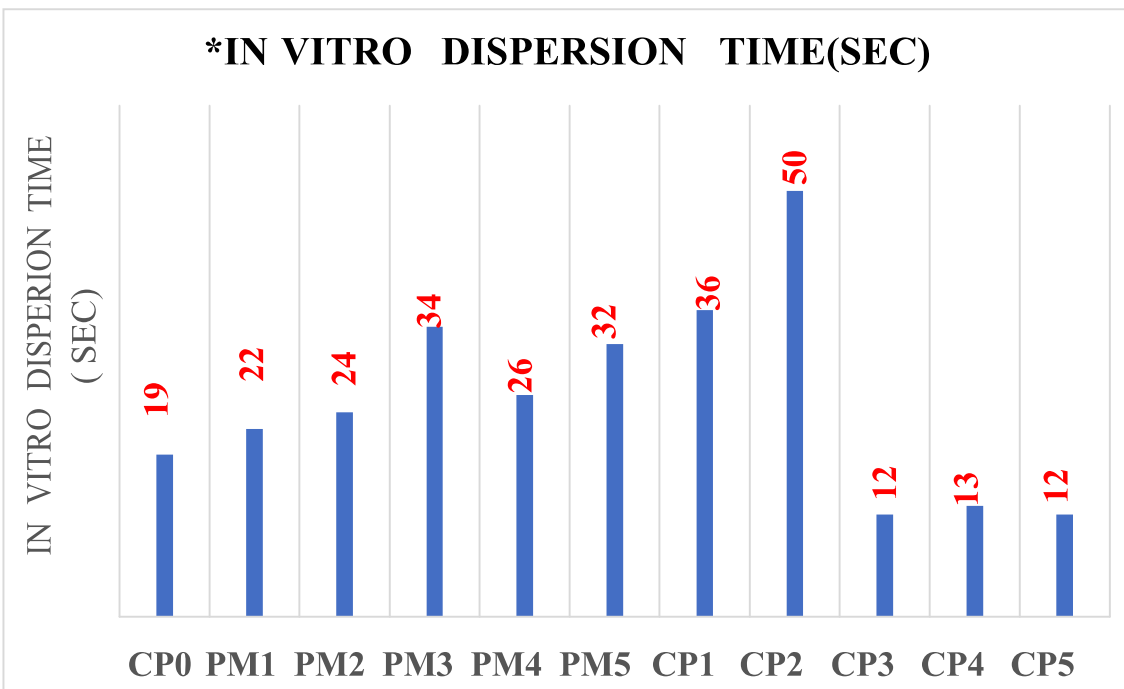


Fig 6.12 IN VITRO DISPERSION TIME (SEONDS) OF DAPSONE FDT (b)

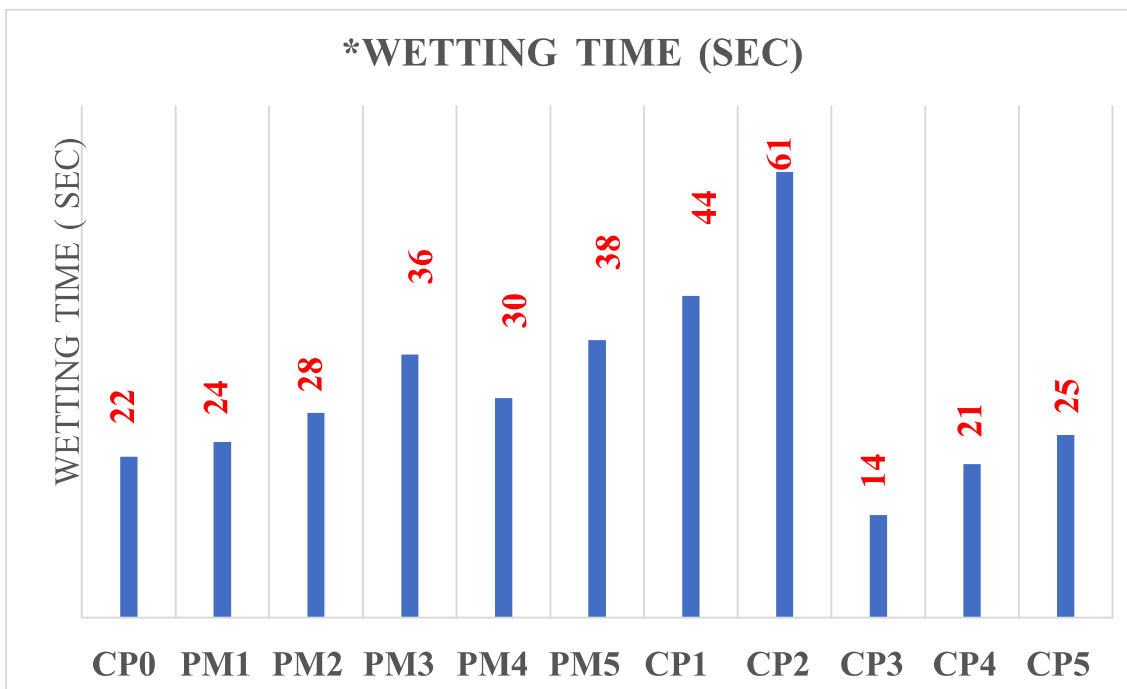


Fig 6.13 Wetting time of Dapsone FDT

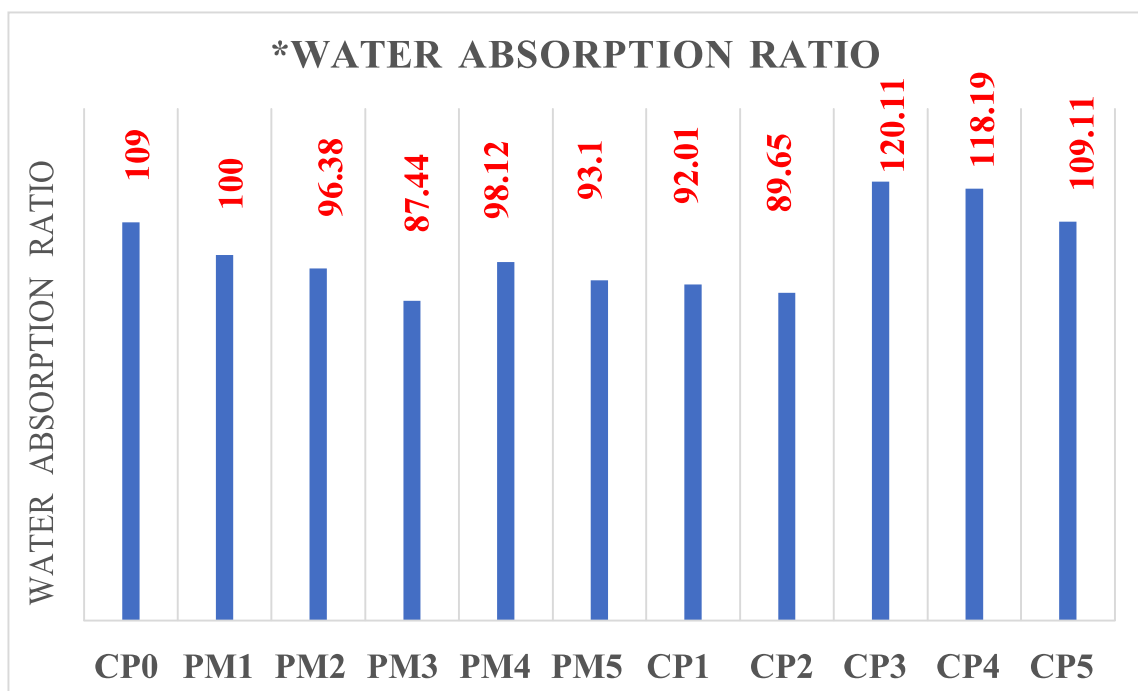


Fig 6.14 Water Absorption Ratio of Dapsone FDT

Table 6.12 Invitro Dissolution Studies

Time (min)	CP0	PM1	PM2	PM3	PM4	PM5	CP1	CP2	CP3	CP4	CP5
0	0	0	0	0	0	0	0	0	0	0	0
2	14.11	17.33	17.94	18.7	21.641	28.34	18.33	21.94	23.7	26.941	34.34
4	23.7	23.27	25.47	25.57	30.17	37.22	24.27	29.47	30.57	35.47	43.22
6	27.57	31.86	32.31	36.52	37.01	48.29	32.86	36.31	41.52	42.31	54.29
8	32.86	30.06	41.05	42.873	42.75	59.11	31.06	45.05	47.873	48.05	65.11
10	31.06	48.83	47.18	47.051	48.88	67.98	49.83	51.18	52.051	54.18	73.98
12	49.83	60.49	59.63	59.8	62.5	77.87	61.49	63.63	64.8	67.8	83.87
14	63.63	71.52	70.68	71.12	74.22	82.76	72.52	74.68	76.12	79.52	88.76
16	67.12	78.1	76.19	76.63	85.33	86.18	79.1	80.19	81.63	90.63	92.18
18	73.19	85.7	83.67	88.75	90.4	90.13	86.7	87.67	93.75	95.7	96.13
20	81.34	91.66	90.78	92.98	94.69	94	92.66	94.78	97.98	99.99	100

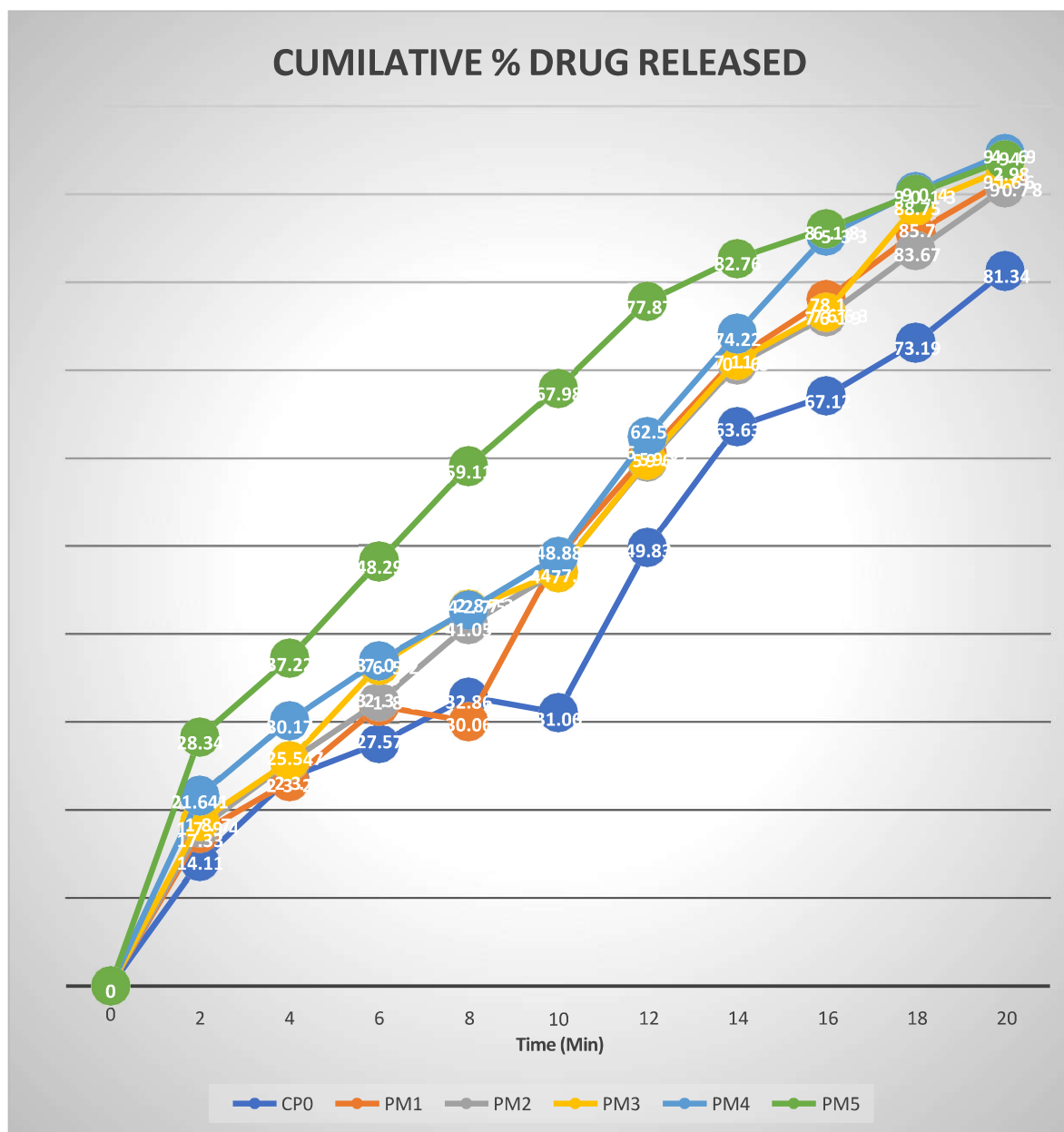


Fig 6.15 Cumulative % Drug release time for Physical mixture

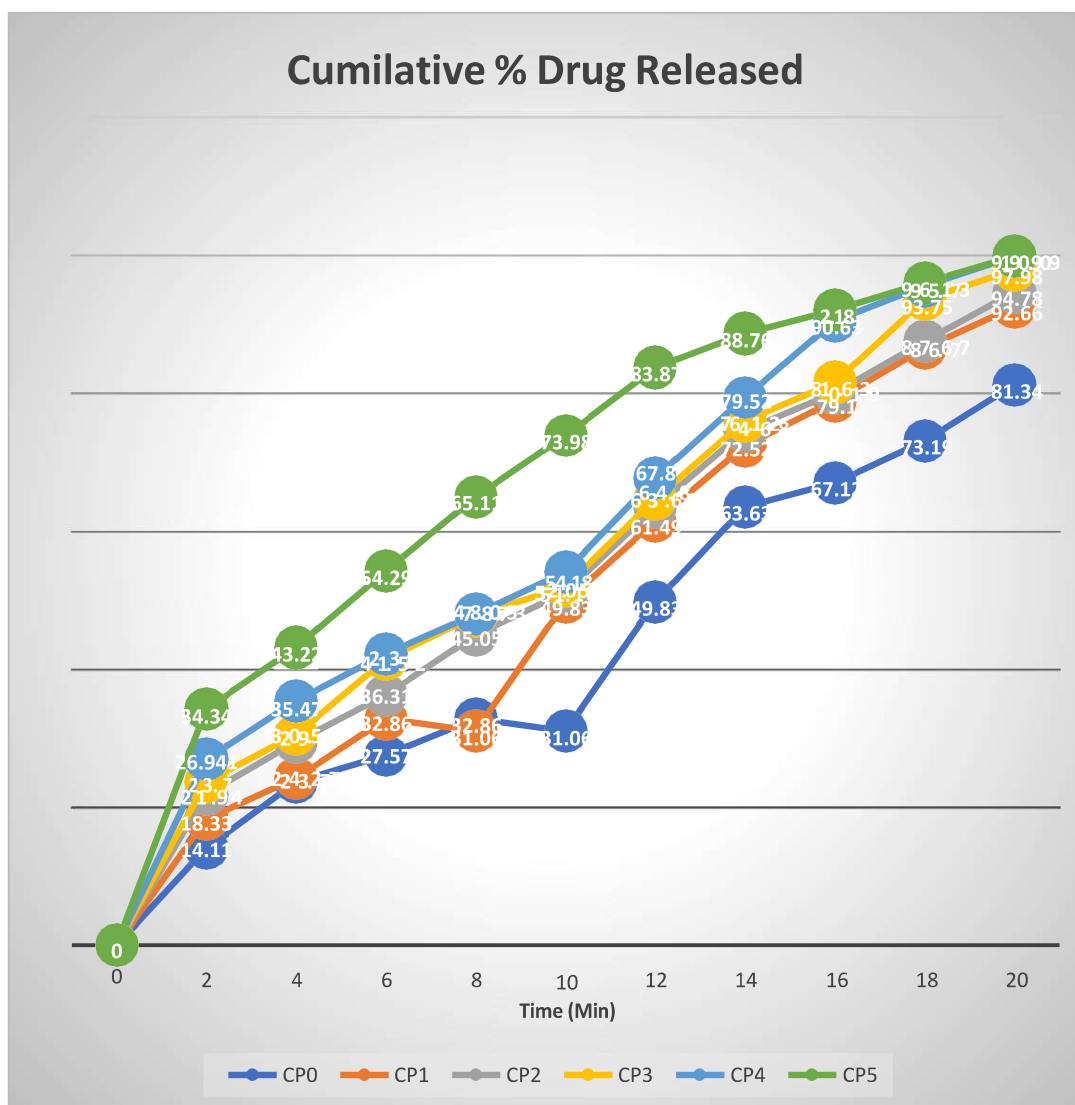


Fig 6.16 Cumulative % Drug release time for Co-processed Excipients

CHAPTER 7

SUMMARY AND CONCLUSIONS

PREFORMULATION STUDIES

- The solubility of Dapsone reveals that it was freely soluble in pH 6.8 Phosphate buffer and also soluble in ethanol and methanol.
- The melting point of Dapsone was found to be 178°C, thus indicating purity of obtained drug sample (Dapsone)
- In Preformulation studies, it was found that, the λ_{max} of Dapsone by UV spectroscopic method was found at 260 nm in pH 6.8 buffer as shown in Fig 6.1. A standard calibration curve Dapsone was made in phosphate buffer pH 6.8 by taking absorbance V/S concentration between 2-10 $\mu\text{g/ml}$ ranges, the data was given in Table 6.4 and calibration curve is shown in Fig 6.1.

Drug –excipient compatibility by FTIR studies

FTIR of drug-excipient interaction studies are shown in Fig 6.6 to 6.9 and the data are reported in Table 6.7. It was found that Dapsone was compatible with super disintegrants used in the formulation and there were no extra peaks observed.

Pre-compression parameters

Precompression parameters play an important role in improving the flow properties of pharmaceuticals especially in tablet formulation. These include angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Before formulation of tablets the drug and super disintegrants were evaluated for all the above said parameters and it was found that all the observations were within the prescribed limits of IP.

Angle of repose of all the formulations was found to be ranging from 20.55-21.82, bulk density was found to be 0.64-0.65g/cc, tapped density was in between 0.722-0.735g/cc,

Carr's index was found to be within 9.97-12.80 and Hausner's ratio was found to be within 1.11-1.14 indicating compressibility of the tablet granules is good as reported in Table 6.9

POST-COMPRESSION PARAMETERS

Tablet thickness and hardness

The thickness of the tablet indicates that die fill was uniform. The thickness depends upon the size of the punch (7 mm) and the weight of the tablet (200 mg). The thickness of the batch from PM1-PM5 was found to be 2.438- 2.483mm & CP 1 - CP 5 was found to be 2.436- 2.459 and hardness of PM 1-PM5 was found to be 3.12-3.69kg/cm² & CP1-CP5 was found to be 3.12-3.66 kg/cm² as reported in Table 6.10 and thus tablets were having good mechanical strength.

Friability

Friability is needed for tablets to withstand force of compression applied during the manufacture of tablets. The friability of all the formulated tablets of Dapsone from PM1-PM5 was found to be between 0.296-0.376% & CP1-CP5 was found to be 0.227-0.339 are reported in Table 6.10 and all the formulated tablets of Dapsone were shown the % friability within the official limits. (i.e. not more than 1%).

Weight variation

Prepared tablets were evaluated for weight variation and percentage deviation from the average weight for PM1-PM5 was are reported in Table 6.10 and was found to be within (± 200) the prescribed official limits.

In vitro dispersion time

All the formulated tablets from PM1-PM5 were 22-34 & CP1-CP5 was 12-50 have shown in vitro dispersion time of less than 60 seconds, showing that formulated Dapsone tablets were better and effective for the treatment than conventional tablets. Among all the formulations, tablets prepared with crospovidone were shown less than 60 sec. of dispersion time. The obtained results were showed in Table 6.11

Wetting time

The wetting time of all the formulations for PM - 24-38 sec & CP - 21- 61 sec which complies with the official specifications. The results were showed in Table 6.11. A comparison of in vitro dispersion time and wetting time was shown in Fig 6.11

Water absorption ratio

The water absorption ratio of all the formulated batches for PM--87.44-100 & CP 89.65-120.11 which was satisfactory in giving effective and better formulations of rapid dissolving tablets. The results were shown in Table 6.11. The water absorption ratio of all the formulations was represented in Fig 6.11

Drug content

The drug content of all the eleven formulations of Dapsone tablets were found to be within the range for PM - 98.53-100.61 & CP - 98.56 .. 900.52 %which were within the limits of IP specifications. The drug content of all the formulations of Dapsone tablets is shown in Table 6.11

In vitro dissolution study

- Total 11 formulations were formulated among CP0 is prepared without super disintegrants, PM1-Pm5 prepared with super disintegrants crospovidone and Sodium Starch Glycolate in Physical form and CP1-CP5 formulations prepared with Co-processed excipients
- The formulation CP0 without super disintegrants showed 81.34% of drug release at the end of 20th minute
- The formulations PM1-PM5 showed the drug release in the end of 20th minute in the range between 90.78% (PM2) & 94,69% (PM4)
- The formulatiuons CP1-CP5 showed the drug release in the end of 20th minute in the range between 92.66% (CP1) & 100% (CP5)
- From this data it was found that Co-processed excipients showed the highest drug release in comparison with Physical form

CHAPTER - 8

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Comprehensive Review of Oro Dispersible Tablets and Co Processed Super disintegrants

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Abstract

Due to their ease of administration, self-administration, and improved patient compliance, solid dosage forms are most popular. The most normally utilized strong dose structures are tablets and capsules, which is challenging for pediatric and geriatric patients. Considering these prerequisites endeavors have been made to foster rapid dissolving Tablets. The solid dosage form of a medicine that dissolves in a matter of seconds when swallowed is known as orodispersible tablet. The utilization of Superdisintegrants improves the crumbling season of the tablet. Fast Dissolving Tablets are generally liked because of their convenience, higher bioavailability, quick disintegration and breaking down of the medication. The various technologies utilized in the formulation of Orodispersible tablets (ODT) and their evaluation are the primary focus of this review.

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INTRODUCTION

Conventional tablets bring about high frequency of rebelliousness and ineffectual treatment regarding gulping uniquely on account of pediatric, geriatric, or any intellectually impeded people. This prompted the improvement of tablets that break down quickly in the oral pit which are named as oral crumbling tablets Orodispersible,

Speedy deteriorating, Mouth dissolving, Quick crumbling, Permeable tablets, and Rapimelts.

As of late, European Pharmacopeia has utilized the term orodispersible tablets. This might be characterized as uncoated tablets planned to be set in the mouth where they scatter promptly inside 3 min prior to gulping. US Pharmacopeia has additionally endorsed these dose structures as orodispersible tablets. According to the US Pharmacopeia (USP) crumbling method or oral surgery, the FDA specifically recommends that ODTs be regarded as strong oral arrangements that deteriorate quickly in the oral cavity, with an in vitro breaking down season of around 30 sec or less [1].

Hence, orodispersible tablets have powerful unit dosage constructions just like regular tablets, but they are also constructed of super disintegrants, which let the tablets dissolve in the mouth in the blink of an eye almost without requiring gulping.

These tablets can be distinguished from buccal, capsule, and conventional sublingual tablets because the former take longer to dissolve in the mouth [2].

Advantages of Orally Disintegrating Drugs [3][4]

a. Pharmacological

Expanded drug assimilation

Quick beginning of activity

Limited first-pass impact

Further developed bioavailability

b. Patient compliance

No need to chew or swallow tablets or capsules

No requirement of water

Taste masking

Enhanced efficacy and safety

Better safety is achieved since there is no chance of choking or suffocating with oral delivery of standard formulations because there is no physical barrier.

c. Technical

More precise dosage compared to liquid goods.

Can make use of sugars and other excipients that are generally thought to be safe.

Unit-dose packaging contributes to increased stability. Producing goods using standard procedures and tools.

d. Marketing advantage

Extensive patent protection

Value-added product line extension

Life cycle management

Limitations of Oro Dispersible Tablets

ODTs may not be the best option for patients using anticholinergic drugs concurrently, and these tablet formulations may not be appropriate for those with Sjogren's syndrome or dry mouth from reduced salivary flow.

Formulating drugs with comparatively higher dosages into ODTs is a challenge.

ODT requires unique bundling for appropriate adjustment and security of stable item [5].

Significance of Orally Disintegrating Tablets [6]

Simple administration for young patients, elderly patients, those with mental illnesses, people with disabilities, and patients who refuse to cooperate Administration ease for patients (older and/or pediatric, mentally ill, crippled, and uncooperative) who refuse to take a pill.

Patients who are traveling and do not have rapid access to water will find the dose form highly handy as it does not require water to be consumed.

Rapid drug absorption and dissolution, which may result in a rapid onset of action.

Some medications are absorbed from the mouth, throat, and oesophagus as saliva moves down into the stomach; in these cases, the medication's bioavailability is increased.

Challenges in Formulating ODT's [7][8]

a. **Palatability:** Formulation scientists face a formidable obstacle when trying to cover up the bitter taste of oral disintegrating tablets. Since most medications are not appetizing, oral disintegrating drug delivery systems usually contain the medication in a taste-masked form. As a result, drug taste masking becomes essential for patient compliance.

b. **Mechanical strength:** ODTs are stuffed into tablets with very low-tension power, which makes the tablets friable or delicate and hard to deal with, or they are built of staggeringly penetrable and gently shaped networks, permitting them to separate in the oral opening. Not many advances can make tablets that are adequately tough and hard, dissimilar to Wowtab® by Yamanouchi and Durasolv® by CIMA research centers, which can be stuffed in multidose bottles.

c. **Hygroscopicity:** Because they are hygroscopic, various dosage forms for oral dissolution are unable to maintain their physical integrity at room temperature and relative humidity. Accordingly, they require security against tenacity, which requires exceptional bundling of the items.

d. **Dose /Amount of drug:** The utilization of advancements used for ODTs is confined by

how much drug that can be coordinated into each unit segment. There are three main obstacles to the development of quick break down measurement structures caused by particles that require large amounts: a) taste veiling of the powerful fixing, b) mouth feel or soil and c) tablet size. The degree of bitterness of the drug in relation to its dose determines the amount of taste masking materials used in various dosage forms. This will also influence the final tablet size, so these challenges are related

- e. **Aqueous solubility:** Water-dissolvable meds structure eutectic mixes, which achieve edge of freezing over distress and the improvement of a sparkling solid that could fall subsequent to drying because of loss of supporting plan during the sublimation connection. Such breakdown every so often can be thwarted by using different cross section outlining excipients, for instance, mannitol than can provoke crystallinity and subsequently, award rigid nature to the vague composite.
- f. **Size of tablet:** The size of a tablet decides that it is so natural to take. It has been accounted that tablets bigger than 8 mm are the simplest to deal with while tablets less than 7-8 mm are the most straightforward to swallow. Likewise, the tablet size that is both easy to take and easy to manage is trying to achieve.
- g. **The Drug Property:** Numerous drug properties could really impact the presentation of Fast disintegrating tablets. For example, the dissolvability, pearl morphology, particle size and mass thickness of a medicine can impact the last tablet characteristics, similar to tablet strength and weakening.
- h. **The sensation in the mouth:** The ODT shouldn't separate into greater particles in the oral opening. The particles made after disintegration of the ODT should be essentially pretty much as little as could be anticipated. After oral organization, ODT ought to leave little to no buildup in the mouth. In addition to the expansion of flavors, cooling agents like menthol further enhance the mouthfeel.
- i. **Aversion to ecological circumstances:** Since the majority of the materials used in ODTs are intended to disintegrate with the least amount

of water, they should generally exhibit low aversion to climate conditions like humidity and temperature.

Criteria for Drug Selection [9]

The best characteristics for an oral dispersible tablet medicine are,

The medication should be stable in both water and saliva.

ODT should not use drugs that require frequent dosage and have a short half-life.

Minimal subatomic weight direction.

Ideal dosage for sedative effects is less than 50 mg.

Able to diffuse and parcel into the upper gastrointestinal tract epithelium.

Formulation Aspects of Oro Dispersible Tablets

Excipients used in the manufacturing of orodispersible tablets [10][11]

Diluents:

Fillers that are used to create the necessary bulk of a tablet. Disintegrants that are used in tablets that can be dispersed or taken orally serve a secondary purpose of improving the properties of a tablet, such as improving cohesion, flow, compactibility, and stability.

Eg: Lactose, Shower dried lactose, Mannitol, Sorbitol

Binders:

Binders are used to give powdered materials a cohesive quality. They can be added dry or wet to make granules.

Eg: Gelatin, glucose, Lactose, starch, Polyvinylpyrrolidone (Povidone) etc.

Super disintegrants:

Work with the breaking of the tablet when it comes into contact with water in the oral depression or GIT.

Eg: Croscopovidone (Polyplasdone), Sodium starch glycollate, Starch, and Croscarmellose sodium (Ac-di-sol).

Lubricants:

Reduce inter-particulate friction, stop tablet material from adhering to die and punch surfaces, and make it easier to eject tablets from die cavities.

Example: Insoluble- Stearic acid, Magnesium stearate, Calcium stearate, Talc, Paraffin Soluble- Sodium lauryl sulphate, Sodium benzoate, PEG 400, 600, etc.

Glidants:

Improve the powder mixture's flow characteristics.

Reduce friction between particles in the following ways:

Colloidal Silicon dioxide (Aerosil), Cornstarch, Powder Example s: Colloidal Silicon dioxide (Aerosil), Cornstarch, Talc etc.

Anti Adherents:

They were included to stop tablet material from sticking to dies and punches.

Example: Talc

Sweeteners:

These are added to further develop taste of dose structure

Example: Sucrose, Sucralose, Saccharin, Aspartame, acesulfame potassium etc.

Flavors:

These are added for better appearance of dose structure

Example: Peppermint, Vanilla, Orange, Banana, Cinnamon, Mango etc.

Colors:

These are used to improve the dosage form's appearance.

Example: Sunset yellow (Supra), amaranth.

Role of Superdisintegrants in ODT

The oral disintegrating tablet is primarily composed of superdisintegrant. These are included to improve the dosage forms. The disintegration efficiency is based on the force-equivalent idea, which is the combined measurement of swelling force generation and water absorption. Superdisintegrants are often

used in strong dosage structures at low levels, typically 1–10% by weight in relation to the measuring unit's total weight.

Classification of Super Disintegrants

Superdisintegrant property is seen both in natural and synthetic sources which can be listed as follows [12][13]:

- a) Natural superdisintegrants
- b) Synthetic superdisintegrants
- c) Co-processed superdisintegrants

Co-processed Super Disintegrants

Superdisintegrants continue to be developed at an ever-increasing rate to solve the challenges associated with advanced tablet fabrication. It necessitates the development of various additional helpful excipients, which are applied to details with desired outcomes. Previously, the only excipients available to construct dosage forms were superdisintegrants; however, a range of excipient mixes are now available that can impart disintegration qualities. The purpose of some co-handled excipient blends is to satisfy the demand for several excipients.

Need For Developing Co-processed Excipients

Co-processed of excipients with moderate supporting information prompts

Regulation of solubility, Penetrability and strength of drug

The development of excipients with proven unsurpassed properties and real combinations of parts or individual parts, particularly suitable for direct printing.

Provide an ideal film filler that can replace at least two excipients.

Great compressibility and reduced weight diversity even with short dwell times and high compression rates.

To overcome the shortcomings of existing excipients, for example, loss of densification of microcrystalline cellulose during wet granulation, high reactivity to moisture and unfortunate powder filling due to agglomeration.

Address the needs of patients with diabetes and hypertension explicitly and ensure knowledge of lactose and sorbitol.

Table 1 Natural Super Disintegrants

Natural polymer	Drug	Results
Locust bean gum	Nimesulide	Disintegration time with 10% was found to be 13 sec.
Mangifera indica gum	Metformin HCl	Better drug release when used in low concentration
Hibiscus rosa sinensis	Famotidine	Rapid wetting time and 90% of drug release in 10 min.
Dehydrated banana powder	Ondansetron, propranolol	Immediate release dosage form
Plantago ovate	Granisetron	Better drug release
Cucurbita maxima pulp powder	Diclofenac	Good release rate
Fenugreek seed mucilage	Metformin	Disintegration in 15 sec. and 100% release in 18 min.

Table 2 Synthetic Super Disintegrants Classification

Method	Super Disintegrant	Drugs employed
Direct compression	Cross povidone and croscarmellose sodium	Glipizide, metaclopramide, terbutaline
	Sodium starch glycollate, crospovidone and croscarmellose sodium	Carvedilol, valsartan, Glucalazide
Wet granulation	Kollidion, Explotab	Ibuprofen
	Ac-di-sol, Sodium starch glycollate	Aceclofenac
Sublimation	Croscarmellose sodium, sodium starch glycollate	Metoprolol succinate

Solve problems such as decomposition, decay and bioavailability.

The awareness of strong measuring forms, a reduced range of new auxiliary materials and a growing inclination towards direct printing processes create a decisive freedom to improve the high usefulness of auxiliary materials [14].

Advantages of Co-Processed Excipients [15][16]

1. Lack of chemical change

Numerous in-depth analyses of the characteristics of excipient substances during co-handling have shown that these excipients exhibit no synthetic alteration. No chemical entity with a covalent link is formed when the separate components are mixed to make the co-processed excipients. To demonstrate that individual components do not create covalent bonds, analytical data supporting the suggested shelf life or retest period of the co-processed excipient must be shown.

2. Physico-mechanical properties

a. Increased flow property

Co-processed excipients have superior flow properties without the need for glidants thanks to controlled optimal particle size and distribution. SMCC's volumetric flow characteristics were compared to those of MCC. The molecule size scope of SMCC was viewed as like that of the parent excipients, However, because of its round form and level surfaces, the co-handled excipient's advancement was better than that of the simple real blends.¹⁶ Although calcium phosphate is normally not suitable for use in direct pressure operations, when granulated with larger levels of unsaturated fats, it demonstrated excellent compressibility and stream characteristics as compared to single excipients.

b. Improved compressibility

Direct compression tableting results in a net improvement in flow characteristics and compressibility profiles and produces a filler-binder excipient, co-processed excipients have

mostly been utilized in this procedure. Excipients with higher compressibility performance than simple physical mixes of their component excipients include Cellactose 18, SMCC, and Ludipress. When water is added to excipients like MCC, their compressibility decreases—a process known as quasihornification. Yet, when it is co-processed into SMCCt, this feature is enhanced.

c. Improved potential for diluting

Since most active medicinal compounds are poorly compressible, excipients need to have greater compressibility qualities in order to retain adequate compaction even when diluted with a poorly compressible material. It has been shown that the dilution potential of cellulose is greater than that of a physical combination of its constituent excipients.

d. Variation in fill weight

Co-processed excipients have been shown to have less fill-weight variation problems than parent materials or simple mixes. The main reason of this phenomenon is the impregnation of one particle into the matrix of another, which leads to a near-optimal size distribution, better flow characteristics²¹, and decreased roughness of the particle surfaces. When compared to solo excipients, the co-handled calcium phosphate excipient exhibits a consistent molecular size dispersion, resulting in less particle separation and a smaller weight variety.

e. Decreased lubricant sensitivity

The majority of co-processed products have a relatively large amount of delicate material, like lactose monohydrate, and a relatively small amount of plastic material, like cellulose, which is adhered to or fixed between the weak material's particles. Since plastic creates a sturdy structure with a large holding area, it has excellent gripping characteristics. Due to the large amount of fragile material, which separates the oil organization and prevents the formation of a clear oil network by framing newly exposed areas under pressure, the oil network responds poorly to oil.

3. Non Physico-Mechanical Advantages

Utilizing a single excipient with multiple functional properties allows pharmaceutical manufacturers to reduce their inventory of excipients. Customized planner excipients can be

fostered by co-handled excipients, since they can provide utilitarian advantages while explicitly reducing barriers. This may help to reduce the amount of time needed to cultivate details. Improved organoleptic properties, such as those found in Avicel CE-15, a co-handled excipient of MCC and guar gum, were shown to have noticeable advantages in pleasant tablets in terms of less dirt, less tooth pressing, slight whiteness, improved mouth feel, and improved overall taste. Despite the fact that co-handling adds some expense, the general item cost diminishes on account of further developed usefulness and less test prerequisites contrasted and individual excipients. Drug companies can employ coprocessed excipients as proprietary blends and maintain internal models, which might support the development of a strategy that is difficult to replicate and provides advantages in terms of licensed invention privileges.

Limitations of Co-Processed Excipients

1. Constant ratio

One significant disadvantage of the co-processed excipient combination is that the excipients' ratio to one another is set. A fixed ratio of the excipients may not be the ideal choice for the API and the dose that is presently being developed for each tablet in the process of generating a new formulation.

2. High price

Specialized goods manufactured by patented techniques such as roller drying, fluid bed drying, and spray drying are known as directly compressible excipients. These goods are therefore more costly than the raw resources used to make them.

3. Potential dilution of up to 40%

The majority of easily compressible co-handled excipients can bind up to 40% of the dynamic elements that are ineffectively compressible, such as acetaminophen. This means that the final tablet containing 500 mg of medication would be heavier than 1.3 grams, making it large and potentially difficult to swallow.

4. Reworkability of the splash-dried coprocessed excipient

If the excipient particles are redesigned, they will lose their original round shape, which will result in the loss of their distinctive quality and an increase in the deterioration and disintegration profiles.

5. Lack of approval by pharmacopoeia

The pharmacopoeia has not formally approved coprocessed adjuvant. Therefore, until a mix filler folio shows significant advantages in tablet compaction over genuine excipient combinations, the pharmaceutical industry will not accept it.

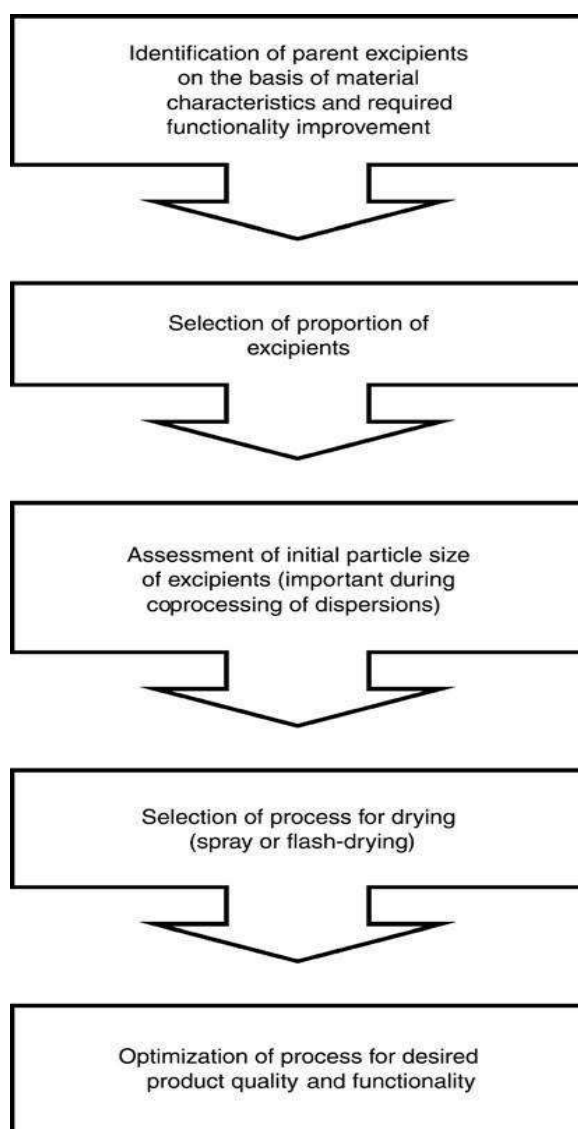


Figure 1 Outline of Co-Processing Technique

Role of Material Characteristics in Co-processing

An Input Material science has a major role in altering the excipients' physico-mechanical properties, especially in relation to pressure and stream characteristics. Three categories of strong materials may be made based on how they respond to applied mechanical power.

Table 3 Classification of materials based on how they react to mechanical force

Classification of material	Description
Flexibility	Any adjustment of shape is totally reversible, and the material re-visitations of its unique endless supply of applied pressure.
Plastic	A material's shape changes forever when stress is applied, like MCC, corn starch, and sodium chloride.
Fragile	Fast engendering of a break all through the material on use of pressure, e.g., sucrose, mannitol, sodium citrate, lactose, and di-calcium phosphate.

The lattice structure of a material controls its propensity to deform, i.e., whether or not its lattice planes are intrinsically weakly linked. Suffice it to say, most of the items are too diverse to be clearly classified into one or more categories. Drugs exhibit all three qualities, with the overpowering reaction being one of them, therefore it is difficult to distinguish the feature good for compressibility clearly. "A decrease in the mass volume of materials because of relocation of the vaporous stage" is what pressure refers to [17].

Stages Encountered During Compression [18]

- Initial particle repacking.
- Elastic deformation of the particles up to the yield point, or elastic limit, after which plastic deformation and/or brittle fracture take over and almost completely remove the voids, leading to the compression of the solid crystal lattice.
- The properties of the individual particles influence the packing characteristics of a bulk of dry powder. When a powder mass is subjected to external mechanical forces, closer packing usually results in a volume decrease.

Table 4 Description and Applications of Co-processed Excipients

Grade	Description	Applications
Ludiflash	Have a cooling effect in the mouth and a mild sweet taste. have a low hygroscopicity and superior flowability. does not completely dissolve in organic solvents or water.	Excellent excipient for rapid release via direct compression of solid oral medication forms that dissolve quickly.
F-melt	Exceptionally flowable with roundly thick particles, deterioration time in no less than 30 seconds, efficient and practical, less staying or covering.	Suitable for the direct compression assembly of oral tablets that dissolve quickly and contain greases and APIs..
Pharmaburst	It is an easy-to-use, quick-to-dissolve delivery stage that is rich, smooth, and extremely feasible.	allows for the flexibility to provide effective "Fast Break down" information internally at a reasonable cost.
Modified chitosan with silicon dioxide	enhanced compaction, flow, and swelling qualities combined with water-wicking capabilities.	Serves as superdisintegrant and filler.
Pearlitol SD	Granulated mannitol spheronized, Pearlitol® 100SD, mean diameter 180 µm, mean width Pearlitol® 200SD, 100 m approximately 40% more powerful than sucrose.	Excellent excipient for direct compression, especially in chewable, effervescent tablet form.
Mannogem EZ	Its outstanding compressibility can be attributed to its open crystal-line structure. Approximately half the power of sucrose is improved.	a great carrier for active moieties that are susceptible to hydrolysis and for applications that dissolve quickly.
Polacrillin Potassium	No protuberance formed following the disintegration. excellent compatibility with excipients and popular treatment agents.	used as a pill disintegration agent and flavor masking ingredient for a variety of medications.
Glucidex IT	less tiny particles, rapid dispersion, and rapid disintegration result in free-flowing.	Utilized as a diluent for spray-dried tablets, capsules, and maltodextrin that is directly compressed and employed in the immediately compressible formulation of vitamin <u>and supplement tablets.</u>

Techniques for Super Disintegrant Addition [19][20]:

In essence, disintegrants are added to tablet granulation to cause the compacted tablet to crumble or break in a fluid environment. Three approaches are available for adding dissolving agents to the tablet:

I. Intragranular Internal Addition**II. Extragranular External Addition****III. Internal and External Elements in Part**

The disintegrant is added to the sized granulation with mixing before compression in the external addition technique. Before soaking the powder mixes in the granulating solution, the disintegrant is combined with other powders in the internal addition process. The disintegrant is thereby integrated into the granules. A portion of the disintegrant can be added externally and internally when these techniques are applied.

Mechanism of Action of Super Disintegrants

After the tablets are broken up into tiny fragments, a homogenous suspension is created using the following mechanisms:

Capillary action/ Water wicking: The first phase is almost always a collapse by thin activity. The tablet absorbs the medium, which replaces the air adsorbed on the particles, when it is submerged in the suitable aqueous medium. As a result, the tablet disintegrates into tiny particles and the intermolecular link is weakened. Tablet water uptake is dependent on tableting conditions and the hydrophilicity of the drug or excipient. A disintegrant's ability to introduce water into a tablet's porous structure is essential to its effective breakdown. In actuality, wicking is not joined by a volume increase.

Swelling: It seems that the most prevalent overall mode of action for pill disintegration is swelling. It is important to remember that if the pressing portion is very high, liquid cannot enter the pill and the rate of deterioration decreases [21].

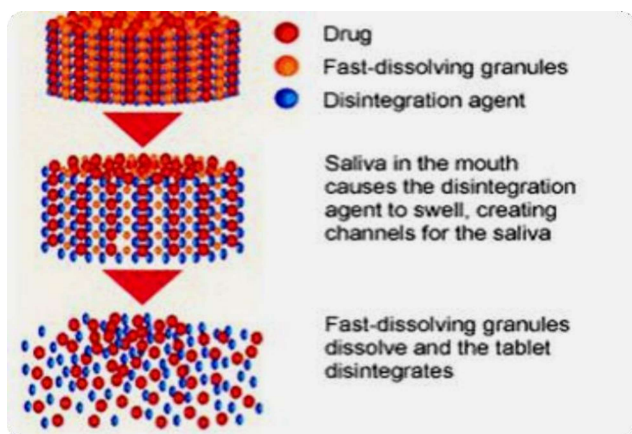


Figure 2 Swelling behavior of superdisintegrants

Air expansion /Heat of wetting: When exothermic disintegrants are wetted, capillary air expansion produces localized stress that promotes tablet disintegration

Due to disintegrating particle/particle repulsive forces: An additional instrument of deterioration attempts to explain the enlargement of tablets composed of "non-swellable" disintegrants. Water is anticipated for the component of breaking down that is caused by the horrifying electric forces between particles. The

investigators conclude that wicking is more significant than repelling.

Due to deformation: When degraded particles come into contact with fluid medium or water, they become twisted and take on their normal shape. This phenomenon occurs during tablet pressure. The distorted particles get bigger until the tablet crumbles. It is possible that this is a starch mechanism, but research on it is quite new.

Owing to gas release: When tablets are wet, bicarbonate and carbonate react with citrus extract or tartaric corrosive to produce carbon dioxide. The tablet fractures as a result of internal pressure building up. The bubbly mixture can be introduced to two different parts of the plan or added right before pressure.

By Enzymatic reaction: The body's enzymes function as disintegrants in this scenario. These enzymes break down the binder's capacity to bind, which speeds up its dissolution.

TECHNIQUES FOR PREPARATION OF ODT'S [22][23]

The use of direct compression in the production of ODTs

One popular method for ensuring these measurement structures are ready is direct compression. Simple implementation, the use of conventional equipment in conjunction with frequently available excipients, a preset number of handling steps, and cost viability are some advantages of this approach. Directly compressed tablets dissolve and break down with the help of effervescent agents, disintegrants, and water-soluble excipients, either separately or in combination. The basic idea behind the creation of these dosage forms using this technique is the addition of superdisintegrants in the right amounts to promote quick disintegration and a pleasing mouthfeel.

The prepared tablets are thought to be the ideal approach for creating oral disintegrating dosage forms because they don't contain a binder and have a low moisture content. This method is also regarded as innovative disintegrant growth.

Wet granulation technique

Wet granulation is the most widely used granulation process in the pharmaceutical sector.

Rather than compaction, it combines powders with an adhesive to produce granules, or it adds a liquid solution to powders to make a wet mass (with or without a binder). After drying, the wet mass is measured to obtain granules. Using a mix of capillary and viscous forces, the additional liquid binds the moist powder particles together in the wet state. On the other hand, there are several drawbacks to ODTs, such as high moisture content, which can be reduced by adding a dry folio like PVP, and high crumbling time. Additionally, the cost of creation is high because more resources are needed for assembly.

Alternative methods used in the production of ODTs

When creating dosage forms that dissolve in the mouth, several methods are frequently used. These methods, which are explained below, each have benefits and drawbacks of their own

Freeze Drying

Also known as lyophilization, this process involves extracting a dissolvable substance from a frozen pharmaceutical solution or suspension that contains excipients that frame the structure of the medication. Tablets designed using this method are often incredibly light and porous, allowing for a rapid breakdown. The drug material and the excipients made from freeze-drying, which have a glassy, amorphous, porous structure, improve solubility.

Three phases are typically involved in the freeze-drying process:

The material is brought beneath the eutectic point by freezing it.

Essential drying reduces the moisture content by approximately 4% weight/weight of the dried object.

Optional drying reduces the bound moisture content to the necessary final volume.

The entire freeze-drying procedure is carried out at room temperature, negating any potential negative thermal effects on medication security.

Sublimation

It is because of their low porosity, compressed tablets with highly water-soluble excipients as

matrix material usually do not dissolve in water quickly.

Along with other tablet excipients, urea, urethane, ammonium carbonate, naphthalene, camphor, and other inert, volatile compounds are added and the mixture is compressed into a tablet. Sublimation removes volatile molecules and creates a porous structure. Additionally, certain solvents like benzene, cyclohexane, and so on can also be used as specialists in pore framing [24].

Moulding

The goal of tablets that have been molded is to facilitate the active components' absorption by the oral mucosa. This is made possible by the water-soluble components in the tablet dissolving completely and quickly. Shaped tablets have a superior flavor and break down faster because of the scattering grid, which is mostly made of sugars with a water solvent. The powdered mixture (which contains the medication and excipients such as binding agents such as sucrose, acacia, PVP, and so on) is passed through a very fine screen to ensure quick disintegration. It is then moistened with a hydroalcoholic dissolvable and formed into tablets using less pressure than is used for regular packed tablets. After that, the dissolveable is removed by air drying.

Spray Drying

This process creates a very fine and porous powder by shower-drying a wet item with a support lattice and other components. This creates a particulate help grid. In these formulations, mannitol functioned as a bulking ingredient, sodium starch glycolate or croscarmellose sodium as a disintegrating agent and hydrolyzed or unhydrolyzed gelatin as a matrix support. The dissolution and breaking down processes were further enhanced by the inclusion of bubbly ingredients such sodium bicarbonate and citrus essence. Finally, the definition was spray dried to produce a porous powder.

Mass Extrusion

This innovation comprises of mellowing the dynamic mix utilizing a dissolvable combination of water solvent polyethylene glycol with methanol and ejection of relaxed mass through the extruder or needle to get chamber of the item into even

Table 5 Patented technologies in ODT's [25]

Technology	Process Involved	Patent Owner	Drugs Used (Brand Name)	Drug Release
Zydis	Freeze drying	R.P. Scherer Inc.	Loratidine (Claritin Reditab & Dimetapp quick dissolve)	Dissolves in 2-10 sec.
Quicksolv	Freeze drying	Jansen Pharmaceuticals	Cisapride monohydrate (Propulsid Quicksolv)	-----
Flashtab	Freeze drying	Ethypharm	Ibuprofen (Nurofen Flashtab)	Dissolves within 1 min.
Lyoc	Multiparticulate Compressed tablets	Farmlyoc	Phloroglucinol Hydrate(Spasfon Lyoc)	-----
Orasolv	Compressed tablets	Cima Labs Inc.	Paracetamol (Tempra Quicklets), Zolmitriptan (Zolmig Rapimelt)	Disintegrates in 5-45 sec.
Durasolv	Molding	Cima Labs Inc.	Hyoscyamine Sulphate (NuLev),	Disintegrates in 5-45 sec.

fragments utilizing warmed edge to frame tablet. The dried chamber can likewise be used for covering the granules of unpleasant medications and consequently veiling their taste.

Cotton candy process

The cotton candy technique gets its name from the unique turning tool that is used to provide a structure that resembles glass and resembles floss, just like cotton candy. This approach involves arranging a grid of saccharides or polysaccharides while simultaneously softening and twisting the sparkle. To improve stream characteristics and compressibility, the lattice frame is partially recrystallized. Compressed into ODTs, this matrix is combined with active and excipient components and then ground. This cycle delivers worked-on mechanical strength and can require large quantities of medication. However, the high temperature limits the use of the method.

Phase Transition

The novel method for preparing ODTs with the right amount of hardness. By compacting and then heating tablets containing two different sugar alcohols one with a high liquefying point and the other with a low one—this approach delivers ODTs. Because the particles are not compactible, the heating process strengthens the bonds that hold the particles together, making the tablets more durable than they otherwise would have been.

Melt Granulation

This is a cycle in which medication powders are effectively combined by using a fastener, which can be a powerful liquid or one that melts during the interaction. High shear blenders, in which the item temperature is elevated over the liquefying point of cover by a warming coat or by the grinding intensity generated by the impeller edges, are employed to achieve this interaction.

CONCLUSION

FDTs are imaginative portion forms designed to break down in spit without the need for water. Fast-dissolving tablets have improved biopharmaceutical properties, effectiveness, and safety when compared to conventional tablets. Additionally, they have increased patient compliance in pediatric and geriatric populations. The prominence of FDTs has soar lately. Disintegration or dissolution occurs in the buccal cavity without the use of water, so FDTs must be developed for psychotic individuals, patients who are immobile, geriatric, or pediatric patients, and FDTs must have sufficient mechanical strength and speed. The FDTs were created using cutting-edge technologies. convey more compelling portion definitions with extra advantages.

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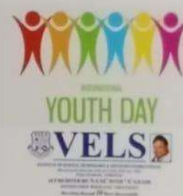
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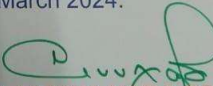
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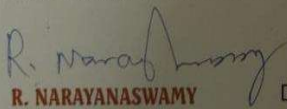
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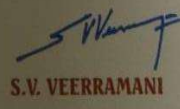
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