

FORMULATION AND *IN VITRO* CHARACTERIZATION OF DAPSONE FAST DISINTEGRATING TABLETS USING NATURAL SUPERDISINTEGRANTS

Submitted in 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 natural superdisintegrants**" 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 "**Mrs.M.Nandhini, 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 objective of this study was to enhance the solubility of Dapsone, a poorly soluble drug, by preparing solid dispersions using urea through the solvent evaporation method.

METHODS:

1. Characterization of natural superdisintegrants for morphological characteristics.
2. Solubility testing of natural excipients in various solvents to assess their gel formation properties.
3. Determination of swelling index to evaluate porosity, using *Plantago ovata* as an example.
4. Analysis of moisture content, loss on drying, and total ash for natural excipients, conforming to standards.
5. Phytochemical screening of natural excipients for absence of saponins, steroids, and alkaloids.
6. Characterization of Dapsone purity through organoleptic characteristics and melting point determination via capillary tube method.
7. Solubility testing of Dapsone in different solvents.
8. Preparation of solid dispersions using urea through solvent evaporation method.
9. Characterization of solid dispersions for drug content, dissolution, X-ray diffractions, and FTIR studies.

RESULTS:

1. All natural superdisintegrants exhibited favorable morphological characteristics.
2. Natural excipients formed gel in water and were insoluble in organic solvents.
3. *Plantago ovata* showed the highest swelling index, indicating increased porosity.
4. Moisture content, loss on drying, and total ash values for natural excipients met standards.
5. Phytochemical screening revealed absence of saponins, steroids, and alkaloids in natural excipients.
6. Dapsone purity was confirmed through organoleptic characteristics and melting point determination.
7. Dapsone showed poor solubility in water but was soluble in some organic solvents.

8. Solid dispersions prepared with a ratio of 1:3 of Dapsone to urea showed better drug content and dissolution (99.62% at 20 minutes).

CONCLUSION:

Solid dispersions of Dapsone with urea prepared by the solvent evaporation method significantly improved its solubility and dissolution rate. This approach could be promising for enhancing the bioavailability of poorly soluble drugs like Dapsone.

KEYWORDS:

Solid dispersions, Dapsone, Urea, Solvent evaporation method, Solubility enhancement, Drug dissolution, Natural excipients, Phytochemical screening.

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LIST OF ABBREVIATIONS

1. ODT -oral disintegrating tablet
2. DDS -drug delivery system
3. AIDS -acquired immunodeficiency syndrome
4. NDDS -novel drug delivery system
5. FDT -fast dissolving tablet
6. CDER -center for drug evaluation and research
7. EFVDAS -effervescent drug absorption system
8. GIT -gastrointestinal tract
9. DCL -direct compressible lactose
10. ICH -international conference of harmonization
11. USFDA -united state food and drug administration
12. IP -Indian pharmacopeia
13. BP -british pharmacopeia
14. USP -united state pharmacopeia
15. WT - weight
16. HPC -hydroxypropyl cellulose
17. HPMC -hydroxypropyl methyl cellulose
18. PVP - polyvinyl pyrrolidone
19. Mg -milligram
20. PEG-6 -poly ethylene glycol
21. Sec -second
22. Min -minutes
23. MADDS -monoacetyl dapsone
24. G6PD -glucose 6 phosphatedehydrogenase
25. Mm -milli meter
26. G -gram
27. WHO -world health organization
28. Hcl -hydrogen chloride
29. Mz - meclizine
30. DSC -differential scanning calorimetry
31. Kp -kiloponds
32. MH -midazolam hydrochloride
33. DT -disintegration time

34.FTIR	-fouriertransform infrared _x
35.NMR	-nuclearmagneticresonance
36.SSG	-sodiumstarchglycolate
37.Ac-di-sol	-croscarmellosesodium
38.DSC	-differentialscanningcalorimetry
39.UV	-ultraviolet
40.XRD	-x-raydiffractometer
41.API	-activepharmaceuticalingredients
42.MCC	-microcrystallinecellulose
43.Ph	-potentialofhydrogen
44.Hrs	-hours
45.Mc	-moisturecontent
46.NaoH	-sodiumhydroxide
47.H2so4	-sulfuricacid
48.Nm	-nanometer
49.Pms	-physicalmixture
50.DSD	-dapsonesoliddispersions
51.DPM	-dapsonephysicalmixture
52.Rpm	-revolutionsperminute
53.PXRD	-powerx-raydiffraction
54.IR	-infraredradiation

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CHAPTER-1

MOUTHDISSOLVINGTABLETS

1 INTRODUCTION:

Drug delivery system is an efficient tool for enhancing market, extending product life cycles and creating opportunities. Drug delivery system (DDS) makes a significant contribution to global pharmaceutical sales through market segmentation, and is moving rapidly¹. Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self medication, noninvasive method and ease of administration leading to high level of patient compliance². The most popular dosage forms are being conventional tablets and hard gelatin capsules.

One study showed that approximately 26% of 1576 patients do not take their prescribed medication as they encountered problems when swallowing conventional tablets. Often, the main complaints are the size, surface and taste of the tablets. An estimated 35% of the general population, and an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long-term care facilities, suffer from dysphagia. This disorder is associated with many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy.

The conventional dosage forms (tablet and capsule) have wide acceptance up to 50–60% of total dosage forms. Tablet is still most popular conventional dosage forms existing today because of ease of self administration, compact in nature, easy to manufacture and it can be deliver in accurate dose. One important drawback of solid dosage forms is the difficulty in swallowing (dysphagia) or chewing in some patients particularly pediatric and geriatric patients. The problem of swallowing is common phenomenon in geriatric patient due to fear of choking, hand tremors, dysphasia and in young individuals due to underdeveloped muscular and nervous systems and in schizophrenic patients which leads to poor patient compliance. Difficulties in swallowing of tablet and capsule are also occur when water is not available, in diarrhea, coughing during the common cold, allergic condition and bronchial infection³.

Recent advances in the novel drug delivery systems (NDDS) aim to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance i.e., one which will rapidly disintegrate or dissolve in the mouth without the need of water; fast dissolving tablets (FDT) ^{4, 5}.

The Center for Drug Evaluation and Research (CDER), US FDA defined Fast-dissolving/disintegrating tablets (FDTs) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". Recently European Pharmacopoeia also adopted the term Oro Dispersible Tablet defined as uncovered tablet for buccal cavity, where it disperses before ingestion. Fast disintegrating tablets (FDT) are also known as fast dissolving, mouth dissolving, rapid-dissolve, quick disintegrating, orally disintegrating, rapid melt, fast melts, orodispersible, melt-in-mouth, quick dissolving, porous tablets, EFVDAS or Effervescent Drug Absorption System ⁶.

Taste-masking is of critical importance in the formulation of acceptable FDTs. Traditional tablet formulations generally do not address the issue of taste masking, because it is assumed that the dosage form will not dissolve until passing the oral cavity. Elimination of the bitterness of the tablet can be achieved by adding flavors and sweetening agent or by sugar coating on the tablets.

To increase the tablet disintegration, super-disintegrants are added in it, which are very helpful to increase the bioavailability of tablet and to increase the disintegration property of tablet in saliva. The patients can feel the normal disintegration time of FDT from 5-30 sec. FDT's are mainly prepared by various methods like direct compression, wet granulation, solid dispersion and tablet molding etc. Direct compression method is the most widely used and easiest or cost effective method for FDT as compared to other methods.

1.1 REQUIREMENTS OF FAST DISSOLVING TABLETS

- ✓ Have a pleasing mouth feel

- ✓ Have an acceptable taste masking property
- ✓ Should be hard and friable
- ✓ Leave minimal or no residue in the mouth after oral administration
- ✓ Exhibit low sensitivity to environmental conditions such as humidity and temperature
- ✓ Allow the manufacture of tablet using conventional processing and packaging equipments.

1.2 ADVANTAGES OF FDT

FDTs offer dual advantages of solid dosage forms and liquid dosage forms along with special features which include:

- **Accurate dosing:** Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for pediatric and geriatric patients.
- **Enhanced bioavailability:** Bioavailability of drugs is enhanced due to absorption from mouth, pharynx and esophagus.
- **Rapid action:** Fast onset of therapeutic action as tablet gets disintegrated rapidly along with quick dissolution and absorption in oral cavity.
- **Patient compliance:** No need of water to swallow the dosage form. Hence, it is convenient for patients who are traveling and do not have immediate access to water.
- **Ease of administration:** Convenient to administer specially for geriatric, pediatric, mentally disabled and bed ridden patients who have difficulty in swallowing.
- **Obstruction free:** No risk of suffocation in airways due to physical obstruction when swallowed, thus providing improved safety and compliance.
- **Enhanced palatability:** Good mouth feel, especially for pediatric patients as taste masking technique is used to avoid the bitter taste of drug. **Simple packaging:** No specific packaging required. It can be packaged in push through blisters.

- **Business avenue:** Provide new business opportunities in the form of product differentiation, line extension, uniqueness and life cycle management.
- **Cost effective:** Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.

1.3 DISADVANTAGES

- Fast dissolving tablet is hygroscopic in nature so must be kept in dry place.
- It requires special packaging for proper stabilization and safety of stable product.
- Sometime it possesses mouth feeling^{11,12}

1.4 THE NEED FOR DEVELOPMENT OF FDTs

a. Patient factors: Fast dissolving dosage forms are suitable for those patients (particularly pediatric and geriatric patients) who are not able to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following:

- ✓ Patients who have difficulty in swallowing or chewing solid dosage form
- ✓ Patients in compliance due to fear of choking
- ✓ Very elderly patients of depression who may not be able to swallow the solid dosage forms
- ✓ A eight-year old patient with allergies desires a more convenient dosage form than antihistamine syrup
- ✓ A middle-aged patient undergoing radiation therapy for breast cancer may be too nauseous to swallow her H₂- blocker
- ✓ A schizophrenic patient who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic
- ✓ A patient with persistent nausea, who may be journey, or has little or no access to water.

b. Effectiveness factor: Dispersion in saliva in oral cavity causes pre-gastric absorption of drug which dissolves. Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs. Any pre-gastric absorption avoids first pass hepatic metabolism which increases the bioavailability. Furthermore, safety profiles

may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and pre-gastric segments of GIT.

c. Manufacturing and marketing factors: As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value-added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form.

This leads to increased revenue, while also targeting underserved and under-treated patient populations. As examples, Eisai Inc. launched Aricept FDT, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and in the U.S. in 2005 in response to a generic challenge filed in the U.S. by Ranbaxy. Merck's Japanese subsidiary launched Lipola M (simvastatin FDTs), a line extension of its block-buster, Zocor®, a cholesterol-lowering drug, in response to seven generic registrations of simvastatin applied for in Japan in 2004. Marketers build a better brand and in this way company's reputation can be improved.

1.5 CHALLENGES IN THE FORMULATION OF FDTs

- Mechanical strength and disintegration time
- Taste masking
- Mouthfeel
- Sensitivity to environmental conditions
- Cost

1.6 FORMULATION OF FDTs:

- **Bulking materials:** Bulking materials are significant in the formulation of fast-melting tablets. The material contributes functions of a diluent, filler and cost reducer. Bulking agents improve the textural characteristics that in turn enhance the disintegration in the mouth, besides; adding bulk also reduces the concentration of the active in the composition. The recommended bulking agents for this delivery system should be more sugar-based such as mannitol,

polydextrose, lactitol, DCL (direct compressible lactose) and starch hydrolystate for higher aqueous solubility and good sensory perception. Bulking agents are added in the range of 10 percent to about 90 percent by weight of the final composition.

- **Emulsifying agents:** Emulsifying agents are important excipients for formulating fast-melting tablets; they aid in rapid disintegration and drug release without chewing, swallowing or drinking water. In addition, incorporating emulsifying agents is useful in stabilizing the immiscible blends and enhancing bioavailability. A wide range of emulsifiers is recommended for fast-tablet formulation, including alkyl sulfates, propylene glycol esters, lecithin, sucrose esters and others. These agents can be incorporated in the range of 0.05 percent to about 15 percent by weight of the final composition.
- **Lubricants:** Lubricants, though not essential excipients, can further assist in making these tablets more palatable after they disintegrate in the mouth. Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach.
- **Flavours and Sweetners:** Flavours and taste-masking agents make the products more palatable and pleasing for patients. The addition of these ingredients assists in overcoming bitterness and undesirable tastes of some active ingredients.

1.7 SUPERDISINTEGRANTS

The Super-disintegrants can be classified into two categories

1. Natural Super-disintegrants
2. Synthetic Super-disintegrants

1.7.1. Natural super-disintegrants: They are natural in origin and are preferred over synthetic substances because they are comparatively cheaper, abundantly available, non irritating and non toxic in nature.

a. Advantages of natural plant-based materials:

- **Biodegradable:** Naturally available biodegradable polymers are produced by all living organisms. They represent truly renewable source and they have no

adverse impact on humans or environmental health (e.g., skin and eye irritation).

- **Biocompatible and non-toxic:** Chemically, nearly all of these plant materials are carbohydrates composed of repeating sugar (monosaccharides) units. Hence, they are non-toxic.
- **Low cost:** It is always cheaper to use natural sources. The production cost is also much lower compared with that for synthetic material. India and many developing countries are dependent on agriculture.
- **Environmental-friendly processing:** Gums and mucilages from different sources are easily collected in different seasons in large quantities due to the simple production processes involved.
- **Local availability:** In developing countries, governments promote the production of plant like guar gum and tragacanth because of the wide applications in a variety of industries.
- **Better patient tolerance as well as public acceptance:** There is less chance of side and adverse effects with natural materials compared with synthetic one. For example, PMMA, povidone.

b. Disadvantages:^{20,21}

- **Microbial contamination:** The equilibrium moisture content present in the gums and mucilages is normally 10% or more and, structurally, they are carbohydrates and, during production, they are exposed to the external environment and, so there is a chance of microbial contamination. However, this can be prevented by proper handling and the use of preservatives.
- **Batch to batch variation:** Synthetic manufacturing is a controlled procedure with fixed quantities of ingredients, while the production of gums and mucilages is dependent on environmental and seasonal factors.
- **Uncontrolled rate of hydration:** Due to differences in the collection of natural materials at different times, as well as differences in region, species, and climate conditions the percentage of chemical constituents present in a given material may vary. There is a need to develop suitable monographs on available gums and mucilages.

- **Reduced viscosity on storage:** Normally, when gums and mucilages come into contact with water there is an increase in the viscosity of the formulations. Due to the complex nature of gums and mucilages (monosaccharides to polysaccharides and their derivatives), it has been found that after storage there is reduced in viscosity.

Table 1.1: Examples of natural superdisintegrants in marketed formulations

Polymer	Botanical name	Drug	Result
Yellow potato starch	<i>Solanum tuberosum</i>	Rizatriptin benzoate	Fast disintegration
Chitosan	<i>Shell of crustaceans</i>	Cinnarizine	Good mouth feel & decreased disintegration time.
Cucurbita maxima powder	<i>Cucurbita maxima</i>	Diclofenac sodium	Disintegrating agent
Hibiscus rosa sinensis & treated agar	<i>Hibiscus rosa sinensis</i>	Famotidine	Decreased wetting time
Hibiscus rosa sinensis mucilage powder	<i>Hibiscus rosa sinensis</i>	Aceclofenac	Decreased disintegration time
Lallemantia rayana seed mucilage	<i>Lallemantia rayana</i>	Nimesulide	DT decreases with increase in concentration
Garden cress	<i>Lepidium sativum</i>	Nimesulide	Decreased disintegration time

Modified aegle marmelos gum	<i>Aegle marmelos</i>	Aceclofenac	Increased solubility
Mango	<i>Mangifera indica</i>	Metformin hydrochloride	Better drug release properties
Basil mucilage powder & seed powder	<i>Ocimum gratissimum</i>	Metformin hydrochloride	Decreased disintegration time
Orange peel pectin	<i>Citrus sinensis</i>	Paracetamol	Binding agent
Plantago ovata, gum karaya, agar	<i>Plantago ovata</i> , <i>Sterculia urens</i> <i>Gelidium maxima</i> <i>nsii</i>	Granisetron HCl	Better disintegrant than synthetic disintegrants
Glasswort mucilage powder	<i>Salicornia frutescens</i>	Aceclofenac	Better disintegrating agent than Acid-disol.

1.7.2 Synthetic superdisintegrants: Superdisintegrant used is the one that is effective at low concentration and has greater disintegrating efficiency and they are more effective intragranularly. The problem is, it is hygroscopic therefore not used with moisture sensitive drugs. And these superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes the tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

Examples: Croscarmellose sodium, crospovidone, carmellose, carmellose calcium, sodium starch glycolate ion exchange resins (e.g. Indion 414) Sodium starch glycolate has good flowability than croscarmellose sodium. Crospovidone is fibrous in nature and

highly compactable. Granules with superdisintegrants in aqueous media swelling of granules due to superdisintegrants.

Table 1.2: Examples of synthetic superdisintegrants in marketed formulations

DRUG	SUPERDISINTEGRANTS	METHOD
Carvedilol	Cross povidone, Cross carmellosesodium, Sodium starch glycolate	Directcompression
Valsartan	Cross povidone, Cross carmellosesodium, Sodium starch glycolate	Directcompression
Ziduovudine	B-cyclodextrin, crosspovidone	Directcompression
OndasetronHcl	Crosscarmellosesodium, Sodium starch glycolate	Directcompression
LevocetirizineHcl	Cetricacid, Sodium bicarbonate	Directcompression
ChlorpromazineHcl	Crosspovidone, Acid-di-sol, Sodium starch glycolate	Directcompression
ReloxifeneHcl	Crosscarmellosesodium, Sodium starch glycolate	Directcompression
Terbutalinesulphate	Crosspovidone, Cross carmellose sodium	Directcompression
Disulfuram	Sodiumstarchglycolate	Drygranulation
Aceclofenac	Acid-di-sol, Sodiumstarch glycolate	Wetgranulation

Lisinopril	Acid-di-sol, Sodium starch glycolate	Wet granulation
Fentanyl citrate	Kollidon CL	Sublingual method
Losartan potassium	Crosscarmellosesodium, Sodium starch glycolate	Direct compression

1.7.3 Mechanism of superdisintegrants by swelling

Swelling index of the superdisintegrants is commonly studied in simulated saliva. Volume occupied by the material at the end of 4 h should be noted and swelling index is calculated by the formula.

$$\text{Swelling Index} = \left[\frac{\text{Final volume} - \text{Initial volume}}{\text{Initial volume}} \right] \times 100$$

1.8 Selecting the superdisintegrant^{22, 23}: Although the superdisintegrant primarily affects the rate of disintegration, when used at high levels it can also affect mouth feel, tablet hardness, and friability. Thus, several factors must be considered when selecting a superdisintegrant.

a. Disintegration: The disintegrant must quickly wick saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth. Compactability. When manufacturing an FDTs, it is desirable to have tablets with acceptable hardness at a given compression force to produce robust tablets that avoid the need to use specialized packaging while maximizing production speed. Thus, a more compactable disintegrant will produce stronger, less-friable tablets.

b. Mouth feel: To achieve patient compliance, FDTs must provide a palatable experience to the patient. Large particles can result in a gritty feeling in the mouth. Thus, small particles are preferred. If the tablet forms a gel-like consistency on contact with water, however, it produces a gummy texture that many consumers find objectionable.

c. Flow: As with all direct-compression tablet formulations, attaining good flow and content uniformity is important to achieving the required dosage per unit. In typical tablet formulations, superdisintegrants are used at 2-5 wt.% of the tablet formulation. With FDT formulations, disintegrant levels can be significantly higher. At these higher use levels, the flow properties of the disintegrant are more important because it makes a greater contribution to the flow characteristics of the total blend.

d. Taste-masking agents: Taste masking of drug may be achieved with preventing the exposure of drug to the tongue through processing or adding competing taste-masking agents. Exposure of solubilized drug to the oral cavity can be prevented by encapsulation in polymer systems or complexation. The approaches are as follows:

- Layering the drug onto inert beads using a binder followed by coating with a taste-masking polymer.
- Granulating the drug and coating with a taste masking polymer.
- Spray drying the drug dispersed or dissolved in a polymeric solution to get taste-masked particles.
- Complexation by the use of inclusion in cyclodextrins.
- Psychological modulation of bitterness.
- Coacervation to form microencapsulated drug within a polymer.
- Formation of pellets by extrusion spheronization.

e. Sweeteners: Sucrose and other natural sweeteners, such as sorbitol, can be used in effervescent products, although artificial sweetening agents are customary. However, the application of artificial sweeteners is restricted by health regulations. Saccharin or its sodium and calcium salts are used as sweeteners. Aspartame is also employed as a sweetener in effervescent tablets. Earlier, cyclamates and cyclamic acid were the artificial sweeteners of choice, but their use has now been restricted. Some commonly used sweeteners are:

Example: Sorbitol, Mannitol, Maltitol solution, Maltitol, Xylitol, Erythritol, Sucrose, Fructose, Maltose, aspartame, Glycerin, sugars derivatives etc.

Disintegrating agents are substances routinely included in the tablet formulations to aid in the breakup of the compacted mass when it is put into a fluid environment. They promote moisture penetration and dispersion of the tablet matrix. These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the superdisintegrants swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective superdisintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs.

f. Binders: Main role of Binders is to keep the composition of these fast melting tablets together during the compression stage. Binders can either be liquid, semisolid, solid or mixtures of varying molecular weights such as polyethylene glycol. The right selection of a binder or combination of binders is essential to maintain the integrity and stability of the tablet. The temperature of the excipient should be preferably around 30–35°C for faster melting properties. Further, its incorporation imparts smooth texture and disintegration characteristics to the system.

Example: Binders commonly used are cellulosic polymers such as ethylcellulose, hydroxypropylcellulose (HPC), and hydroxypropylmethylcellulose (HPMC), alone or in admixtures with povidones, polyvinyl alcohols, and acrylic polymers. Acrylic polymers used are the ammonium methacrylate copolymer, polyacrylate, and polymethacrylate. Among the cellulosic

g. Lubricants: Lubricants remove grittiness and assist in the drug transport mechanism from the mouth down into the stomach. Example: Magnesium stearate, stearic acid, leucine, sodium benzoate, talc, magnesium lauryl sulphate, liquid paraffin etc.

h. Flavours: Example: Peppermint flavour, clove oil, anise oil, eucalyptus oil. Flavoring agents include, vanilla, citrus oils, fruit essences etc.

i. Fillers: Example: Directly compressible spray dried Mannitol, Sorbitol, xylitol, calcium carbonate, magnesium carbonate, calcium phosphate, pregelatinized starch, magnesium trisilicate, aluminium hydroxide etc.

j. Surface active agents: Example: sodiumdoecylsulfate, sodium laurylsulfate, Tweens, Spans, polyoxyethylene stearate

1.8.1 Mechanism of tablet disintegrants: The tablet breaks to primary particles by one or more of the mechanisms listed below.

- a. By capillary action
- b. By swelling
- c. Because of heat of wetting
- d. Due to disintegrating particle/particle repulsive forces
- e. Due to deformation
- f. Due to release of gases
- g. By enzymatic action

a. By capillary action: Disintegration by capillary action is always the first step. When we put the tablet into a suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug / excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

b. By 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 worth noting that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slowed down.

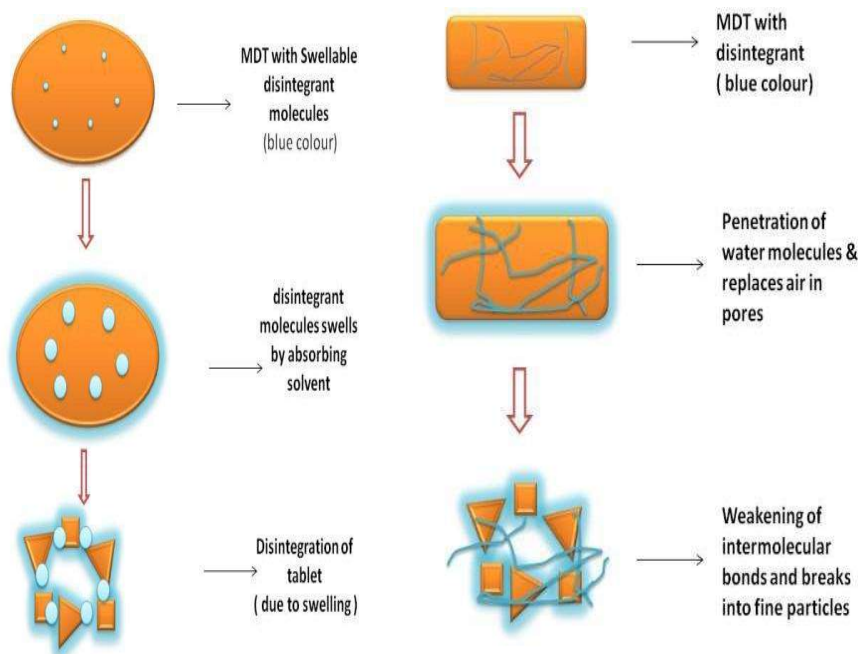


Fig.no1.1:Disintegrationoftabletbywickingandswelling

c. Because of heat of wetting

When disintegrants with exothermic properties get wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

d. Due to deformation

Hess had proved that 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.

e. Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Guyot-Hermann has proposed a particle

repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

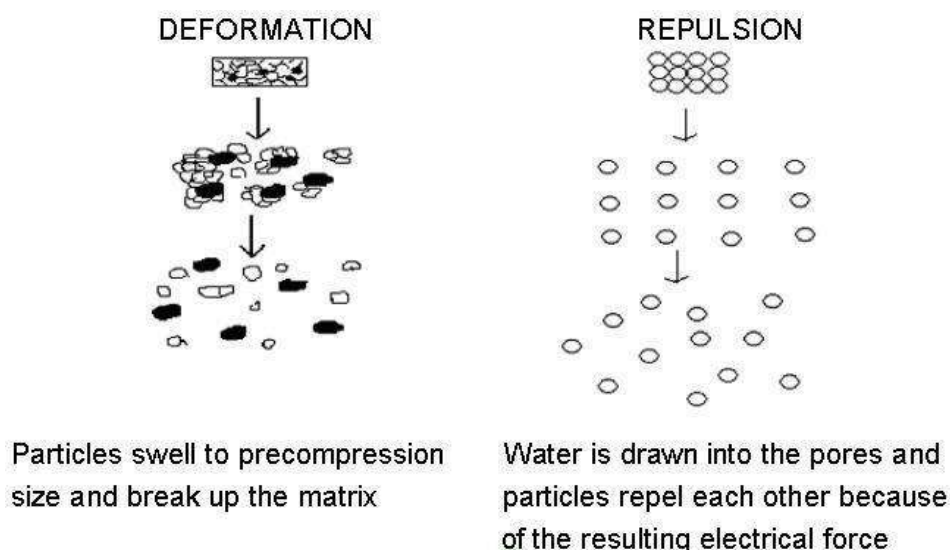


Fig.no1.2:Disintegrationbydeformationandrepulsion

f. Duetoreleaseof gases

Carbon dioxide released within tablets on wetting due to interaction between bicarbonateandcarbonatewithcitricacidortartaricacid.The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when pharmacist needs to formulate very rapidly dissolving tablets or fast disintegrating tablet.

As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

e.Byenzymaticreaction

Here,enzymes presents in the body act as disintegrants.These enzymes destroy the binding action of binder and helps in disintegration.

Table 1.3: List of Disintegrating Enzymes

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

Superdisintegrants	Example	Mechanism of action	Special comment
Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol®	Crosslinked cellulose	Swells 4-8 folds in <10 seconds. Swelling and wicking.	Swells in two dimensions. Direct compression or granulation Starch free
Crospovidone CrospovidonM® 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
Sodium starch glycolate Explotab® Primogel®	Crosslinked starch	Swells 7-12 folds in <30 seconds	Swells in three dimensions and high level as sustain release matrix
Alginate-chitosan NF Satialgine®	Crosslinked alginate-chitosan	Rapid swelling in aqueous medium or wicking action	Promote disintegration

			both dry or wet granulation
Calcium silicate		Wicking action	Highly porous, light weight, optimum conc. is between 20-40%

Table 1.4 List of superdisintegrants

1.9 CONVENTIONAL TECHNIQUES FOR FDT

Table 1.5. List of conventional techniques for fast dissolving tablets

S.No.	Techniques	Method and characteristics of prepared FDTs
1	Disintegrant addition	The basic principle involved in formulating Fast disintegrating tablets by disintegrant addition technique is addition of superdisintegrants in optimum concentration so as to achieve mouth dissolving along with the good mouth feel. Sodium starch glycolate, croscopolone and croscarmellose are some of the popular superdisintegrants. Characteristics: Similar to conventional tablets with higher % of disintegrants, lower hardness and higher % of friability.
2	Freeze Drying or Lyophilization	Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biologicals at low temperature under conditions that allow removal of water by sublimation. The drug is dissolved or dispersed in an aqueous solution of a carrier. The mixture is poured into the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen freezing tunnel to freeze the drug solution. Then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying.

		Characteristics: The preparations are highly porous, have high specific surface area, dissolve rapidly and ultimately show improved absorption and bioavailability.
3	Tablet Molding	In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydroalcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air drying. Characteristics: Molded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution.
4	Sublimation	Inert solid ingredients that volatilize rapidly like urea, camphor ammonium carbonate, ammonium bicarbonate, hexamethylenetetramine) were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structure. Characteristics: Porous structure that enhances dissolution by using volatile material or solvent e.g. cyclohexane, benzene etc.
5	Spray-Drying	The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or cross-carmellose sodium as disintegrating and an acidic material (e.g. citric acid) and or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. Characteristics: Prepared tablet disintegrates within 20 seconds when immersed in an aqueous medium.
6.	Direct Compression²⁴	Direct compression method is the easiest way to manufacture tablets. Conventional equipment, commonly

		available excipients and a limited number of processing steps are involved in direct compression. Characteristics: It is most cost effective tablet manufacturing technique.
7	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. Characteristics: The dried product can be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.
8.	Cotton candy process	Involves the formation of matrix of polysaccharides by simultaneous action of flash melting and spinning. This candy floss matrix is then milled and blended with active ingredients and excipients after re-crystallization and subsequently compressed to FDTs. Characteristics: It can accommodate high doses of drug and offers improved mechanical strength
9	Nanonization	Involves size reduction of drug to nanosize by milling the drug using a proprietary wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into FDTs. Characteristics: It is used for poorly water soluble drugs. It leads to higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wider range of doses (up to 200 mg of drug per unit).
10	Compaction a) Melt granulation	Prepared by incorporating a hydrophilic waxy binder (super polystate) PEG-6-stearate. Super polystate not only acts as binder and increases physical resistance of tablet but also helps the disintegration of tablet.

	b)Phase-transition process	Characteristics: It melts in the mouth and solubilizes rapidly leaving no residue. Prepared by compressing a powder containing two sugar alcohols with high and low melting points and subsequent heating at a temperature between their melting points. The tablet hardness was increased after heating process due to increase of inter particle bond induced by phase transition of lower melting point sugar alcohol. Characteristics: The compatibility increased and so sufficient hardness gained by the formulation.
11	Fast Dissolving Films	A non-aqueous solution is prepared containing water soluble film forming polymer drug and other taste masking ingredients are used to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated micro particles of the drug can be incorporated into the film. Characteristics: The thin film size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavored after taste.

Table 1.6: Promising Drugs to be incorporated in Fast Dissolving Tablets²⁵

Sl.No	THERAPEUTIC ACTIVITY	DRUGS USED
1	Analgesic and Anti-inflammatory agents	Piroxicam, Nabumetone, Ibuprofen, Oxypenbutazone, Oxaprozin, Meclofenamic Acid, Fenbufen, Aloxiprin.
2	Anthelmintics	Hydroxyl Napthoate, Thiabendazole, Mebendazole, Praziquantel, Pyrantel, Ivermectin, Cambendazole, Albendazole
3	Antiarrhythmic agents	Vanidine Sulphate, Flecainide Acetate, Disopyramide, Amiodarone HCl
4	Antibacterial agents	Trimethoprim, Sulphapyridine, Sulphabenzamide, Sulphadoxine, Penicillin, Banethamine, Ethionamide, Nitrofurantoin, Doxycycline, Cloxacillin, Clofazimine, Cinoxicam

5	Anticoagulants	Nicoumalone, Phenindione, Dipyrimidine, Dicoumarol
6	Antidepressant	MaprotilineHcl, TrimipramineMaleate, TrazodoneHcl, MianserinHcl, Clazindol, Amoxapine.
7	Antidiabetics	Tolbutamide, Glipizide, Gliclazide, Glibenclamide, Chlorpropamide, Acetohexamide
8	Antiepileptics	Methylphenobarbitone, Oxycarbazepine, Phenytoin, Sulthiame, Phenobarbitone, Phenacetamide, Methion, Clonazepam
9	Antifungal	Itraconazole, Tioconazole, Terconazole, Amphitericin, Natomycin, Griseofulvin, Flucytocine, Clotrimazole
10	Antimalarial	Mefloquine, Chloroquine, Pyramethamine, CholoroproguanilHcl, Amodiaquine
11	Antimuscarinic agents	Tropecamide, OxyphencyclamineHcl, Hyoscyamine, Biperidine, Atropine
12	Antiprotozoal agents	Tinidazole, Benznidazole, Metronidazole, Diloxamidefuroate, Clloquinol
13	Cardiac inotropic agents	Enoximone, Medigoxin, Digoxin, Digitoxin, Amrinone
14	Antiparkinsonian agents	YsurideMaleate, Mesylate, Bromocriptine
15	Antithyroidagents	Carbimazole, Propylthiouracil.
16	Localanaesthetics	Lidocaine
17	Neuromuscular agents	Pyridostigmine

CHAPTER-2

DRUG AND EXCIPIENT PROFILE

2.1 DAPSONE

Chemical structure:

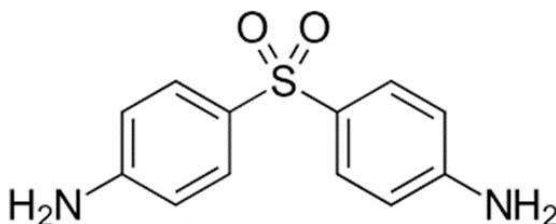


Figure 2.1 structure of dapsone

Molecular formula	: C ₁₂ H ₁₂ N ₂ O ₂ S
Molecular weight	: 248.302
Chemical name	: 4,4'-sulfonyldianiline (SDA) or diaminodiphenyl sulfone
Solubility	: Dapsone is soluble in organic solvents such as DMSO and Dimethylformamide and is low soluble in water
Melting point	: 175-176°C
p^{Ka} and pH	: 2.41 and 6-8
Dose	: Adults and teenagers—50 to 100 milligrams Children—Dose is based on body weight
Category	: Antileprotic

Storage : Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Keep from freezing.

Keep out of the reach of children.

Do not keep outdated medicine or medicine no longer needed.

Beer's Range :1.6-9.6

Physical Properties : 4,4'-sulfonyldianiline appears as odorless white or creamy white crystalline powder. Slightly bitter taste.

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

Pharmacokinetics:

Absorption

Bioavailability is 70 to 80% following oral administration.

Distribution

The volume of distribution of dapsone is reportedly 1.5-2.5 L/kg in adults. Dapsone is reportedly retained in skin, muscle, kidneys, and liver; trace concentrations of the drug may be present in these tissues up to 3 weeks after discontinuance of dapsone therapy.

Metabolism

Dapsone is acetylated in the liver to monoacetyl and diacetyl derivatives. The major metabolite of dapsone is [monoacetyl dapsone](#) (MADDS).

Elimination

Approximately 20% of each dose of dapsone is excreted in urine as unchanged drug, 70-85% is excreted in urine as [water-soluble](#) metabolites, and a small amount is excreted in feces. Dapsone is excreted in urine as an acid-labile mono-N-glucuronide and mono-N-sulfamate derivatives in addition to some unidentified metabolites.

Contraindications

Avoid use in cardiac or pulmonary disease, anemia, G6PD deficiency.

Methemoglobin reductase deficiency.

Hypersensitivity to dapson or any of its components.

Adverse effects:

More common:

- Back, leg, or stomach pains
- Bluish fingernails, lips, or skin
- Difficult breathing
- Fever
- Loss of appetite
- Pale skin
- Skin rash
- Unusual tiredness or weakness

Rare:

- Itching, dryness, redness, scaling, or peeling of the skin, or loss of hair
- Mood or other mental changes
- Numbness, tingling, pain, burning, or weakness in hands or feet
- Sore throat
- Unusual bleeding or bruising
- Yellow eyes or skin

Drug interactions:

Although certain medicines should not be used together at all, in other cases two different medicines may be used together even if an interaction might occur. In these cases, your doctor may want to change the dose, or other precautions may be necessary. When you are taking this medicine, it is especially important that your healthcare professional know if you are taking any of the medicines listed below. The following interactions have been selected on the basis of their potential significance and are not necessarily all-inclusive.

Using this medicine with any of the following medicines is usually not recommended, but may be required in some cases. If both medicines are prescribed together, your doctor may change the dose or how often you use one or both of the medicines.

- Methotrexate
- Warfarin
- Zidovudine

Using this medicine with any of the following medicines may cause an increased risk of certain side effects, but using both drugs may be the best treatment for you. If both medicines are prescribed together, your doctor may change the dose or how often you use one or both of the medicines.

- Amprenavir
- Atazanavir
- Fosamprenavir
- Rifabutin
- Rifapentine

2.2 EXCIPIENT PROFILE

2.2.1 PLANTAGO OVATA



Figure 2.2.1 plantago ovata

NAME: Plantago ovata

BOTANICAL NAME: Plantago ovata forssk

FAMILY: Plantaginaceae

PART USED: seed, leaves

VERNACULAR NAME:

TAMIL: Iskolvirai, Iskol, Isphagol, Ishappukolvirai, Ishappukol

ENGLISH: Ispaghula, Psyllium, Blond Psyllium, Spigel Seeds, Ripple Grass

TELUGU: Isphagula, Isapgaluvittulu,

Isapagala **SANSKRIT:** Ashwagol, Ishadgola,

Ashwakarna **HINDI:** Isabgol, Isabgul, Issufgul,

Ispaghul,

Isabgol **BENGALI:** Esphopgol, Isabgul, Isshopgul, Ispag

hul

MORPHOLOGICAL CHARACTERISTICS:

The plant is cultivated largely in Gujarat, Punjab, and South Rajasthan. The factory for preparation of husk is located at Sidhpur in North Gujarat. In Maharashtra, it is found to be grown successfully near Pune, about 30 thousand hectares of area is said to be under cultivation for the drug in India.

ORGANOLEPTIC CHARACTERS:

Colour: Pinkish–grey or brown

Odour: None **Taste:** Mucilaginous, bland

Size: 10 to 35 mm in length and 1 to 1.75 mm in width,

Shape: It is ovate cymbiform. One thousand seeds weigh about 1.5 g.

2.2.2 FENUGREEKSEED:-



Figure 2.2.2 fenugreek seed

NAME: Fenugreek Seed.

BOTANICAL NAME: *Trigonella foenum-graecum*.

FAMILY: Fabaceae.

PART USED: Seed, Dried leaves.

VERNACULAR NAME:

TAMIL:

Venthayam **ENGLISH:** F

enugreek **TELUGU:**

Menthulu **SANSKRIT:**

Methika

HINDI: Methi, Saagmethi, Kasurimethi

MALAYALAM: Uluva

KANADA: Menthia

MORPHOLOGICAL CHARACTERISTICS: - The plant grows wild in Northern India and is cultivated as a crop throughout India. It is also cultivated in Southern and

Eastern Europe, Pakistan, France, Morocco, and Egypt.

Colour:light to dark yellow, brown.

Odour:Characteristics

Size:5-8mm long and 1-2mm thick.

Shape:Rhomboidal, smooth

Taste:Mucilaginous and slightly bitter.

PHYTOCHEMICAL CONSTITUENTS:-

The phytochemical analysis showed that Fenugreek seed contained Saponin, glycosides, Coumarin, Alkaloids, choline, proteins, flavonoids, prolamine.

2.2.3 BANANA POWDER:-



Figure 2.2.3 Banana powder

NAME:Banana powder.

BOTANICAL NAME:*Musa acuminata*

FAMILY:Musaceae

PART USED:Stem, Flower and Fruits.

VERNACULAR NAME:

TAMIL:vaazhappazham

ENGLISH: Banana

TELUGU:Aratipandu**SA**

NSKRIT:

kadalika**HINDI:** kela

MALAYALAM:vaazhappazham

KANADA:Balehannu

MORPHOLOGICAL CHARACTERISTICS:-

Banana is grown in India on a variety of soils such as the heavy clay soil of the Cauvery delta, alluvial soil of the Gangetic delta, black loam in Maharashtra, coastal sandy loams and the red lateritic soil of the hilly tracts of Kerala.

Colour: yellow

Odour: Naturally sweet banana smell

Taste: sour taste

PHYTOCHEMICAL CONSTITUENTS:-

The Phytochemical analysis showed that Banana powder contained flavonoids, fatty acid, carotenoids, phytosterols, tannins, terpenoids, glycosides and alkaloids

2.3 MANNITOL:-

Structural formula:

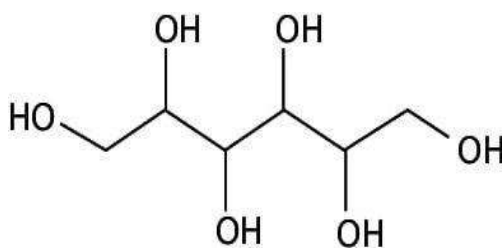


Figure 2.3 Mannitol

Synonyms: Mannitol, mannidex, mannazucker.

Non-proprietaryName : USP-Mannitol,

Functionalcategory : Sweetener, humectant, texturizer, stabilizer, bulking agent

Chemicalnames: D-Mannitol

MolecularWeight : 182.17g/mol

Incompatibilities: Incompatible with omeprazole.

Solubility : Soluble in water, very slightly soluble in ethanol; practically insoluble in ether.

Description : mannitol appears as odorless, white crystalline powder or free-flowing granules, Sweet taste.

Stability and storage conditions: Mannitol 25% (Invenex) was chemically and physically stable. Mannitol solutions should be stored at room temperature and protected from freezing.

Applications: It is Used in the food industry as anti-caking and free flowing agent, stabilizer, thickener, and non-nutritive sweetener.

2.4 MICROCRYSTALLINE CELLULOSE

Structural formula:

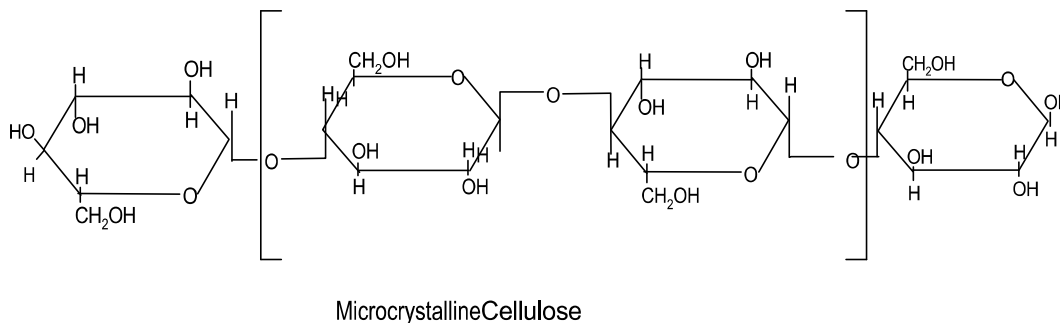


Figure 2.4 microcrystalline cellulose

Synonyms : Cellulosegel, Crystallinecellulose, AvicelPH10.

Non-proprietaryname: NF-Microcrystallinecellulose, USP-Microcrystalline
cellulose.

Chemical names : Cellulose.

Chemical formula

$:(C_6H_{10}O_5)_n$ **Mole**

cular weight : 36,000(approx.)

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

Functional category: Tabletandcapsulediluent, tablet disintegrant, suspending and
viscosity increasing agent.

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

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

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

2.5 POLYVINYLPIRROLIDONE(PVP):

Structural formula:

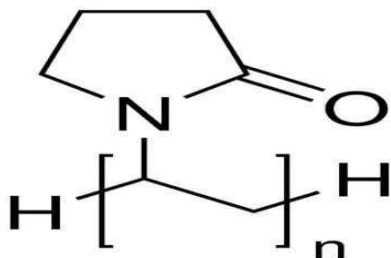


figure 2.5 polyvinylpyrrolidone (pvp)

Synonyms : Povidone, PVP, Polyvidone, Plasdone, Kollidon, Poly[1-(2-oxo-1-pyrrolidinyl) ethylene], 1-vinyl-2-pyrrolidinone polymer, 2-pyrrolidinone-1-

ethenyl- homopolymer.

Non-proprietary Name : BP-Polyvinylpyrrolidones, USP-Polyvinylpyrrolidone, JP-Polyvinylpyrrolidone.

Functional category : Stabilizing agent.**Chemical**

names : 1-Ethyenylpyrrolidin-2-one

Chemical formula : $(C_6H_9NO)_n$

Incompatibilities : Incompatible with Indomethacin, Ibuprofen.

Solubility : Soluble in water, ethanol, methanol, chloroform, acids, and amines. Insoluble in ethers, hydrocarbons, some esters, some ketones, and mineral oil.

Description: Fine, white to off white odourless, very hygroscopic, amorphous powder.

Stability and storage conditions: Chemically stable in dry form. Can be stored in ordinary conditions but in a tightly closed container as it is highly hygroscopic.

Applications: It is used as a Binder, Lubricant, Stabilizing agent.

2.6 MAGNESIUM STEARATE:

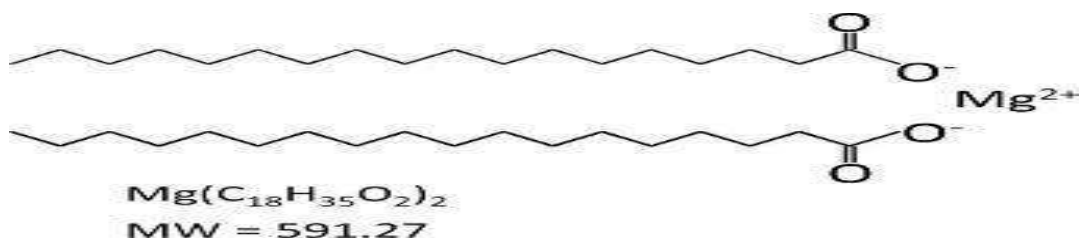


figure 2.6 magnesium stearate S

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

Molecularweight : 591.3.

Density(He) :1.03-1.08 g/cm³

Bulkvolume :3.0-8.4ml/g

Tapped volume :2.5-6.2ml/g

Functional category :Tabletandcapsulelubricant.

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%)

Stabilityandstorageconditions:Stable,non-selfpolymerizable.Storeinacool,dry place in a well closed container.

Incompatibilities: Incompatiblewith strongacids, alkalies, iron salts and with strong oxidising materials.

Safety:Describedasinertornuisancedust.OSHAhasadoptedlimitsof15mg/m³for 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 antiadherent in the concentration range of 0.25 to 2.0%.

2.7 Aspartame:

Structural formula:

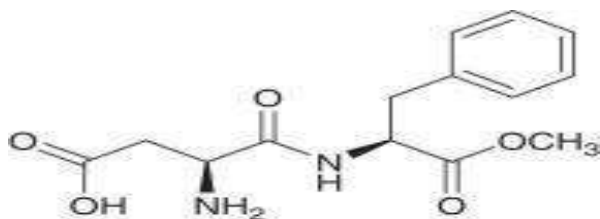


Figure2.7Aspartame

Synonyms :APM, Sanecta, Aspartylphenylaminemethylester,
Nutrasweet, Tri-sweet.

Nonproprietaryname: USP–Aspartame, IP –Aspartame, BP–Aspartame.

Chemicalname :L-aspartic acid, L-phenylalanine.

Functional category :Sweetening agent.

Description: It occurs as white and almost odorless 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.

2.8 TALC:

Synonyms : Mussolinite, Agalite, Asbestine

Non-proprietaryname: IP-Talc, USP-Talc, BP-Talc

Empirical formula : $\text{H}_2\text{Mg}_3\text{O}_{12}\text{Si}_4$

Chemical names : hydroxy-oxido-oxosilane

Molecularweight:379.27g/mol

Density:Bulkdensity,0.5g/cm³;TappedDensity,0.8g/cm³

Description :Fine white powder, odourless, free from grittiness, readily adhered to skin,unctuoustothetouchisLight,homogeneous,whitepowder,greasytothetouch (non-abrasive)

Functionalcategory:tabletglidantandlubricant,coating agent.

Solubility: Practically insoluble in water, dilute acids and alkalies, and organic solvents.

stability and storage conditions: Talc is a stable material and hence it can be sterilizationbyheatingat1600Cfor notlessthananhour.Itmayalsobesterilizedby exposure to the ethylene oxide or gamma irradiation. Talc is a stable material and henceitcanbesterilizationbyheatingat1600Cfor notlessthananhour.Itmayalso be sterilized by exposure to the ethylene oxide or gamma irradiation.

Applications: Talc is used as an excipient in tablet formulations. It helps prevent stickingduringtabletcompressionandimprovespowderflowproperties.Talcisused as a coating agent on pills and tablets to improve their appearance and ease of swallowing. It can also act as a filler in certain pharmaceutical formulations.

CHAPTER-3

LITERATURE REVIEW

1. Goyani Sandip M et al.,¹ Formulated meclizine HCl as fast disintegrating tablets using different disintegrants which would disintegrate tablets rapidly in oral cavity. Nine batches of meclizine HCl orally disintegrating tablet were prepared by direct compression method using sodium starch glycolate, croscarmellose sodium, crospovidone as disintegrant in different concentrations in order to achieve faster disintegration of the tablets. The influence of the disintegrant concentration on the release of meclizine HCl was studied. The formulated batches were characterized by different physical parameters. Physical parameters of all formulated tablets were within acceptable limits. The study revealed that the formulation containing crospovidone as disintegrants showed faster disintegration compared to others.⁸

2. Gamal M. Mahrous et al.,² Prepared and developed ODTs of Meclizine (MZ HCl) with sufficient mechanical integrity, content uniformity, and acceptable palatability to assist patients of any age for easy administration. Meclizine HCl is an anti-emetic drug used for management of dyspepsia, heartburn, epigastric pain, nausea, and vomiting. The interaction of meclizine and used excipients was studied using differential scanning calorimetry (DSC). The ODTs were prepared by direct compression method. The effect of varying concentrations of different superdisintegrants such as crospovidone, croscarmellose sodium, and sodium starch glycolate on disintegration time and dissolution rate was studied. The prepared tablets were evaluated for hardness, friability, and disintegration time and in-vitro drug release. DSC studies revealed that no interaction between the drug and the used excipients. All tablets had hardness in the range 4.2–5.6 kp and friability less than 1%. Weight variation and drug content of all formulations were within official limits according to BP. In-vitro drug release study of ODTs showed that more than 90% of the drug was released within 10 min. Palatability test by 12 volunteers showed acceptable taste and mouth feel. Thus, results obtained

conclusively demonstrated successful rapid disintegration of the formulated tablets and acceptable palatability.⁹

3. Gupta M.M et al.,³ Investigated use of tablets for motion sickness during repeated motions such as from the swell of the sea, the movement of a car, the motion of a plane in turbulent air, etc. Most medications for motion sickness need to be taken at least 30 minutes prior to exposure to the activity that can cause the problem. These dosage forms would be preferred by pediatric and geriatric patients since these are not associated with fear of choking. Meclizine HCl, a poorly water soluble and bitter drug could be successfully incorporated in the fast dissolving films with the help of solubilizers such as β -Cyclodextrin and PEG-400.¹⁰

4. Reshu Gupta et al.,⁴ Has formulated fast dissolving tablets of midazolam hydrochloride (MH), an antiemetic drug. Fast disintegrating tablets (FDT) of midazolam hydrochloride were prepared with the addition of different superdisintegrants like Kollidon CL, AcDiSol SD711 and Glycolys. Each of these superdisintegrants were used in concentrations of 2-4% w/w. Formulation with 3% w/w Kollidon CL showed minimum disintegration time (<20 seconds). Furthermore, increasing the concentration of the superdisintegrants did not decrease the disintegration time (DT) significantly. The excipients used for this study were based on the compatibility studies. All the formulations were prepared by direct compression method. Among all the formulations Kollidon CL at 2.4 mg/tablet gives 99.65% drug release in 10 min. by spectroscopic method. It was considered as optimized batch. The optimized batch passed all the evaluation parameters and stability studies.¹¹

5. H.A. Patel et al.,⁵ Developed and characterized fast dissolving tablets of Domperidone using direct compression and wet granulation technique. In this method the different excipients used were microcrystalline cellulose, Cross carmellose sodium, Cross povidone, Sodium starch glycolate, Magnesium Stearate, Talc etc. Pre compression and post compression parameters were evaluated for all the ten formulations (D1-D10). In vitro drug release showed that the drug released was almost in the range of 94-97% in 10 minutes. By comparing cumulative drug release, in vitro disintegration time and wetting time, it was found that direct compression method was

better than wet granulation method. Depending upon cumulative drug release, in vitro disintegration time, and wetting time results formulation D1 was selected for stability studies and subjected to stability studies at 25°C, 30°C and 40°C for 2 months. Overall, formulation D1 formulated by direct compression was found to be the best formulation.¹²

6. Mohd Azharuddin et al.,⁶ Formulated and evaluated fast disintegrating tablets of Granisetron HCl using natural polymers. Tablets were prepared by direct compression method using different drug polymer concentrations. Fourier Transform Infrared Spectroscopy (FT-IR) study revealed no chemical interaction between drug and polymers used. Precompression and postcompression parameters were within the pharmacopoeia limits. Disintegration and dissolution data of tablets were directly proportional to the superdisintegrants concentration. Selected fast dissolving tablet F8 containing plantago ovate 5% w/w has released 99.66 % within 3 min.¹³

7. Malviya et al.,⁷ have extracted and evaluated mango peel pectin as a Superdisintegrants in tablets, mango peel pectin had comparatively lesser release of drug as compared to sodium starch glycolate for a specific period of time¹⁷.

8. MATahiretal.,⁸ Prepared fast dissolving tablets of diclofenac sodium using isabgol mucilage as superdisintegrant. Rapidly disintegrating tablets were developed by compression methods using dry & wet powders containing drugs. Drug content in all the formulations were also found to be in the acceptable range between 98 to 100 %. Friability was found to be below 1.0%. Water absorption ratio was found to be in the range 60 & 90 % for directly compressed tablets as compared to wet granulation method where a maximum of 51% was observed. 2-5 % of mucilage can be used as Superdisintegrants as above this concentration tablets were more fragile. Stability studies were conducted for formulation FD4 & FW4 (Table 3) which indicated that there were no significant changes in physical appearance and drug content at the end of 90 days of storage period ($p < 0.05$).

9. Gupta GD et al.,⁹ Formulated dispersible tablets of nimesulide using natural substances as disintegrants such as Plantago ovate seed husk, Cassia tora and Cassia nodosa in different concentrations. The formulations were evaluated and were

compared with marketed products. It was observed that all the formulations were acceptable with the reasonable limit of standards required for dispersible tablets. The study revealed that the natural gums used as disintegrants were effective in low (5%) concentration.

10. Srinivas K et al.,¹⁰ Studied disintegrating properties of *Plantago ovata* mucilage powder, *Plantago ovata* husk powder, *Ocimum basilicum* mucilage powder and *Ocimum basilicum* seed powder using Ibuprofen. The formulations were evaluated for their disintegrating properties by comparing with the formulations of starch powder as standard disintegrant. This study revealed that *Plantago ovata* seed powder and mucilage powder were effective in low concentrations (5%) as disintegrants compared to others and revealed the poor relation between the swelling index and disintegrating efficiency⁷. The physiologically active, gel-forming fraction of the alkali-extractable polysaccharides of *Plantago ovata* Forsk seed husk and some derived partial hydrolysis products were studied by compositional and methylation analysis and NMR spectroscopy. The material was found to be a neutral arabinoxylan.

11. Shanmugam S et al.,¹¹ Developed fast dissolving tablets of aceclofenac using microcrystalline cellulose as a direct compressible vehicle were designed with an aim to compare the effects of natural superdisintegrant i.e., isolated mucilage of *Plantago ovata* and synthetic superdisintegrants like sodium starch glycolate (SSG) and croscarmellose sodium (Ac-di-sol). The tablets were evaluated for post-compression parameters. *Plantago ovata* showed the highest swelling index than SSG and Ac-di-sol. Hence, they concluded natural superdisintegrants like *Plantago ovata* mucilage showed better disintegrating property than the most widely used synthetic superdisintegrants like SSG and Ac-di-sol in the formulations of fast dissolving tablets.

12. Santanu Chakraborty et al.,¹² Developed Piroxicam dispersible tablets using natural disintegrants such as *Plantago ovata* seed husk, Cassia tora, and cross-linked tragacanth were prepared with an objective to release the drug rapidly with predetermined rate. The formulated batches were characterized by different physical parameters. This study revealed that the formulation prepared by direct compression exhibited better dissolution, disintegration at low concentration of natural disintegrants.

13. Kuchekar BS et al.,¹³ Developed dispersible tablets of famotidine using mucilage and seed powder of *Isapgghulat* to study the disintegrant property. The formulated tablets were evaluated and were found to be within the prescribed limits. The wetting time decreased with the increase in concentration of seed and mucilage powder. The *in-vitro* dissolution profile showed maximum drug release from all the formulations and concluded that both the mucilage and seed powder exhibited potentially as a rapidly disintegrating agent for faster drug dissolution and improved bioavailability.

14. Deveswaran R et al.,¹⁴ Developed fast disintegrating tablets of metoprolol tartrate by direct compression using different concentrations of *Plantago ovata* mucilage as natural superdisintegrant. Compatibility of drug with the excipients was checked by FTIR and DSC studies. The pre and post-compression parameters evaluated were within the prescribed limits. *In-vitro* dispersion time decreases with the increase in concentration of natural superdisintegrant. The formulations were found to be stable on conducting the stability studies as per the ICH guidelines. They concluded that the tablets of Metoprolol tartrate showing enhanced release rate may lead to improved bioavailability and effective therapy by using *Plantago ovata* mucilage as natural superdisintegrant.

15. Pande S.D et al.,¹⁵ Prepared amlodipine Besylate fast dissolving tablet by direct compression method using different concentrations of *plantago ovate* mucilage as a natural superdisintegrant. All formulations were evaluated for weight variation, hardness, friability, disintegration time, drug content and dissolution. The optimized formulation shows less *in vitro* disintegration time 11.69 sec with rapid *in vitro* dissolution within 16 mins. *In vitro* disintegration time decreases with increase in concentration of natural superdisintegrant. The conclusion is clear that the dried isabgol mucilage as a superdisintergrant in the tablet is suitable for the formulation of fast disintegrating tablet.

CHAPTER-4

AIM, OBJECTIVE, PLAN OF WORK

AIM:

The aim of the current investigation is to formulate and evaluate the Dapsone fast disintegrating tablets of Dapsone.

OBJECTIVES:

The objectives of the current research work are as follows

- To collect and authenticate Natural Superdisintegrant
- To conduct preformulation study
- To formulate solid dispersion
- To formulate fast disintegrating tablets using natural superdisintegrants

PLAN OF WORK

- Literature review
- Selection of drug and natural excipients
- Identification of the drug by UV spectroscopy and by melting point test
- Solubility study for the drug (Class-II)
- Preparation of solid dispersion to improve the solubility
- Characterization of solid dispersion by XRD studies
- Precompression parameters / Derived properties for the API & Excipients
 - a. Bulk density
 - b. Tapped density
 - c. Angle of Repose
 - d. Carr's Index
 - e. Hausner's Ratio
- Formulation of Dapsone FDT using superdisintegrants by direct compression method
- Postcompression Evaluation studies
 - a. Morphological characteristics of the tablets

- b. Thickness
- c. Hardness
- d. Friability
- e. Weightvariation
- f. Drugcontentuniformity
- g. Wettingtime
- h. Waterabsorption ratio
- i. Disintegrationtime
- j. In-vitrodissolutionstudy
- k. Drugreleasekineticstudies
- Comparativestudieswithmarketedformulations

CHAPTER-5

MATERIALS AND METHODS

Table No 5.1: Materials used

S.NO.	MATERIALS	SOURCE
1.	Dapsone	Gift Sample from Invitron Labs
2.	Fenugreek Seeds Mucilage	Purchased from the Local Market
3.	Banana Powder:	Purchased from the Local Market
4.	Plantago ovata	Purchased from the Local Market
5.	PVP K30	Gift Sample from Invitron Labs
6.	MCC	Gift Sample from Invitron Labs
7.	Mannitol	Gift Sample from Invitron Labs
8.	Magnesium Stearate	Gift Sample from Invitron Labs
9.	Purified Talc	Gift Sample from Invitron Labs
10.	Aspartame	Gift Sample from Invitron Labs
11.	Phosphate buffer pH 6.4	Gift Sample from Invitron Labs

TableNo5.2:Equipmentused

Sl. No.	EQUIPMENT	MODEL/SOURCE
1.	UV-spectrophotometer	A125357series,Shimadzu
2.	DigitalBalance	Scale-tec,cwsseries
3.	MicroprocessorpH meter	kLPM-116,7246series,Kinglab
4.	Dissolutionapparatus	Lagindia,model-912
5.	Hotairoven	Kavinscientificproducts
6.	Hardnesstester	MonsantotypeHardnessTester
7.	Friabilitytestapparatus	Duralab
8.	Stabilitychamber	i-therm

Methodology

5.1 Isolation of Mucilage of Plantago ovata:

- Theseeds of Plantago ovata were soaked in distilled water for 48 hrs and then boiled for few minutes for complete release of mucilage into water.
- The material was squeezed through muslin cloth for filtering and separating out the marc.
- Then, an equal volume of acetone was added to the filtrate so as to precipitate the mucilage. The separated mucilage was dried in oven at temperature less than 60°C, powdered, sieved (#80) and stored in a desiccator until use.

5.2 Isolation of Fenugreek Seeds Mucilage:

- Theseeds were washed with double distilled water to remove any adherent material.
- The seeds were pulverized and about three times its volume of water was added and kept aside with occasional stirring using mechanical stirrer.
- The process continued for about 5 hours until the slurry was prepared.
- The viscous solution was then filtered through eight-fold muslin cloth.
- The process was repeated 4 times with the residue on the muslin cloth.
- All the filtrate was added together. Then the filtrate was precipitated in about three times its volume of ethanol with mechanical stirrer.
- The precipitate was washed for three times with ethanol and dried at 40°C. The dried mucilage was ground by a mechanical grinder and passed through #60 mesh sieve and kept in a desiccator.

5.3 Preparation of Banana Powder:

- The collected fresh whole bananas were cleaned for any debris and weighed.
- The skin peeled bananas were dipped in ethanol in 5 minutes.
- Then banana was weighed and squashed to paste, this paste was added with citric acid (2-3%) to remove the sticky nature.
- Then water is separated by centrifugation and processing.
- The pressed mass is subjected to drying in tray-dryer.
- The dried substance was milled and screened in sieve (#80) to get fine powder.

5.4 Physicochemical Characterization of Natural Super Disintegrants:

The purified and dried extracted gum powder was evaluated for its micrometric properties, Solubility, swelling index, loss on drying, Moisture content, pH determination and determination of Total Ash.

a) Micrometric properties:

The purified and dried extracted powders were evaluated for its organoleptic characteristics like colour, odour, taste, taste, shape, texture by visual and Microscopical observations.

b) Solubility test:

Solubility test was carried out using aqueous and non-aqueous solvents. In this test, various solvents are used and M. acuminata powder solubility was determined. A known amount of the solvent was put in a container then the M. acuminata powder was added and stirred vigorously.

c) Swelling index:

The study was carried out by using a 100 mL stoppered graduated cylinder. The initial bulk volume of 1 g of Powder was noted. Water was added in sufficient quantity to ensure 25 mL of uniform dispersion by vigorously shaking every 10 min for 1 h and then allowed to stand for 24 h. The dispersion was stored at room temperature and the sediment volume of the swollen mass was measured after 24 h

$$\text{Swelling index} = 100 \times (V_2 - V_1 / V_1)$$

Where, V_1 = Initial volume of material before hydration; V_2 = Volume of hydrated material

d) Loss on drying:

The loss on drying technique is used to determine high levels of moisture or solvents present in the sample. The material sample was weighed (W_1) and heated in an oven for 2 h. It was cooled in the dry atmosphere of desiccators and then finally weighed (W_2).

$$\% \text{ Loss on drying} = [(W_1 - W_2) / W_1] \times 100$$

Where, W_1 = Initial weight of the powder; W_2 = Final weight of the powder

e) Moisture content:

The moisture content was then determined as the ratio of weight of moisture loss to weight of sample expressed as a percentage

$$\%MC = \frac{b-c}{b-a} \times 100$$

a: Weight of weighing bottle,

b: Weight of weighing bottle with 1 g of sample,

c: Weight of weighing bottle with sample after drying at 105°C for 2 h

f) pH determination:

1% w/v solution of sample was prepared by shaking powder in water for 5 min, and pH is determined by digital pH meter.

G) Determination of total ash:

3 g of powder accurately weighed, in a suitable tared dish. Incinerate the material by gradually increasing the heat, not exceeding 450°C, until free from carbon, cooled, and weighed. Total ash content can be calculated from

$$\% \text{ash content} = \frac{c-a}{b-a} \times 100$$

Weight of empty silica crucible = (a),

Weight of crucible with 3 g of sample = (b), and Weight of crucible with ash = (c)

5.5 Phytochemical Screening of the Natural Super Disintegrants:

Phytochemical Screening All the powder extracts (0.05 g/ml) were prepared for preliminary phytochemical screening based on standard methods for detecting the following components.

a) Flavonoid Test: Alkaline reagent test:

Approximately 3 mL of powder extract was treated with 1 mL of 10% NaOH solution. The formation of the intense yellow color showed an indication of the presence of flavonoids.

b) Saponins Test:

Approximately 3 mL of powder extract were added to 3 mL of distilled water and shaken vigorously. The formation of a stable, persistent froth was taken as a positive test for saponins.

c) Steroids Test:

Approximately 2 mL of chloroform and concentrated H₂SO₄ were added to 5 mL of the prepared powder extract.

A layer of red colour indicated the presence of steroids in the lower chloroform.

d) Alkaloids Test:

Approximately 500 mg of powder extracts was stirred with a few of 2N HCl and 9 mL of aquadest, then heat on the water for 2 minutes. The mixtures were then cooled and filtered. The filtrate was used to perform a test with various reagents.

5.6 Preformulation studies

a) Organoleptic Characteristics

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

b) Melting Point

The melting point of the drug substances was determined by using melting point apparatus (PMP-D, Veego). The melting point was determined by introducing small amount of substance in the capillary attached to graduated thermometer and constant heat was applied with the assembly suspended in the paraffin bath. The drug sample was tested in temperature range 100-250°C and point at which drug melts was noted. The melting point is reported in section.

c) Solubility:

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

d) UV absorption maxima of Cinnarizine

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

e) 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 (pH 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^H6.4) From that solution again 10 ml pipetted out and diluted up to 100 ml in volumetric flask with phosphate buffer the (P^H6.4) to get a stock solution of 10 µg/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 (P^H6.4) 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.

5.7 Preparation of Solid Dispersion:

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 50°C for 4 hours. The resultant mass was passed through sieve no. 60 and stored in desiccator.

Physical Mixture:

Physical mixture (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.

5.8 Characterization of solid dispersions of Dapsone with PVP K30:

A, Drug content:

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

B, Dissolution study

In vitro dissolution studies of Dapsone in powder form, Dapsone Solid Dispersions

(DSD) and Dapsone Physical Mixture (DPMs) were performed by using the USP XXIII type-II dissolution apparatus (Electrolab TDT-06N) employing a paddle stirrer at 50 rpm.

900 ml of pH 6.4 phosphate buffer was used as dissolution medium. The temperature of dissolution medium was maintained at $37 \pm 0.5^\circ\text{C}$ throughout the experiment. Samples of dissolution medium (5 ml) were withdrawn for 20 min by means of a syringe fitted with a pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 260 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent released was calculated and plotted against time.

C, Powder X-Ray Diffraction (PXRD)

PXRD patterns were recorded using Philips PW1729 X-ray generator, USA fitted with a copper target, a voltage of 40 kV, and a current of 30 mA. The scanning rate was $1^\circ/\text{min}$ over a 2θ range of $1-50^\circ$. 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.

5.9 Drug–excipient compatibility:

The selected polymers were characterized by FT-IR spectroscopy and the FTIR spectra of the pure drug Dapsone with used excipients like Banana powder, Gum karaya and Plantago ovate, Microcrystalline cellulose, PVP K30, Aspartame, Mannitol etc.

The instrument was operated under dry air purge and the scans were collected at scanning speed 2 mm/sec with resolution of 4 cm^{-1} over the region $4000-400\text{ cm}^{-1}$. These scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks and appearance of new peaks due to polymer interaction.

5.10 PRECOMPRESSIONAL PARAMETER

5.10.1 DETERMINATION OF FLOW PROPERTIES:

a) Angle of repose

The angle of repose of powder was determined by the funnel method. The accurately weighed powder was taken in a funnel. The height of the funnel was adjusted in such a

way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

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

Where, h and r are the height and radius of the powder cone, respectively.

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

Angle of Repose (°)	Flow
>25	Excellent
25-30	Good
30-40	Passable
<40	Very poor

Table no: 5.10 Angle of repose

b) Bulk Density

An accurately weighed quantity of powder, which was previously passed through sieve #40 [USP] and carefully poured into graduated cylinder. Then after pouring the powder into the graduated cylinder the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density is calculated by following formula;

$$\text{Bulk density} = \text{Weight of powder} / \text{Bulk volume}$$

c) 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 dropper 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 considered as final tapped volume. The tapped density is calculated by the following formula

$$\text{Tapped density} = \text{Weight of powder} / \text{Tapped volume}$$

d) Carr's Index [Compressibility Index] and Hausner's Ratio

Carr's index and Hausner's ratio measure the propensity of powder to be compressed and the flowability of powder. Carr's index and Hausner's ratio can be calculated from the bulk and tapped density.

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Grading of the powders for their flow properties according to Carr's Index is shown in below table

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

Table no: 5.10 compressibility

5.11 Preparation of tablets containing solid dispersion 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 ~250 mg

Direct compression method:

Fast dissolving tablets of Dapsone were prepared by Direct Compression method according to the formulae given in the Tables.

- All the ingredients were powdered separately and passed through # 60 mesh sieve separately.
- The solid dispersion and directly compressible excipient were mixed by adding

small portion of each at a time and blending it together to get a uniform mixture and kept aside.

- Then the other ingredients were mixed in geometrical order, in an inflated polyethylene pouch magnesium stearate and talc were added last and the tablets were compressed using 8 mm flat round punches to get tablets of 250 mg weight.

Tableno:11 Composition of Dapsone tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dapsonesolid dispersionurea (1:3)	50	50	50	50	50	50	50	50	50
Plantagoovata	10	15	20	-	-	-	-	-	-
Fenugreekseedmucilage	-	-	-	10	15	20	-	-	-
Bananapowder	-	-	-	-	-	-	10	15	20
MCC	100	100	100	100	100	100	100	100	
Aspartame	5	5	5	5	5	5	5	5	5
Magnesiumstearate	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Mannitol	80	75	70	80	75	70	80	75	70
Total(mg)	250	250	250	250	250	250	250	250	250

5.12 POSTCOMPRESSIONPARAMETERSOFDAPSONETABLETS

a) Weightvariation:

Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight.

b) HardnessandFriability

Friability of the tablets was checked by using Roche Friabilator. The device subjects a number of tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets from a height of 6 inches with each revolution. Pre-weighed sample tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed.

c) Content uniformity test

Ten tablets were weighed and powdered, a quantity of powder equivalent to 50 mg of Dapsone was transferred to a 25 ml volumetric flask and 15 ml water is added. The drug is extracted in water by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with distilled water and the liquid is filtered. The Dapsone content was determined by measuring the absorbance at 260 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

d) Disintegration test

Tablets were taken and introduced in each tube of disintegration apparatus, and the tablet rack of the disintegration apparatus was positioned into a 1-liter beaker containing 900 ml of distilled water and the time of disintegration was recorded. To discriminate between the formulation's disintegration was done at room temperature and disk was not used for the study

e) In vitro dispersion time

Tablet was added to 10 ml of pH 6.4 phosphate buffer solution at $37 \pm 0.5^\circ\text{C}$. Time required for complete dispersion of a tablet was measured.

f) Wetting time and Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish (internal diameter 5 cm) containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured, the wetted tablet was then weighed.

g) Dissolution study

In vitro dissolution of Dapsone mouth dissolving tablets was studied in USP XXIII type-II dissolution apparatus (Electrolab TDT-06N) employing a paddle stirrer at 50 rpm. 900 ml of pH 6.4 phosphate buffer was used as dissolution medium. The temperature of dissolution medium was maintained at $37 \pm 0.5^\circ\text{C}$ throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5 ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release

by measuring the absorbance at 260 nm The volume withdrawn at each time interval was replaced with fresh quantity of dissolution.

h) Kinetic Release:

Mathematical models that can be applied to the analysis of dissolution data. The models described herein include both empirical and semiempirical models that are applied to the evaluation of dissolution rate data. The use of these models permits the elucidation of the mechanism and type of drug release that can be expected from the mouth dissolving tablets. In order to investigate the mechanism of drug release, the data (F1 to F9) of in vitro release studies was fitted to various kinetic models representing Zero-order, First order, Higuchi's and Korsmeyer-Peppas model.

CHAPTER-6

RESULT AND DISCUSSION

Macroscopic Properties of the Dried Extract Powders:

Table No 6.1: Macroscopic Properties of the Dried Extract Powders

S. No	Physical Property	Fenugreek Seed Mucilage	Banana powder	Plantago Ovata
1	Colour	White	White	Light Brownish
2	Odour	Odourless	Odourless	Odourless
3	Taste	Tasteless	Tasteless	Tasteless
4	Shape	Irregular	Irregular	Irregular
5	Texture	Soft	Soft	Soft

Table No 6.2: Solubility of the Dried Extract Powders

S. No	Type of Solvent	Fenugreek Seed Mucilage	Banana powder	Plantago Ovata
1	Water	Forming Gel	Insoluble	Insoluble
2	Acetone	Insoluble	Insoluble	Insoluble
3	Ethanol	Insoluble	Sparingly soluble	Insoluble
4	Methanol	Insoluble	Insoluble	Insoluble
5	pH 6.8 Buffer	Soluble	Soluble	Soluble

Table No 6.3: Swelling Index of the Dried Extract Powders

S. No	Parameter	Fenugreek Seed Mucilage	Banana powder	Plantago Ovata
1	% Swelling Index	68±0.27	55±0.27	74±0.27

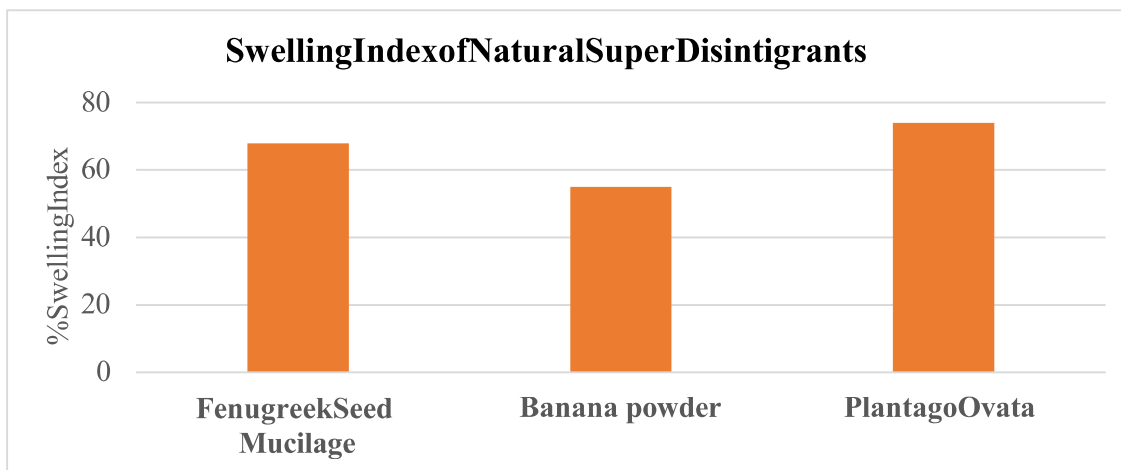


Fig.6.1: Swelling Index of the Powdered Extracts Table

No 6.4: Loss on Drying of the Dried extract powders

S. No	Parameter	FenugreekSeed Mucilage	Bananapowder	PlantagoOvata
1	%Loss on Drying	1.81±0.27	1.55±0.27	0.74±0.27

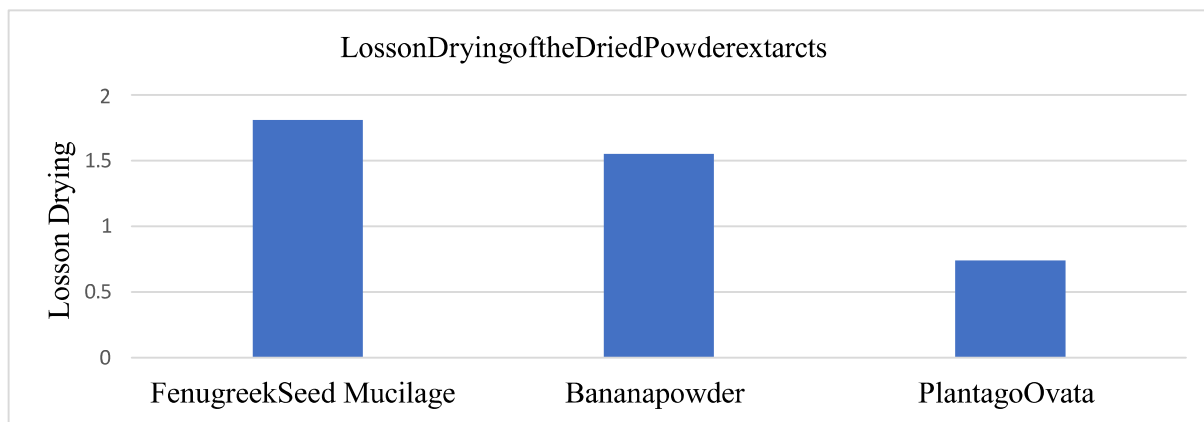


Fig.6.2: Loss on Drying of the Powdered Extracts

Table No. 6.5: Moisture content of the Dried extract powders

S. No	Parameter	FenugreekSeed Mucilage	Bananapowder	PlantagoOvata
1	%Moisture Content	3.81±0.14	2.15±1.11	2.74±0.23

TableNo.6.6:pHoftheDriedextract powders

S. No	Parameter	FenugreekSeed Mucilage	Bananapowder	PlantagoOvata
1	pH	6.6	7.15	6.14

TableNo6.7:TotalAshoftheDriedextractpowders

S. No	Parameter	FenugreekSeed Mucilage	Bananapowder	PlantagoOvata
1	TotalAsh	2.61%	3.15%	2.14%

TableNo.6.8:PhytochemicalScreeningoftheDriedextractpowders

S. No	Test	FenugreekSeed Mucilage	Bananapowder	PlantagoOvata
1	Testfor Flavonoids	Absent	Present	Absent
2	TestforSaponins	Absent	Absent	Absent
3	TestforSteroids	Absent	Absent	Absent
4	TestforAlkaloids	Absent	Present	Absent

TableNo.6.9:OrganolepticCharacteristicsoftheDapsone

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

TableNo.6.10:MeltingPointoftheDapsone

S. No	Method	Result
1	CapillarytubeMethod	176°C

TableNo.6.11:SolubilityoftheDapsone

S. No	TypeofSolvent	Result
1	Water	Insoluble
2	Acetone	Slightly soluble
3	Ethanol	Soluble
4	Methanol	Soluble
5	pH6.8Buffer	Soluble

PREPARATIONOFCALIBRATIONCURVEOFDAPSONE

TableNo.6.12:StandardcurveofDapsoneinphosphatebufferp^H6.4

Concentration n (µg/ml)	Absorbance
0	0.000
2	0.098
4	0.211
6	0.306
8	0.413
10	0.526

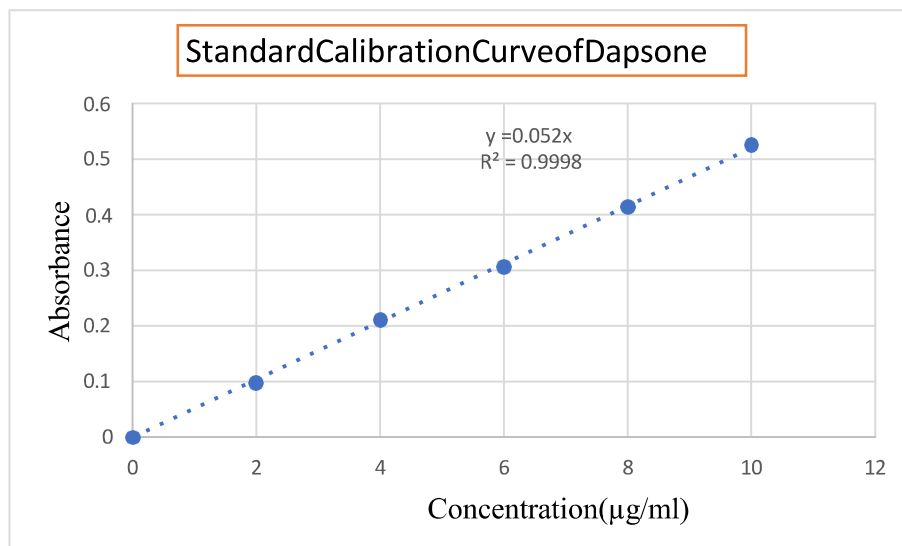


Fig.6.3: Standard Calibration Curve of Dapsone

CHARACTERIZATION OF SOLID DISPERSIONS OF DAPSONE

i) Drug content

Table No 6.13: 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	94.11	DPM 1:1	92.13
DSD 1:2	96.18	DPM 1:2	93.41
DSD 1:3	99.74	DPM 1:3	97.21

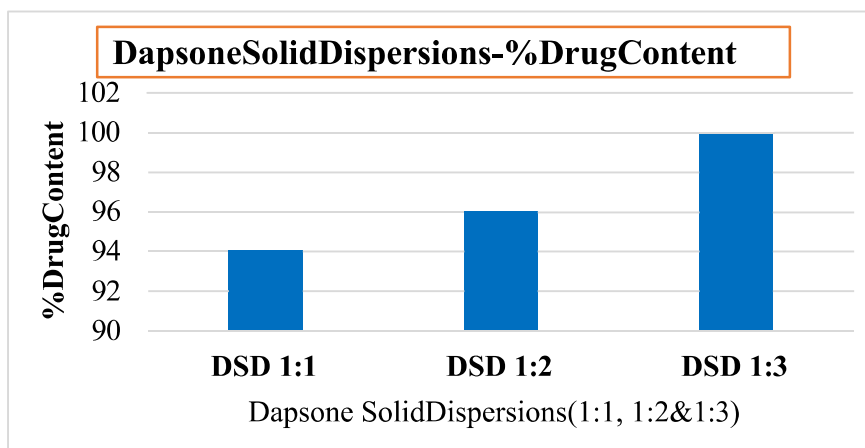


Fig.6.4: % Drug content - Dapsone Solid Dispersions

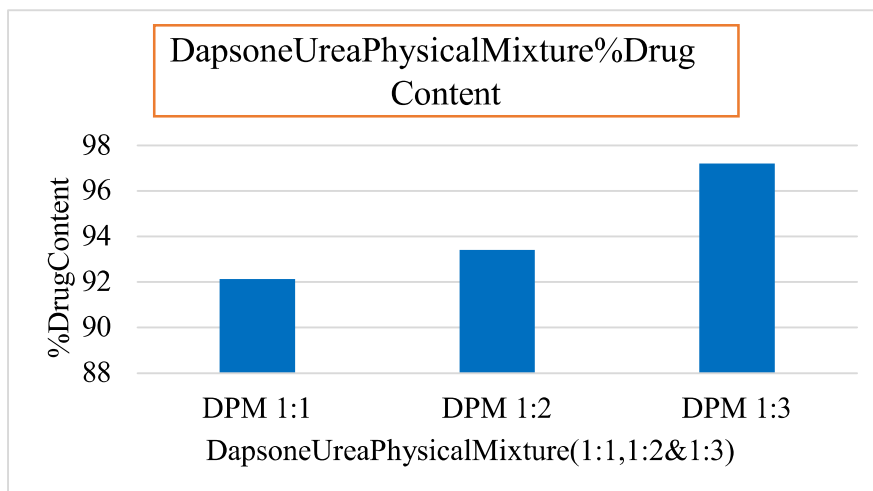


Fig.6.5:%Drugcontent-Dapsone-UreaPhysical Mixture

Dissolution studies of solid dispersions and physical mixtures:

At the different time intervals, the percentage of drug release from the physical mixture and solid dispersions was calculated.

It is evident that dissolution of pure dapsone is very low, about 32.16% 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 99.74% than other ratios of SD's. Like wise at the end of 20 min, Dapsone Physical Mixture DPM containing 1:3 of drug and Urea showed highest drug release 97.21% than other ratios of. From the results, it was observed that Dapsone Solid Dispersions (1:3) showed better results with other samples.

Table No: 6.14. 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%drugreleaseafter20 min.
1	DRUG	32.16±2.45%
2	DPM1:1	39.14±1.05%
3	DPM1:2	51.18±1.27%
4	DPM1:3	62.18±2.11%
5	DSD1:1	92.16±1.34%
6	DSD1:2	97.22±1.24%
7	DSD1:3	***99.62±1.02%

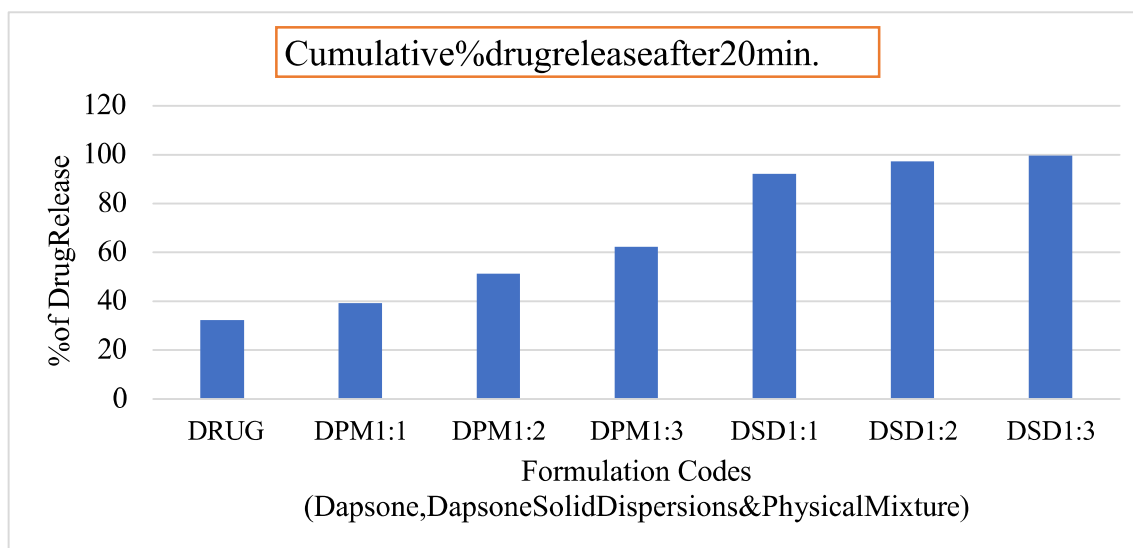


Fig.6.6:%DrugReleaseforthePureDapsone,SolidDispersions&Physical Mixture

ComparisonStudyofSoliddispersion

TableNo:6.15Comparisonofsoliddispersions

Time (minutes)	PureDapsone (%)	DSD1:1 (%)	DSD1:2 (%)	DSD1:3 (%)
0	0	0	0	0
2	1.73	25.73	37.5	52.6
4	3.64	39.64	44.24	56.39
6	6.75	46.75	52.83	63.12
8	9.14	53.14	58.88	68.56
10	11.59	61.59	62.61	73.4
12	14.33	67.33	68.83	76.81
14	18.97	74.97	71.77	80.25
16	21.07	80.07	81.64	86.16
18	28.80	83.80	90.13	97.55
20	32.16	92.16	97.22	99.62

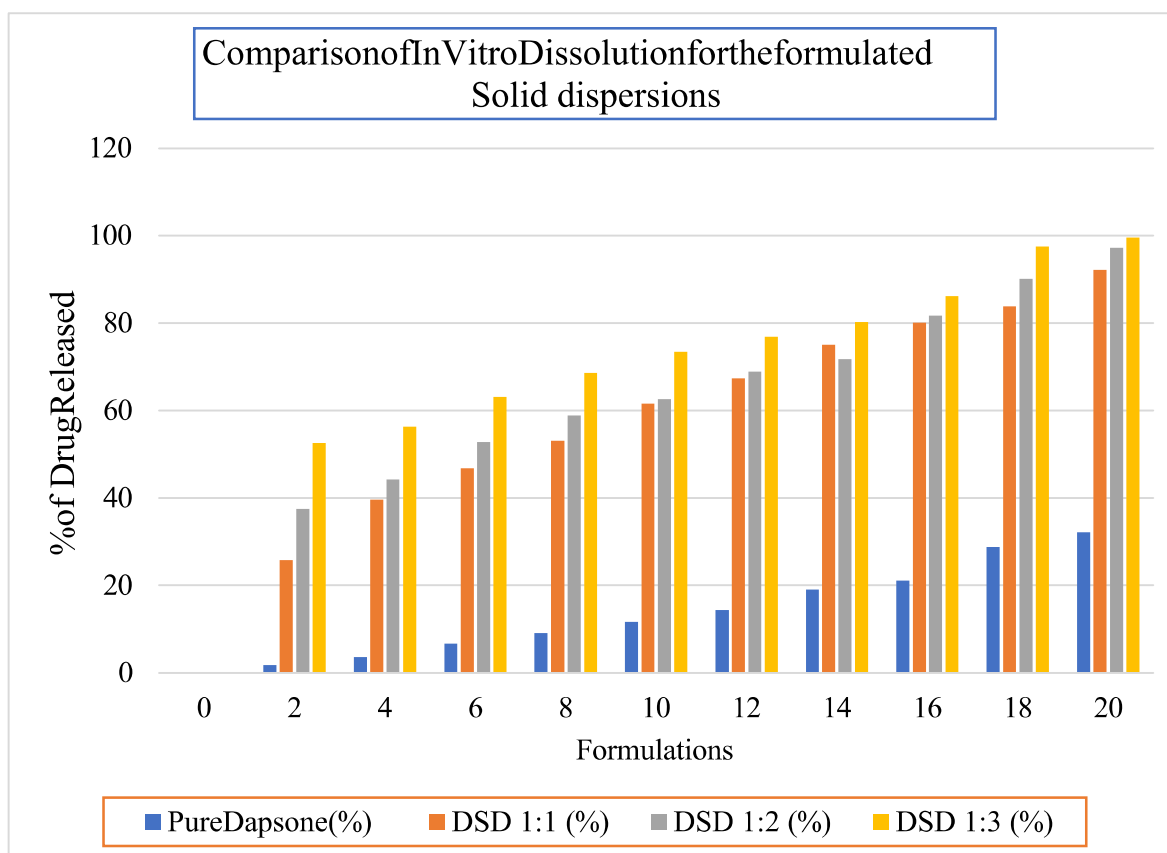


Figure 6.7 :comparison of in vitro dissolution for the formulated solid dispersions

X- RayDiffractionStudies:

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 DSD 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 7.

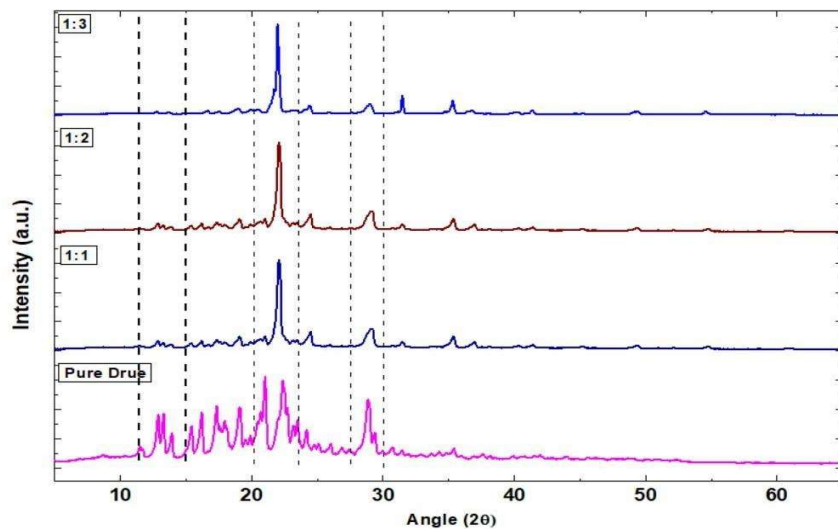


Fig.6.8:XRD studies of the Pure Dapsone and formulated Solid Dispersions (1:1, 1:2 & 1:3)

FTIR spectroscopy of Dapsone and Natural Excipients and Combination.

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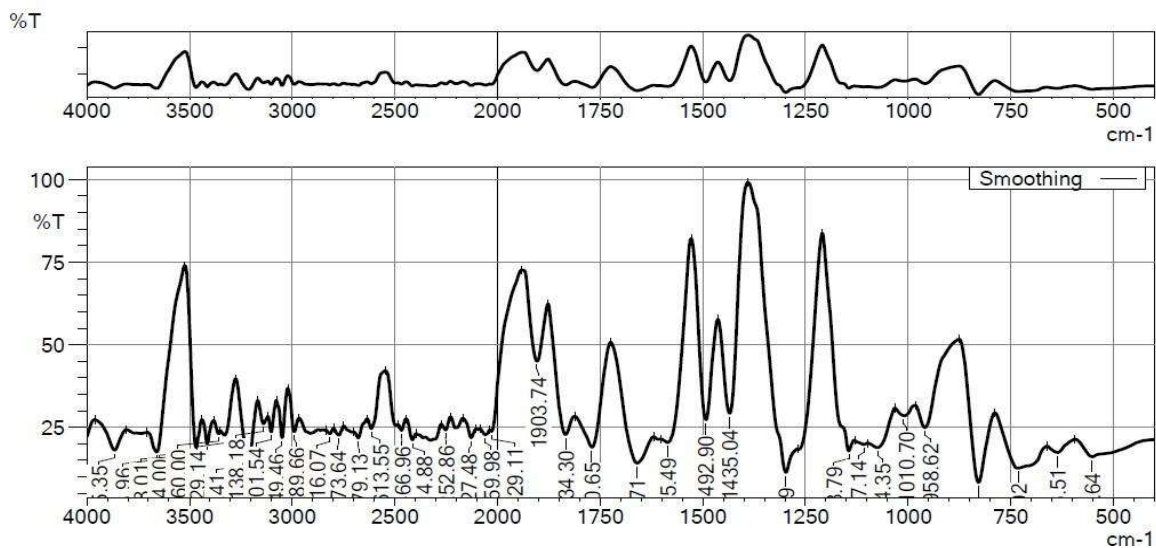


Fig.6.9:FTIR of the Pure Dapsone



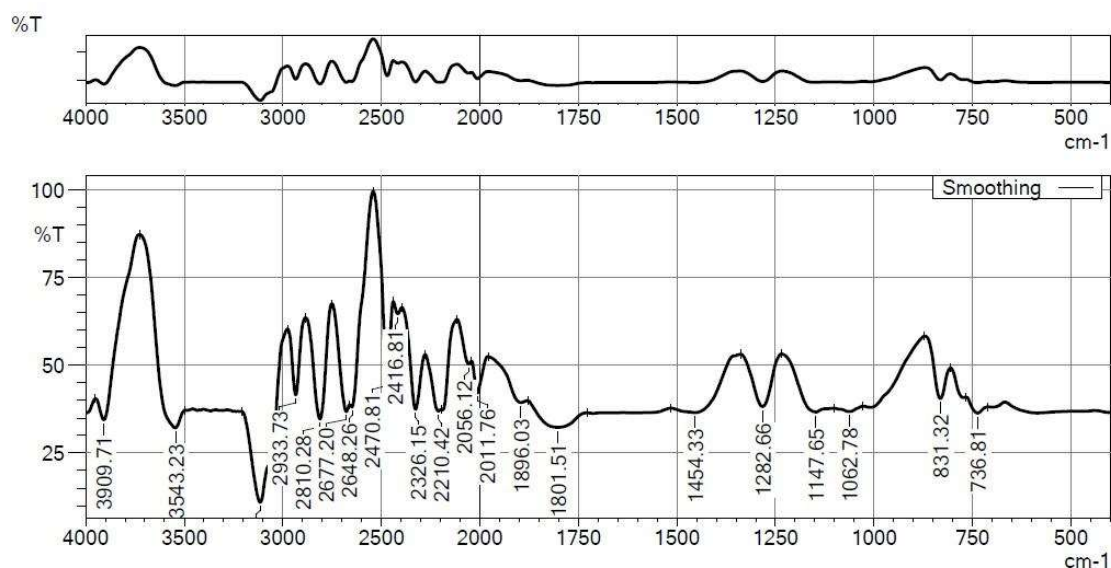


Fig.6.12:FTIR of the Dapsone Solid Dispersions(1:3)

From the FT-IR data it is proved that there is no significant interaction between pure dapsone with urea used for the manufacturing of solid dispersions.

PRE-COMPRESSION PARAMETERS OF DAPSONE TABLETS

Table No 6.16: Precompression parameters of Dapsone tablets

Formulation code	Bulk Density (g/cc)	Tapped density (g/cc)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
F1	0.47	0.57	25.40	14.04	1.14
F2	0.43	0.56	25.06	12.72	1.16
F3	0.45	0.57	24.38	13.20	1.14
F4	0.42	0.49	25.72	12.24	1.15
F5	0.42	0.43	25.94	12.76	1.13
F6	0.38	0.42	25.48	11.36	1.12
F7	0.43	0.66	26.21	14.06	1.12
F8	0.52	0.62	25.74	13.11	1.15
F9	0.46	0.56	23.02	13.79	1.14

PostCompressionalParametersofDapsoneMouthDissolving Tablets

FormulationofDapsoneMouthdissolvingtablets:

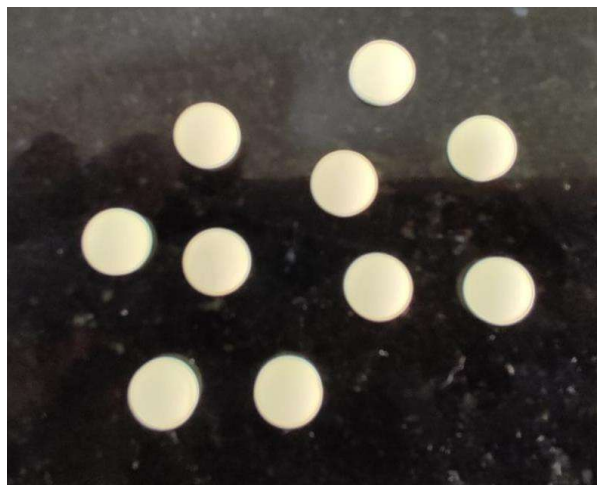


Fig6.13:DapsoneMouthdissolvingtablets

TableNo6.17:PostcompressionparametersofDapsonetables

S. No	Formulation Code	Hardness (kg/cm ²)	%Friability	In vitro Dispersion Time (Sec)	In vitro Disintegration Time (Sec)	% Drug Content	Weight variation
1	F1	2.93	0.33	30.15	32	88.26	246.81
2	F2	2.76	0.32	32.23	30	84.02	248.72
3	F3	2.91	0.35	31.55	29	85.45	248.81
4	F4	2.88	0.36	31.23	28	91.94	249.83
5	F5	2.46	0.37	32.15	28	89.84	248.15
6	F6	2.35	0.32	27.12	25	91.41	246.45
7	F7	2.35	0.35	23.14	25	93.41	249.81
8	F8	2.37	0.36	23.14	23	96.41	249.73
9	F9	2.61	0.32	21.15	20	98.41	248.82

In vitro dispersion time:

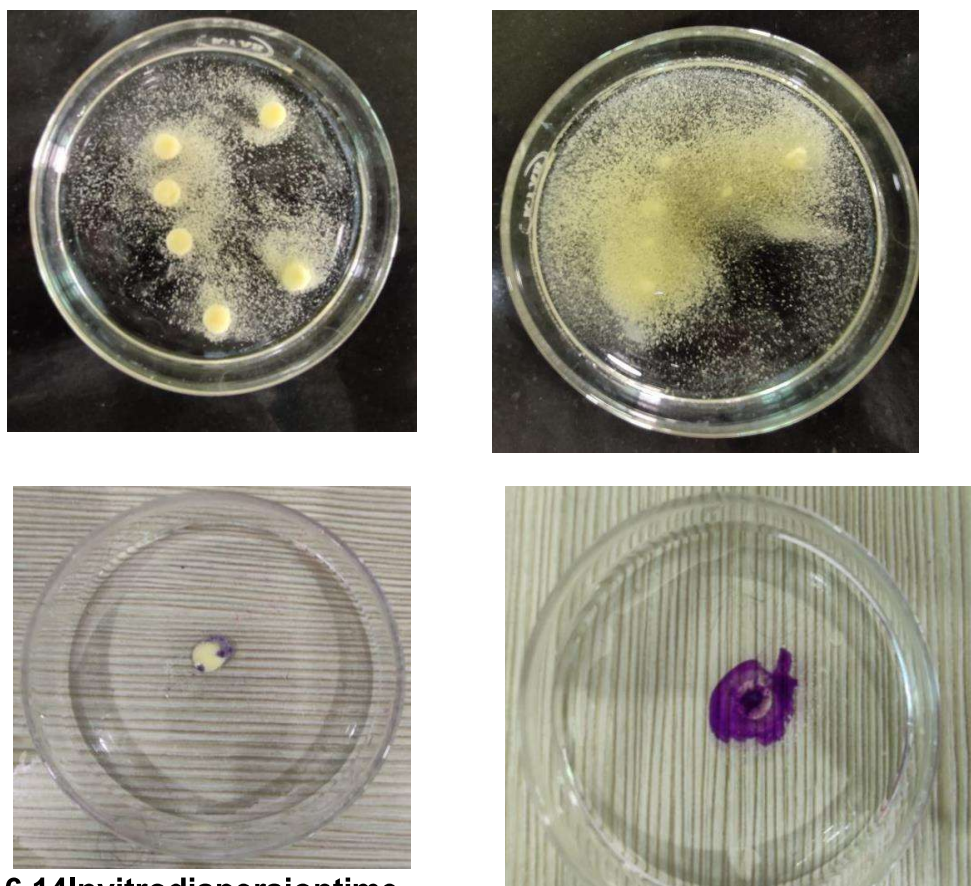


Fig.6.14In vitro dispersion time

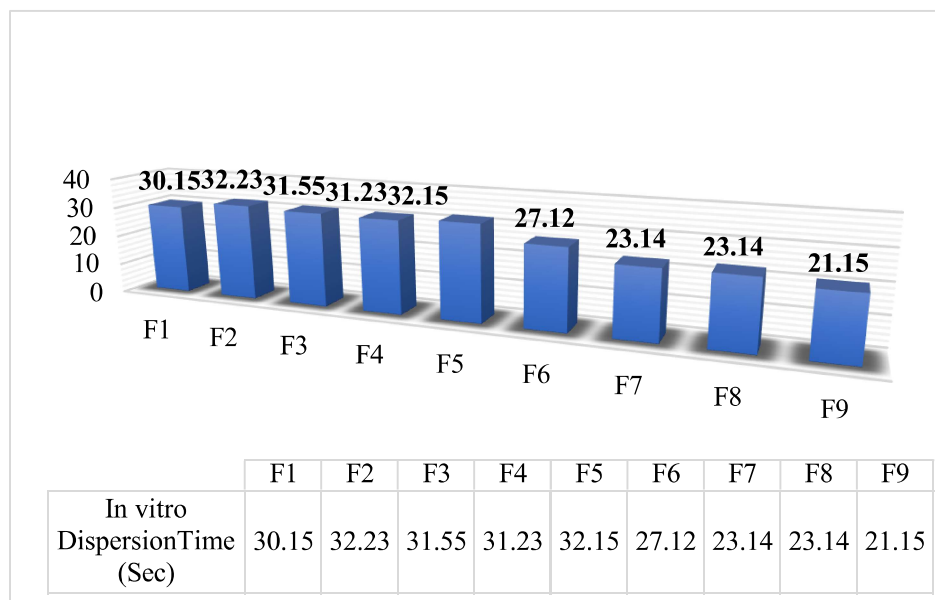


Fig.6.15:*In vitro* Dispersion Time (Sec) of Dapsone Mouth Dissolving tablet

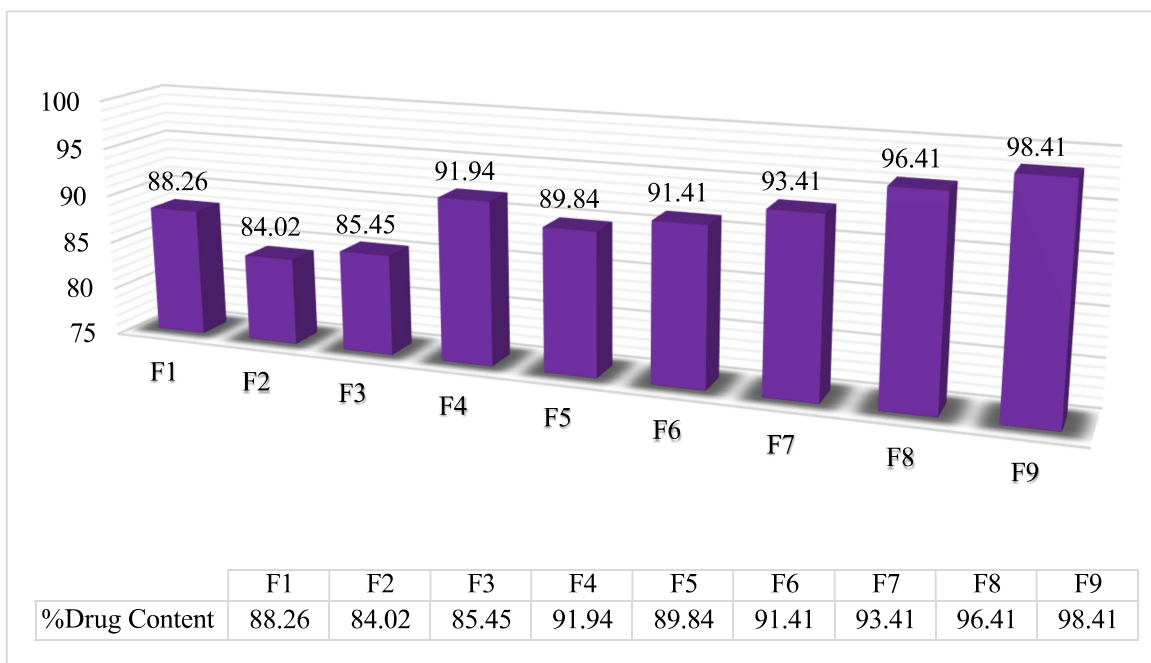


Fig.6.16:%DrugContentofDapsoneMouthDissolvingTablets

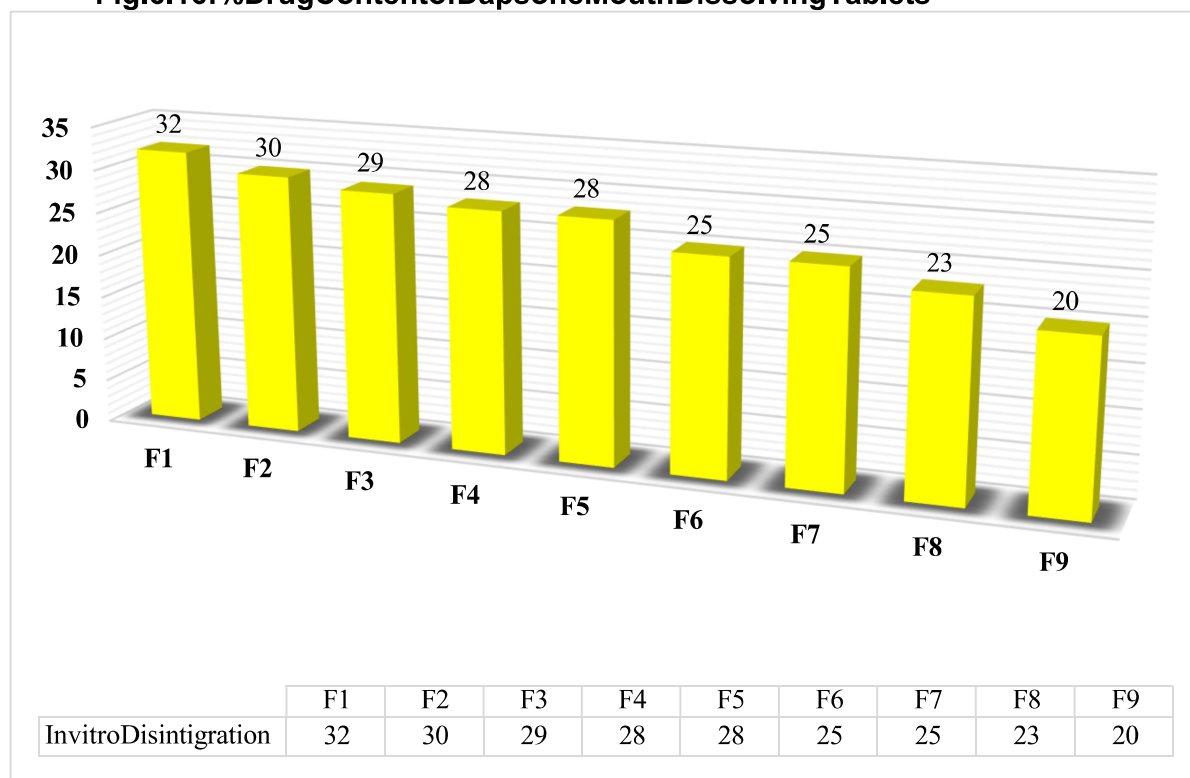


Fig.6.17:InvitroDisintegrationtimeofDapsoneMouthDissolvingTablets

In-vitrodissolutionstudyofDapsonemouthdissolvingtablets

TableNo6.18:InVitrodissolutiondataofformulations(F1-F9)

Time (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)
2	24.31	28.33	21.70	26.94	28.33	21.94	23.7	23.70	26.941
4	29.14	34.27	27.55	32.47	34.27	30.47	26.55	27.557	35.47
6	33.72	40.52	32.86	38.31	41.52	36.31	32.86	32.86	42.31
8	39.41	47.81	38.06	45.05	47.873	45.05	38.06	31.06	48.05
10	45.93	53.05	44.83	52.18	51.051	53.18	44.83	49.83	54.18
12	55.28	66.49	53.63	63.80	61.49	64.80	53.63	63.63	67.80
14	64.85	77.68	62.12	74.52	74.68	72.52	62.12	67.12	79.52
16	72.60	85.109	69.19	85.63	79.10	81.63	69.19	73.19	90.63
18	79.31	94.75	78.27	91.70	93.75	93.70	78.27	78.67	98.70
20	82.73	97.54	82.48	93.65	95.47	95.35	81.75	81.34	99.43

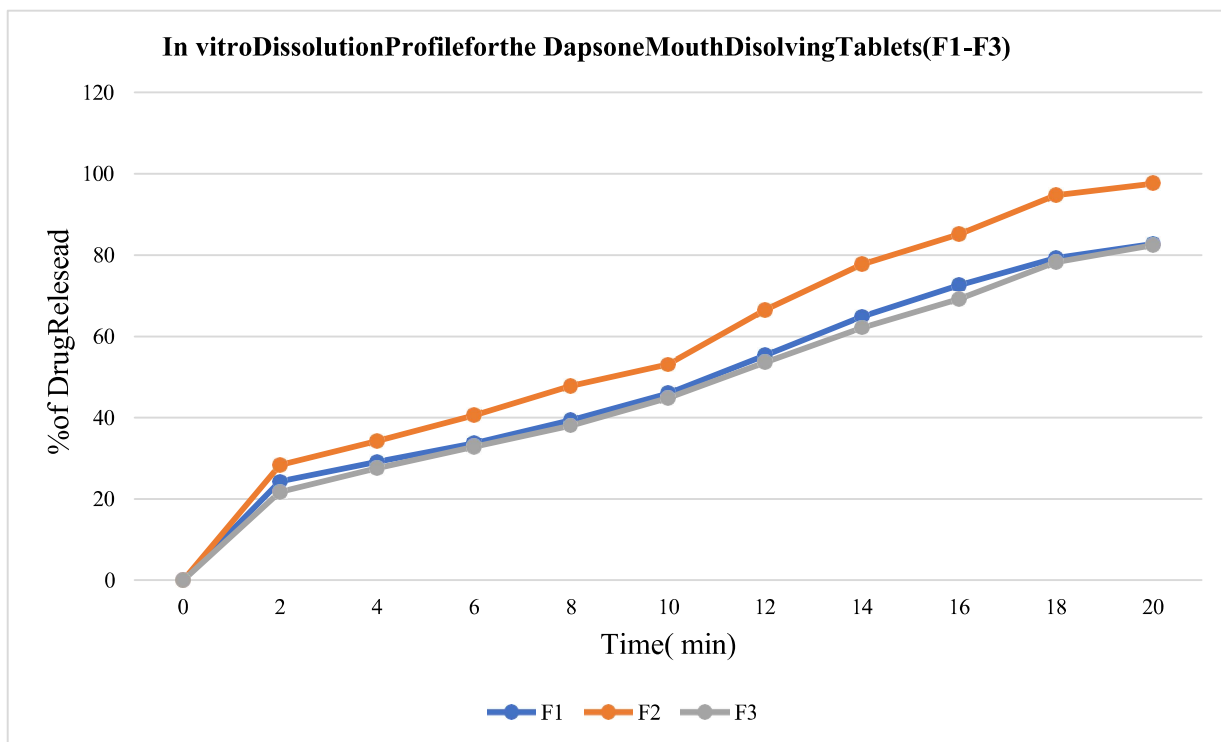


Fig.6.18:InvitroDissolutiontime ofDapsoneMouthDissolvingTablets(F1- F3)

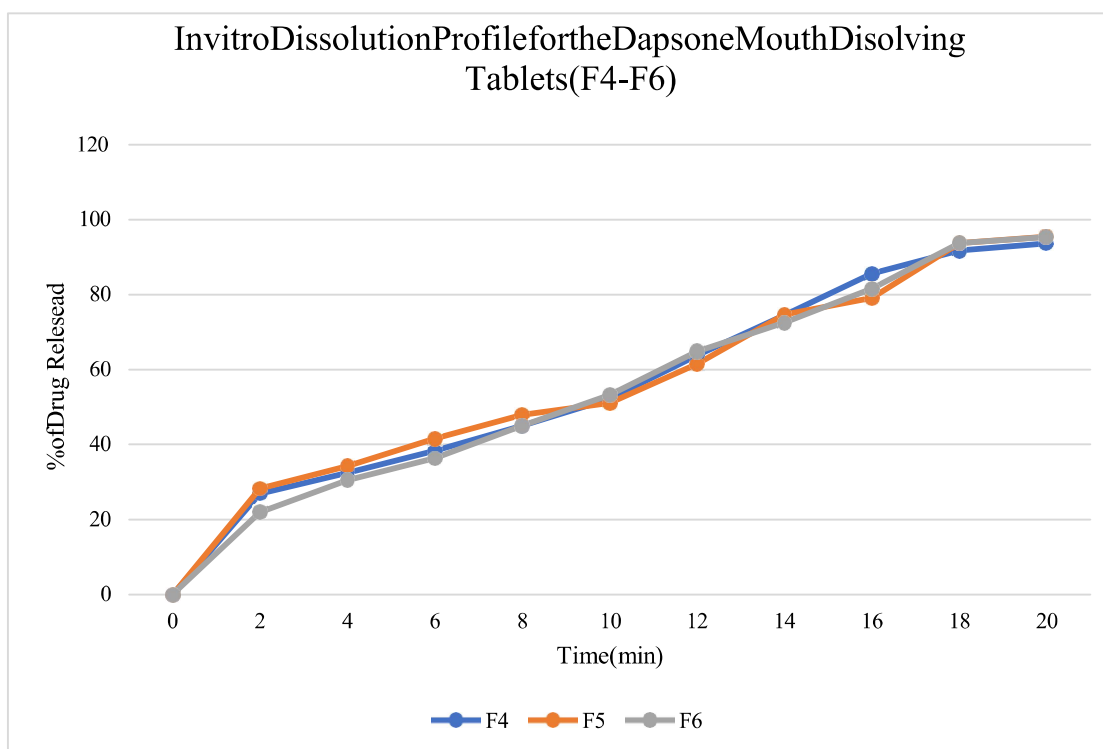


Fig.6.19:InvitroDissolutiontime ofDapsonemouthDissolvingTablets(F4- F6)

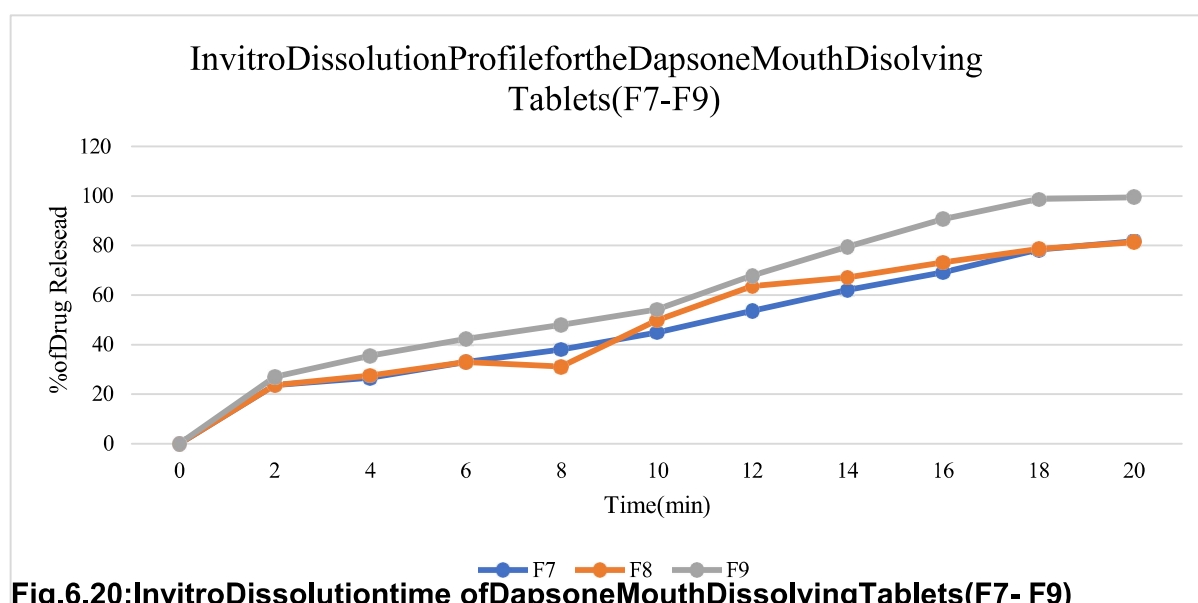


Fig.6.20:InvitroDissolutiontime ofDapsonemouthDissolvingTablets(F7- F9)

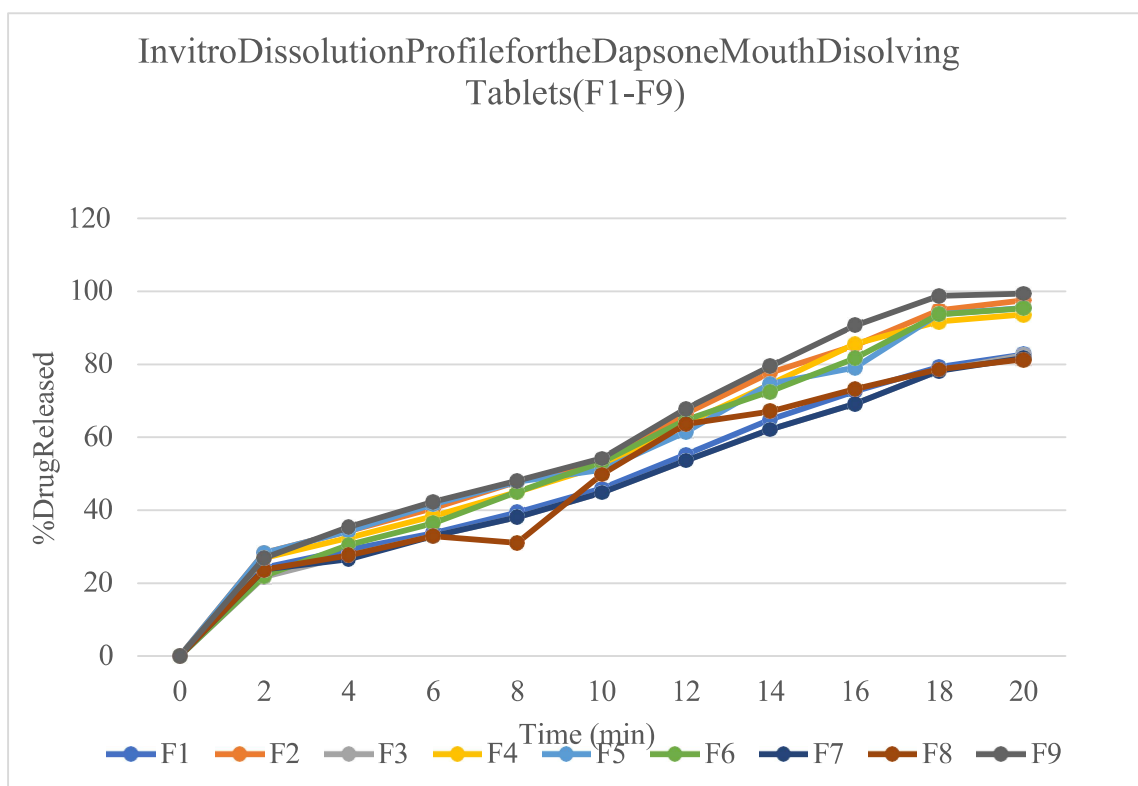


Fig.6.21:InvitroDissolutiontime ofDapsoneMouthDissolvingTablets(F1- F9)

SUMMARY & CONCLUSION

All the Natural super disintegrant's extracted from the natural sources characterized by their morphological characteristics and it was observed that all the super disintegrant's showed the good results.

The solubility of the natural excipients was performed by use of the different solvents and it was proved that all the excipients showed the formation of the gel form in the water and insoluble in the organic solvents.

The swelling index was found to be more for the Plantago ovata i.e 74 % which may indicative of the more porosity, which is required for the drug release.

The moisture content, Loss on drying and Total Ash was performed for the natural excipients, all the values are within the limits as per the standards.

The phytochemical screening was done for the natural excipients, it proved that, absence of the saponins, steroids and alkaloids.

The Dapsone purity was characterized by its organoleptic characteristics and the results showed are as per the standards.

The purity also characterized by the determination of the melting point by the capillary tube method the value is within the limits.

The solubility of the dapsone was done by use of different solvents, it proves that, dapsone showed poor solubility in the water and soluble in some organic solvents.

Based on this point, it was decided to improve the solubility of the dapsone by preparing the solid dispersions with the help of urea by solvent evaporation method.

The formulated solid dispersions characterized for the drug content, dissolution, X-ray diffractions and FTIR studies.

The solid dispersions prepared by the solvent evaporation with the ratio of 1:3 showed better drug content, dissolution (99.62 %) at the 20 min.

Compatibility Study

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug, Dapsone Solid dispersion of various ratios (1:1, 1:2 & 1:3) were studied. This indicates that the drug was compatible with the formulation components.

Discussion of the characterization of the mouth dissolving tablets of dapsone with various super disintegrants

The powder blend was evaluated for angle of repose, Hausner's ratio and % compressibility. The prepared tablet was evaluated for physical parameter, Wetting time, In vitro disintegration time, Assay and In vitro drug release.

Evaluation of powder blend:

A, Angle of Repose (θ)

The angle of repose for the entire formulations blend was found to be in the range 23.02° to 26.21°. The results were tabulated in Table no: 6.15

B, Hausner ratio: Hausner ratio was found to be in the range 1.12 to 1.16 and that indicated that all formulation has good flow properties.

C, Carr's index: Carr's index was found to be in the range 11.36% to 14.06% that indicated all formulation has good flow properties.

PhysicalParameters

Weightvariation

All the formulated (F1 to F9) tablets were passed weight variation test as the % weight variation was within the IP limit of 7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values. The prepared formulation complies with the weight variation test.

Hardness

The hardness of the tablet was found to be 2.3 to 2.93 Kg/cm²

Friabilitytest

The maximum friability of the formulation was found to be 0.37%. The minimum friability of the formulation was found to be 0.32%. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Drugcontent

The maximum drug content for the all formulation was found to be 98.41% and minimum % drug content from the all formulation was found to be 84.02%. The results were within the limit specified by the IP.

In vitro Disintegration test

In vitro Disintegration time was found to be in the range 20 to 32 sec. From all formulations, F9 (10% plantago ovata) has minimum disintegration time 20 sec.

In vitro drug release

Dissolution data shows that formulation F9 having (Plantago ovata) gave improved dissolution as compared to other formulations and total drug release of 99.43% was found at 20 min.

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