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"Formulation and Evaluation of Minoxidil Fast Dissolving Tablet"

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LIST OF ABBREVIATIONS

Avg .....Average
BP .....British Pharmacopoeia
FDT .....Fast dissolving tablets
hr .....Hours
IR .....Infrared
MDT .....Mouth dissolving tablets
Min .....Minutes

Rh .....Relative humidity
sec.....Seconds
USP .....United States Pharmacopoeia
UV .....Ultraviolet
w/w .....Weight by weight

FDT…….. Fast dissolving tablets.

ABSTRACT

In many patients they have difficulty in swallowing tablets and capsules, which results in high incidence of non-compliance and decrease in effectiveness. Recent advances in Novel Drug Delivery Systems (NDDS) aim to increase the safety and efficacy of drug molecule by formulating into a convenient dosage form for administration and to achieve patient compliance. Such advanced approach is fast dissolving tablet formulation. In the current work, fast dissolving tablets of Minoxidil were designed with a view to enhance patient compliance by direct compression and effervescent method also by sublimation method. In the direct compression method, crospovidone, croscarmellose sodium and pre-gelatinized starch were used as superdisintegrants in different concentrations (2-6% w/w) and directly compressible mannitol to enhance mouth feel. Estimation of Minoxidil in prepared tablet formulations was carried out by extracting the drug with methanol (Alcohol) and measuring the absorbance at 285nm. The prepared formulations were further evaluated for hardness, friability, drug content uniformity, wetting time, water absorption ratio and in-vitro dispersion time. Based on in-vitro dispersion time (approximately 6-240s), all formulations were tested for in-vitro drug release pattern (in pH 6.8 phosphate buffer), drug excipients interaction (IR spectroscopy). Among the promising formulations, the formulations MDF6, MEF6and MSF6, containing 6% w/w croscarmellose sodium emerged as the overall best formulation based on drug release characteristics and in-vitro dispersion time of approximately 6 and 2.3 s and IR spectroscopic studies indicated that there is no drug interaction.

Keywords: Minoxidil, Fast dissolving tablets, Directcompression method, Effervescent method, and Sublimation method, Super disintegrants, Directly compressible vehicle, Dilu-ent, FT-IR.

CHAPTER-1

INTRODUCTION

During the past four decades, the pharmaceutical industry has invested vast amounts of time and money in the study of tablet compaction. The expenditure is quite reasonable when one considers how valuable tabletsas a dosage formare to the industry. Because oral dosage forms can be self-administered by the patient, they are obviously more profitable to manufacture than parenteral dosage form which needs a trained person for administration.[1]

Tablets are Popular for Several Reasons

- The oral route represents a convenient and safe way of drugadministration.
- The preparation procedure enables accurate dosing of thedrug.
- Tablets are convenient to handle and can be prepared in a versatile way with respect to their use and to the delivery of thedrug.
- Tablets can be mass produced with robust and quality-controlled production procedures giving an elegant preparation of consistent quality.
- Tablets are the manufacturer's dosage form of choice because of their relatively low cost of manufacture, package and shipment, increased stability, and virtual tamperresistance.[2]

The disadvantage of tablets includes dysphasia or difficulty in swallowing which affect nearly 35% of population. This disorder is also associated with number of medical conditions including stroke, Parkinson's disease, AIDS, head and neck radiation therapy, and other neurological disorders including cerebral palsy. Many elder persons will have difficulty in taking conventional dosage forms because of hand tremors and dysphasia. Swallowing problems are also common in young individuals because of their under developed muscular and nervous tissue. Others who may experience problems in swallowing are the mentally ill,developmentally disabled uncooperative patients, reduced liquid intake plan, and nausea. In some cases, such as motion sickness, sudden episode of allergic attack or coughing and unavailability of water swallowing

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tablets becomes difficult.[3]

To fulfill the above needs pharmaceutical technologists have developed a novel type of dosage form for oral administration known as fast dissolving tablets. Fast dissolving tablets are also called rapimelts, quick disintegrating tablets, oral disintegrating tablets, etc.

Fast dissolving tablets are defined as the tablets, which are meant to disintegrate immediately when come in contact with the saliva leading to faster release of the drugs in the oral cavity and disintegrate rapidly within 15 sec to 3 min.The faster the drug goes into solution, faster is the absorption and onset of clinical effect. For the drug attaining the therapeutic level by the gastric wall and elicit therapeutic effect, both rate and extent of absorption are important.[4]

The conventional tablet shows the delay in absorption and fast dissolving tablets disintegrate and dissolve rapidly and absorption takes place quickly, thus bioavailability increases. Some factors like GI disturbances and blood supply to GI differs with age as the elderly are considered as separate unique Medicare population.[5]

Direct compression is the easiest method to manufacture fast dissolving tablets (FDTs) and fast-melting tablets (FMTs). It uses conventional equipment, commonlyavailable excipient, and a limited number of processing steps[6,7]. The choice of a right type and an optimum amount of disintegrant is important for ensuring a high disintegration rate. The addition of other formulation components such as water-soluble excipient or effervescent agents can further enhance dissolution or disintegration properties. The understanding of disintegrant properties and their effect on the formulation has advanced considerably during the last few years, particularly regarding so called super-disintegrants.

In direct compression method, previously only crystalline compounds or materials were directly compressed, but now-a-days the scenario haschanged[8]. The approach mainly employs impartation or modification of certain physical changing and this technique is being applied for many non-crystalline materials properties of the material under consideration, such as cohesiveness, compactness, and flow properties. Formulations constituted by 25% w/w of drug material are easy to be directly compressed by simply using diluents, which are easy to be compressed and which act as a carrier for the drug. The effervescent system is usually composed of a dry acid and dry base, which when react facilitate a mild effervescent reaction when the tablet contacts saliva. The effervescent reaction accelerates the disintegration of tablet through the release of carbon dioxide, water, and salt. The bitter taste of drug ismasked and a pleasant mouth feel is felt, due to evolution of carbon dioxide[10]. In several cases the disintegrants used have a major role in the disintegration and dissolution process of rapidly disintegrating tablets made by direct compression method. The choice of an appropriate type and an optimum amount of disintegrant is important for ensuring a high disintegration rate. The addition of other formulation components such as water-soluble excipient or effervescent agents can further enhance dissolution or disintegration properties. The major advantages with effervescent formulation approach that it is well-established, easy to implement and mask the bitter taste of drug[9].

A wide range of drugs such as cardiovascular drugs, analgesics, antihistamines, antiemetics, anti-convulsant, anti-parkinson's, anti-psychotic, anti-spasmodic, neuroleptic and drugs for erectile dysfunction can be considered as candidates for this dosage form. Hence there has been an enhanced demand for more patient compliancedosage forms[11].

The importance of rapidly disintegrating oral tablet dosage forms isincreasingly being recognized in both, industry and academia[12]. Their increasing importance was underlined recently when European pharmacopoeia adopted the term.
– Fast dissolving tablets that to be placed in the mouth where it disperses rapidly before swallowing. Minoxidil is effective orally for severe hypertension. It was introduced in the early 1970s as a treatment for hypertension.High blood pressure, also called hypertension, is blood pressure that is higher than normal. Your blood pressure changes throughout the day based on your activities. Although minoxidil has functions of vasodilator when used systemically for hypertension and used in dermatology.[13]

Minoxidil is a piperidino-pyrimidine derivative, with the following chemical structure:2,6-diamino-4-piperidinopyrimidine-1-oxide ($C_9H_{15}N_5O$) with molecular Weight of 209.25 and half-life is : The half-life of topical minoxidil averaged 22 hours, compared to 1.49 hours for the oral formulation. Minoxidil is a crystalline powder that is soluble in methanol but rather insoluble in water, acetone and alkaline solutions. The antihypertensive activity of minoxidil is due to its sulphate metabolite,

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minoxidil sulfate. In large measure, minoxidil acts by opening adenosine triphosphate-sensitive potassium channels in vascular smooth muscle cells.[14]

Criteria for Fast Dissolving Drug Delivery system

The tablets should,

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum of no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipment's at low cost[15].

Salient Features of Fast Dissolving Drug Delivery System:

- No need of water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have immediate access to water.
- Ease of administration to the patients who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure and patients.
- Rapid dissolution and absorption of the drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and oesophagus as the saliva passes down into the stomach. In such cases bioavailability of the drug is increased.
- Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage, improve clinical performance through a reduction of unwanted effects.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly patients.
- The risk of choking of suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.
- Beneficial in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra-rapid onset of action is required.
- An increased bioavailability, particularly in cases of insoluble and hydrophobic drugs, due to rapid disintegration and dissolution of these tablets[15].

Advantages of FDT:

- Achieve increased bioavailability/rapid absorption through Pre-gastric absorption of drugs from mouth, pharynx & oesophagus as saliva passes down.
- Convenient for administration and patient compliant for disabled, bedridden patients and for travellers and busy people, who do not always have access to water.
- Administration to the patients, who cannot swallow, such as the elderly, stroke victims, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as paediatric, geriatric & psychiatric patients.
- Rapid drug therapy intervention.
- Good mouth feel property helps to perception of medication as bitter pill particularly in paediatric patients.
- The risk of choking of suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation, product promotion, patent extension and life cycle management.
- No need of chewing the tablet.
- Better taste.
- Improved stability.
- Suitable for controlled/sustained release actives.
- Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packing machinery.
- Cost effective[15,16].

Limitation of tablets:

- The tablets usually have insufficient mechanical strengths. Hence, careful handling is required.
- The tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly[15,16].

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METHODS USED FOR PREPARING FAST DISSOLVING TABLETS:

1. Tablet Molding:

In this method, the delivery system is formulated in the form of tablets using water soluble additives to allow the tablet to dissolve rapidly and completely inmouth[12,13]. All the ingredients of the formulation are passed through fine mesh, dry blended, wetted with a hydro-alcoholic solvent and then compressed into tablets usinglow compression forces. The solvent is then removed by air drying[15].

2. Freeze Drying (Lyophilization):

Lyophilization is another manufacturing technology, which allows drying of heat-sensitive drugs and biologicals at low temperatures under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and showsenhanced absorption and bioavailability.

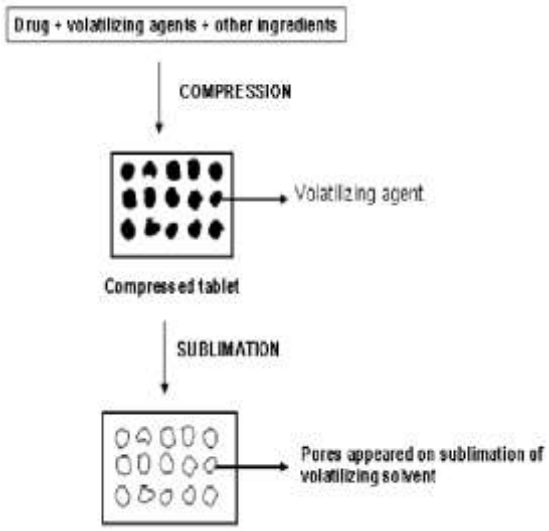
3. Spray Drying:

Spray drying is a process by which highly porous, fine powders can be produced. The composition contains a bulking agent (mannitol and lactose), a disintegrant (sodium starch glycolate and croscarmellose sodium), an acidic ingredient (citric acid) and/ or alkaline ingredients (sodium bicarbonate) which when compressed into tablets shows fast disintegration and enhanced dissolution.

4. Sublimation:

This method includes the addition of a sublime salt to the tableting components, compressing the blend and removing the salt by the process of sublimation. The active ingredient, a diluent, a sublime salt (camphor/ammoniumbicarbonate), a binder and other excipients are blended and are converted into tablets[8].

Because of low porosity, compressed pills composed of excipients as pill matrix cloth frequently do now no longer dissolve unexpectedly within side the water porous pill that show off true mechanical power and dissolve speedy were developed. inert strong ingredients (ex, urea, urethane, ammonium carbonate, camphor , naphthalene) have been brought to different pills excipients and the combination turned into compressed into pill.



5. Addition of Disintegrants:

Addition of disintegrants in fast dissolving tablets, leads to quick disintegration of tablets and hence improves dissolution. Microcrystalline cellulose, cross-linked carboxy methyl cellulose sodium, cross-linked polyvinyl pyrrolidone and partially substituted hydroxy propyl cellulose, absorbs water and swells due to capillary action and is considered as effective disintegrants in the preparation of fast dissolving tablets.

6. Sugar Based Excipient:

Sorbitol, mannitol, dextrose, xylitol, fructose, maltose and polydextrose have been used as bulking agents. Because of their high aqueous solubility and sweetness, which impart a pleasing mouth feel and good taste masking, nearly all formulations for rapidly dissolving tablets contain sugar-based materials.

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 upon heated blade to form tablets.

CHAPTER-2

OBJECTIVES

The main aim of the present work is to formulate fast dissolving tablets containing Minoxidil, which give more rapid onset of action compared to oral conventional dosage form to improve patient compliance. Themajor objectives of the present work are asfollows:

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- To study the pre-formulation factors of Minoxidil such as drug-polymer compatibility, drug identification, flow property, angle of repose, etc.
- To study the pre-formulation factors for powder blend such as angle of repose, tapped density, bulk density, and Carr'sindex.
- To prepare fast dissolving tablets of Minoxidil by direct compression, effervescent and sublimation methods using various super-disintegrants like Crospovidone,Croscarmellose sodium and pre-gelatinized starch.
- To evaluate prepared tablets by various physical characterization tests such as diameter, thickness, hardness, friability, in-vitrodispersion, content uniformity, weight uniformity, wetting time, and water absorption ratio.
- To select the most appropriate formulation for furtherstudies.
- To carry out short term stability studies on the most satisfactory formulation as per ICHguidelines.
- Statistical analysis of thedata.
- To present the results in the most convenient and lucid form for better understanding of the results by representing the data in the tablets andfigures.

CHAPTER-3
REVIEW OF LITERATURE

Review of literature revealed that several studies have been carried out on mouth dissolving tablets using different techniques which are as follows:

Shailesh Sharma, Gupta GD, Jain CP, Naruka PS have prepared fast dissolving tablets of carvedilol using super-disintegrants and solid dispersion technique. The tablets were prepared by direct compression technique. The prepared tablets were evaluated for thickness, uniformity of weight, content uniformity, hardness, friability, wetting time, in-vitro disintegration time and in-vitro drug release. The tablets apart from fulfilling all official and other specifications, the carvedilol dissolution profile from the newly developed tablets was clearly better than those from various conventional tables at the same drug dosage. The stability studies conducted as per ICH guidelines at 40°/75% RH showed insignificant loss in drug content and no physical changes at the end of six months.[30]

SheetalMalke, SupriyaShidhyae and Kadam VK have designed oxcarbazepine fast dissolving tablets containing Avicel PH 102 as a diluent and Ac-Di-sol as a super-disintegrant by wet granulation process. An effective, pleasant tasting and stable formulation containing 12% Ac-di-sol, 25% Avicel pH 102 and 8.5% starch as a binder was found to have a good hardness of 4-4.5 Kg/ cm², disintegration time of 28±5s and drug release of not less than 90% within 30 min. The drug release was found to be comparable to the marketed dispersible tablet.[31]

Suresh Sarasija, Pandit V, Joshi HP have prepared mouth dissolving tablets of salbutamol sulphate using sublimable ingredients. Amongst all, the formulations containing microcrystalline cellulose and ammonium bicarbonate showed the least disintegrating time of 5s.[32]

Shagufta Khan, Prashant Kataria, PremchandNakhat and PramodYeole have taste masked ondensetronHCl by complexing with aminoalkyl methacrylate copolymer in different ratios by the precipitation method. Drug polymer complexes (DPCs) were tested for drug content, in-vitro taste in simulated salivary fluid (SSF) of pH 6.2, and molecular property. Complex that did not release the drug in SSF was considered taste-masked and selected for formulation of RDTs. The complex with drug-polymer ratio of 8:2 did not show drug release in SSF; therefore, it was selected. Polyplasdone XL-10 7%w/w gave the minimum disintegration time. Tablets of batch F_4 containing spray-dried mannitol and microcrystalline cellulose in the ratio of 1:1 and 7%w/w polyplasdone XL-10 showed faster disintegration, within 12.5 seconds, than the marketed tablet (112 seconds).[33]

Patel DM, Prajapati DG and Patel NM have developed Ocimumamericanumlinn as disintegrant in tablets. Mucilage from the seeds of Ocimumamericanumlinn were extracted and developed. The yield was found to be 14%. The disintegration time for tablet formulations prepared using mucilage (10% w/w) was less (154s) than that of the tablet formulations prepared using starch as a disintegrant (269s). The mucilage did not interfere with release of the drug from the tablet formulations.[34]

Shishu, Ashima Bhatti have prepared rapidly disintegrating tablets of chlorpheniramine maleate using taste masked granules. The taste-masked granules were prepared using Eudragit E-100 (amino alkyl methylacrylate copolymers) by the extrusion method. These taste-masked granules

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were directly compressed into tablets using sodium starch glycolate as a super-disintegrant. Tablets had good taste and disintegrated in oral cavity within 30 seconds.[35]

Amrutkar JR, Pawar SP have prepared the tablet formulations of famotidine with various disintegrants like croscarmellose sodium, crospovidone, Indion-414 and sodium starch glycolate with a view to increase the solubility. Among the four disintegrants added, the tablets prepared with croscarmellose sodium were superior with respect to disintegration and dissolution characteristics.[36]

Gohel MC, Parikh RK explored the feasibility of preparing a co-processed super disintegrant to evaluate its functionality. Croscarmellosesodiumand crospovidone were selected in the present investigation. Crospovidone acts by wicking action and croscarmellose sodium acts mainly by swelling action.[37]

Gohel MC, Parikh RK have prepared and evaluated co-processedsuper-disintegrant consisting of Crospovidone and sodium starch glycolate, lactose, microcrystalline cellulose, dibasic calcium phosphate dihydrate, Cefixime trihydrate tablets to assess the efficacy of co-processed super-disintegrant.[38]

Marzia have developed fast dissolving tablet formulation able to assure complete drug dissolution whereas marketed glyburide tablets present unsatisfying dissolution profiles that gives rise to variable bioavailability. Investigated the effect of the addition to a reference tablet formulation of different types (anionic and non-ionic) and amounts of hydrophilic surfactants, as well as the use of a new technique, based on ternary solid dispersions of the drug with hydrophilic carrier (polyethylene glycol – PEG6000) and a surfactant.[39]

Shishu and Kashyap N have prepared taste-masked two child-friendly dosage forms, rapidly disintegrating tablets and liquid oral suspension. Taste-masking was achieved using a pH sensitive polymer Eudragit E-100. Solvent evaporation technique was used to prepare taste-masked microspheres. Taste masked microspheres were directly compressed into tablets using microcrystalline cellulose (MCC) as directly compressible filler and sodium starch glycolate (SSG) as a super-disintegrant.[40]

Bandari S, Mittapalli RK, Gannu R, Rao Y, Madhusudan Rao have given an overview on orodispersible tablets including different methods i.e., lyophilization, molding, cotton candy, spray drying, mass extrusion, compaction and other patented technology with evaluation of orodispersible tablets.[41]

Chakraborty S, Khandai M, Singh SP, PatraNiranjan CH have prepared fast dissolving tablets of aceclofenac using SSG, Ac-di-Sol and mucilage of plantago as super-disintegrants and MCC as direct compressible vehicle by using direct compression method.[42]

Pandey VP, Venkatrao S and Chakravarthy V have prepared cefadroxil dispersible tablets using Crospovidone as super-disintegrants and MCC as diluent by direct compression method andwet granulation technique in which polyvinyl pyrrolidone in water as granulating agent.[43]

Swamy PV, Ali SH, Kori SS and Shirsand SB have prepared dapsone fast dissolving tablets using potato starch and microcrystalline cellulose as inert carriers by utilizing the technique of solvent deposition.[44]

Shetty CM, Prasad DVK, Gupta VRM, Sa B have prepared fast dispersible tablets of aceclofenac using croscarmellose sodium, Crospovidone, sodium starch glycolate as super-disintegrant by direct compression method.[45]

Rao TV, Ramakrishna R, Murthy TEGK, Vidydhara S have formulated cefadroxil dispersible tablets by direct compression technique using super-disintegrants such as Crospovidone, croscarmellose sodium and sodium starch glycolate with PEG-6000 as binding agent.[46]

Mulla JA, Dasankoppa FS, Vilas GJ and Sholapur HP have prepared fast dissolving tablets of promethazine by direct compression technique using Ac-Di-sol explotab and polyplasdone XL tried as super-disintegrant.[47]

Patel SS, Patel MS and Patel NM have tested the flowability and packability of direct compressible excipients.[48]

Sharma V, Philip AK, Pathak K have prepared orodispersible tablets of roxithromycin using modified polysaccharides co-grinded treated agar (C-TAG) and co-grinded treated guar-gum (C-TGG) as rapidly disintegrating excipients with 2^2 factorial designs.[49]

Goddeeris C, Willems T, Vanden MG formulated Fast dissolving tabletsof ternary solid dispersions consisting of d-alpha-tocopheryl polyethylene glycol succinate 1000 (TPGS 1000) and HPMC 2910 or polyvinyl pyrrolidone co-vinyl acetate 64 (PVPVA 64) to improve the dissolution of the anti-HIV drug UC 781.[50]

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Kuno Yoshio, Kojima M, Nakagami H, Yonemochi E, Terada Khave evaluated the effect of lubricant on the characteristics of orally disintegrating tablets using the phase transition of sugar alcohol. Orally disintegrating tablets were produced by directly compressing containing lactose-xylitol granules, disintegrants, glidant, lubricant and subsequent heating.[51]

Bhowmik D, Chandira RM, Venkateshwarlu and Jaykar B have formulated and evaluated fast dissolving tablets of terbutaline sulphate using SSG, CCS as super-disintegrants by direct compression method.[52]

Patel SS, Patel PM and Patel NMhave evaluated direct compression characteristics of co-processed lactose using nimesulide. Lactose was co-processed with talc by using freeze-thaw technique and evaluated as a directly compressible diluent for nimesulide tablet.[53]

Koseki T, Onishi H, Takahashi Y, Uchida M, Machida Y have prepared Fast dissolving tabletsof furosemide by direct compression using sucrose, stearic acid ester as a disintegration-accelerating agent.[54]

Swamy have prepared orodispersible tablets of pheniramine maleate by effervescent method using mixture of sodium bicarbonate & tartaric acid along with pre-gelatinized starch, sodium starch glycolate, croscarmellose sodium &Crospovidone as super-disintegrants. Among the formulations, ECF_4 containing Crospovidone (4%), sodium bicarbonate (12%), tartaric acid (12%), showed over all best formulation.[55]

Mishrahavestudied the taste masked resinate of risperidone orally disintegrating tablets by direct compression method using ambralite IRP 64 and drugloaded in the ratio of 1:4 (drug: resin weight) and this complex was compressed in to orally disintegrating tablet. It showed 92% of drug release in 5 min.[56]

Barhate have prepared fast dissolving tablets of meloxicam by solvent evaporation method using super-disintegrants such as PEG-4000 & PVP K-30.Among the formulations solid dispersion of meloxicam with PVP K-30 (1:6) showed maximum dissolution.[57]

Singh have formulated and optimized anorodispersible tablets of meloxicamby non-aqueous wet granulation method using crospovidone and mannitol. A 2^2 factorial design were used. Theprepared orodispersible tablets were evaluated for weight variation, friability, disintegration time, drug content, wetting time,water absorption ratio and in-vitrodrug release. The formulation F_4 tablets showed 99.5% of drug release within 30 min, as compared to conventional tablet (49.5%).[58]

Renati D. has doneresearch to prepare Diclofenac Sodium quick dissolving tablets by Hole technology. Once these quick dissolving tablets come in contact with gastro enteric fluids, the fluid enters the hole within the tablet and causing immediate breaking of the tablet. The formulated FDTs were subjected to numerous pre and post formulation studies. In-vitro drug release of FDTs (DH6) showed virtually 100.92% of the drug was discharged at sixth minute, whereas the management formulation D12 shows the 99% drug release at 20th minute. Overall, this method is novel and most helpful in formulating quick dissolving tablets.[59]

Dasharath MP, Sweeti P, on Fast dissolving tablet containing domperidone ternary solid dispersion for increasing dissolution rate and stability of formulation. Formulation containing ratio 1:2:1.5 of drug: Gelucire 50/13: Poloxamer 188 shows maximum dissolution. The studies indicated that the dissolution and stability of solid dispersion was faster in the presence of ternary agent (surfactant) when compared to binary solid dispersion. They concluded that fast dissolving tablet containing ternary solid dispersion is stable at accelerated environmental conditions for 1 month.[60]

Rajeev H, Guru PM, Paridhavi M, prepared rapidly disintegrating, mouth dissolving tablets of Sildenafil citrate to achieve quick onset of action and to avoid first pass loss. Tablet formulations were prepared by direct compression method using excipients. The tablets prepared using Pharmaburst® (a co-processed excipient system) in comparison with well-known super disintegrants showed better results in terms of hardness, content uniformity, disintegration time and wettability. Tablets containing sildenafil citrate 10mg,20mg & 40mg were prepared Pharmaburst® and the bioavailability in rabbits was compared with conventional enteral. The study indicates mouth dissolving tablets of Sildenafil citrate prepared using Pharmaburst® provide rapid onset of action and improved bioavailability.[61]

Shakeena G, recently employed Terbutaline Sulfate to treat respiratory disease and respiratory disorders. Where Fast dissolving tablets of terbutaline Sulfate tablets were made by the direct compression technique incorporating with super disintegrants like crystalline cellulose and sodium starch glycolate in numerous

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concentrations. Prepared tablets can be evaluated for various parameters like weight variation, thickness, hardness, friability, wetting time, drug content, water absorption quantitative relation, in-vitro dispersion time, in-vitro disintegration time and in-vitro drug release.[62]

Bhawna M, Rizwana K, Manish R, Anil K,formulated and evaluated fast dissolving tablet ofglimepiridein varying concentration of super disintegrating agents. The fast-dissolvingtablets of glimepiride was prepared by direct compression method.The drug and excipients were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio to determine the flow property of powder. The formulated tablets were evaluated for various parameters like thickness, hardness, friability, wetting time, water absorption and dispersion time. The obtained results indicated F4 was the best formulation among the four formulations and all formulation results are within the range.[63]

Sheetal B, Sandip B, formulated fast dissolving tablets of Albendazole were prepared to provide a quick action, faster dissolution rate and improved bioavailability. An attempt was made to increase the drug release incorporating the super disintegrant and camphor/ammonium bicarbonate as subliming agents. The prepared fast dissolving tablets were subjected to pre-compression analysis and evaluated for hardness, weight variation, friability, wetting time, water absorption ratio and disintegration time. From the results of in-vitro drug release studies, the formulation F9 exhibited fast release profile of about 98.20% in 16 min and disintegration time 65.60 sec when compared with other formulations. The study demonstrates potential for rapid absorption, improved bioavailability, effective therapy and patient compliance.[64]

Ayesha F, Sirisha M, fabricated mouth dissolving tablets of Amiodarone by direct compression method using the natural and synthetic Super-disintegrants to enhance the bioavailability. The blend of all the formulations showed good flow properties. The prepared tablets showed good post compression parameters and they passed all the evaluation parameters as per I.P limits. Among all the different formulations, F-8 (3% w/w Xanthan gum) hasshown faster dissolution profile. Hence, revealing that the natural super-disintegrant are equally potential activity in comparison to synthetic super-disintegrants.[65]

Reddy MS, Kore N, FazalUlHaqSM,designedDiltiazem HCl Fast Dissolving tablets by Direct compression method using Co-processed excipients-Disintequik MCC25, Disintequik MCC, Lubritose MCC, Lubritose SD, Lubritose AN, NF Fast flow Lactose Monohydrate modified spray dried. The Prepared powdered blend and tablets were evaluated for Pre compression parameters and Post compression parameters. IR and DSC study indicated that drug and excipients were compatible with each other. Twelve formulations were prepared by direct compression method in which F10 was the best formulation using Disintequik MCC25 in a concentration of 4% disintegrated within 30 sec and drug release was 99.88% over a period of 15 min. The wetting time and disintegration time decreases significantly with the increase in co-processed excipients.[66]

Sumathi M. Fabricated fast dissolving tablets of Mefenamic acid by direct compression technique using various concentrations of superdisintegrants like croscarmellose sodium (Ac-Di-Sol), TrigonellaFoenum-graceum and Plantago ovata. The formulated tablets were evaluated for crushing strength, friability, thickness, diameter, weight variation, wetting time, water absorption ratio, disintegration time, and percentage of drug release. All formulations indicated satisfactory result.Formulation F5 containing 2% of TrigonellaFoenum-graceum exhibited complete disintegration within 10 seconds. Dissolution data was exhibited an acceptable value >50. All parameters were found within the limit of acceptance.[67]

Sangeetha G et al., have formulated and evaluated fast dissolving tablet of ketorolac tromethamine oral dispersible tablet by using three polymers and in combination of three super-disintegrants and by dry granulation technique. From the study it has been concluded that the in-vitro dissolution data of formulation F1 has shown best drug release of 90.88% when compared to the other formulation.[68]

Meenakshi B et al., have formulated and characterized fast dissolving tablet of Salbutamol Sulphate which gives great importance in reliving acute asthmatic shocks. The tablets were formulated by using different super disintegrants in different ratio and by various techniques from the study it was absorbed that formulation C4 has shown less disintegration time and 99.99% drug release in 50 minutes.[69]

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Madhuri et al., have formulated and evaluated fast dissolving tablet of Lamotrigine inclusion complexes along with various super disintegrants in different ratios by sublimation technique. From the study it reveals that the formulation F3 has shown rapid disintegrating time and 99% of drug release when compared to other formulations.[70]

Abdul Hasan Sathali A et al., have formulated and evaluated Ormeloxifens fast dissolving tablet by using solid dispersion product by direct compression method. From the overall result formulation of F8 which was prepared by combination of super-disintegrants like croscarmellose sodium, sodium starch glycolate, and crospovidone showed shorter disintegrating time, superior drug release and high-water absorption.[71]

Humane SB et al., have prepared fast dissolving tablet of Eprosortan Melysate by direct compression method by using crospovidonein different ratios along with microcrystalline cellulose and Mannitol to enhance mouth feel. Among the nine formulations, the formulation prepared by using 10%W/W of crospovidone and 35% W/W of Microcrystalline cellulose emerged as the overall best formulation (t50% 1.8min) based on in-vitro drug compared to CCF (t50% 16.4min)[72]

Chinmaya KS et al., have studied fast dissolving tablet of carvedilol to treat various cardiovascular disorders the tablets were made by wet granulation technique by using sodium starch glycolate. The formulation of FD4 was considered as the overall best formulation which has shown in-vitro drug release of 97.08% in 50 mins when compared to other formulations.[73]

Shivali S et al., have prepared and optimized fast dissolving tablet of Aceclofenac by 3^2 full factorial designs. Promising batch R8 was compared with three marketed of aceclofenac tablets for in-vitro drug release among all formulation promising formulation R8 exhibited better drug dissolution after 30 min than the marketed tablets.[74]

Ausaf B et al., have formulated and evaluated fast dissolving tablet of Dabigatran. The tablets were formulated by wet granulation technique by using hydrophilic carrier PEG-4000 as solubilizer along with polyplosdone XL-10 and primellose as super-disintegrants. From the study comes that the formulation F6 containing 4% PEG 4000 and 7.5% Primellose showed maximum percentage (85.46%) drug release compared to other formulations.[75]

Acharya A et al., have prepared fast dissolving tablet of Lornoxican by direct compression method using three different approaches; such as super-disintegrant addition, sublimation, and solid dispersion. From the study it was observed formulation L16 has shown better in-vitro dispersion and dissolution which could be due to swelling effect of guar gum amorphization during the solid dispersion.[76]

Arifa Begum et al., have formulated and evaluated fast dissolving tablet of Roflumilast solid dispersions using a direct compression method. From the study it has been concluded that dissolution study SD1 and SD2 formulations has shown best results formulations among all the formulation.[77]

Dattatraya m. Shinkar et al have worked on Formulation and in vitro evaluation of fast dissolving tablet of verapamil hydrochloride. Fast dissolving tablet of verapamil hydrochloride used for the treatment of hypertension. All the prepared formulations were subjected to various assessment parameters, and the findings obtain within the prescribed limit. The calibration curve of pure drug using various solvents like distilled water, phosphate buffer pH 6.8 was plotted. F1-F9 containing croscarmellose sodium and sodium starch glycolate in various concentrations demonstrated the minimum disintegration time. Among all these formulations F8 shows disintegration time up to 19±0.06 seconds due to the high concentration of super-disintegrants. The results obtained in the research work clearly showed a promising potential of fast dissolving tablets containing a specific ratio of croscarmellose sodium and sodium starch glycolate as super-disintegrants for the effective treatment of hypertension.[78]

Amjad Hussain et al have worked on Personalised 3D Printed Fast-Dissolving Tablets for Managing Hypertensive Crisis. Hypertensive crisis (HC) is an emergency health condition which requires an effective management strategy. Over the years, various researchers have developed captopril based fast-dissolving formulations to manage HC; however, primarily, the question of personalisation remains unaddressed. The present study has successfully exhibited the utilisation of additive manufacturing approach to mend the gap of personalisation and manufacturing fast-dissolving captopril 3D printed tablets. The procedure adopted in the present study may be used

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for the development of fused deposition modelling (FDM) based fast-dissolving 3D printed tablets.[79]

Nishita Soni1el al published a review on formulation and evaluation of fast dissolving tablet. In this present scenario, the drug delivery system has become highly competitive and rapidly most evolving with ever increasing demand. Fast dissolving tablet (FDT) is such type of an innovative and unique drug delivery system which is intensely gaining much attention in the research field of rapid dissolving technology. Therefore, recently many pharmaceutical companies developed fast dissolving tablet (FDT) by modifying the physicochemical properties of drugs to their need with enhanced patient compliance and convenience. There are several methodologies that are conventional or patented based on spray drying, sublimation, melt granulation, direct compression, etc. are developed for manufacturing of FDTs. This review includes the requirements, advantages, limitations, various technologies developed for FDTs evaluation.[80]

A. Arunachalam et al published a review on fast dissolving drug delivery system. Swallowing a pill is a major difficulty encountered in case of geriatric and paediatric patient which leads to poor patient compliance due to unpalatable taste of drug. To troubleshoot these problems a new dosage form known as fast-dissolving tablet (FDT), has been developed which rapidly disintegrate and dissolve in saliva. This review discusses the method of preparation, properties, advantages, disadvantage, characterization, mechanisms and drugs to be incorporated in the mouth dissolving tablet. Also discussed evaluation of the product and future trend of the mouth dissolving tablets.[81]

Pratik swarup das et al published a review on Fast dissolving tablets using solid dispersion technique. These are also called as mouth-dissolving tablets, melt-in mouth tablets, orodispersible tablets, quick dissolving etc. The faster the drug dissolved into solution, quicker the absorption and onset of clinical effect. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bio availability of a range of poorly water-soluble drugs. The focus of one part of the review article is based on solid dispersion mainly advantages, disadvantages, types, the method of preparation, and characterization of the solid dispersion at laboratory and industrial level.[82]

Ved Parkash et al published a review on Fast disintegrating tablets (FDTs) and opportunity in drug delivery system. FDT have received ever-increasing demand during the last decade, and the field has become a rapidly growing area in the pharmaceutical industry. This review describes various formulations and technologies developed to achieve fast dissolution/dispersion of tablets in the oral cavity. In particular, this review describes in detail FDT technologies based on lyophilisation, molding, sublimation, and compaction, as well as approaches to enhancing the FDT properties, such as spray drying and use of disintegrants. In addition, taste-masking technologies, experimental measurements of disintegration times, and dissolution are also discussed.[83]

Biswajit Basu et al have formulated and evaluated fast dissolving tablets of cinnarizine.A combination of super disintegrants, i.e., sodium starch glycolate(SSG) and croscarmellose sodium(CCS) were used along with camphor as a subliming agent. An optimized concentration of camphor was added to aid the porosity of the tablet. A32 full factorial design was applied to investigate the combined effect of two formulation variables: Amount of SSG and CCS. Infrared (IR) spectroscopy was performed to identify the physicochemical interaction between drug and polymer. All the formulations were evaluated for their characteristics such as average weight, hardness, wetting time, friability, content uniformity, dispersion time (DT), and dissolution rate.[84]

Devendra Rane et al have worked on the fast dissolving tablets of Albendazole. In the present work, FDT of Albendazole was designed to provide a quick onset of action. The main objective of the study was to formulate fast dissolving tablets prepared by direct compression and using super-disintegrant in different concentration and evaluated for the pre-compression parameters. The prepared tablets were evaluated for post compressional evaluation. Among all, the formulation f3 formulation containing 5%w/w super disintegrant crospovidone and 20%w/w microcrystalline cellulose was considered to be best formulation, which releases up to 99.097% in 40 min.[85]

Sudhir Bhardwaj et al have worked on Formulation and evaluation of fast dissolving tablet of aceclofenac. FDT of Aceclofenac was selected as the model drug. The poor aqueous solubility of the drug results in variable dissolution rate and hence poor bioavailability. In the present study, an attempt had been made to prepare fast dissolving tablets of the drug using various super disintegrates sodium starch glycolate following by direct

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compression technique. The tablets were evaluated for hardness, friability, weight variation, disintegration time, water absorption ratio and wetting time, in vitro dissolution studies. All the formulation showed disintegration time in range of 12.2 to 27.5 second along with rapid in vitro dissolution. It was concluded that the FDTof the poor soluble drug can be made by direct compression technique using selective super disintegrants showing enhanced dissolution, taste masking and hence better patient compliance and effective therapy.[86]

Omkar S et al have worked on development of fast dissolving tablets of hydrochlorothiazide and atenolol co-crystals. Hydrochlorothiazide (HCT) is a class IV drug which has limited solubility and permeability to overcome this problems co-crystallization method is used. Co-crystallization is the process to enhance the physical properties of drug molecule especially the solubility. The saturation solubility was done to evaluate the solubility of co-crystals. Comparative drug release study was carried out between co-crystals and marketed formulation. The prepared co-crystals have shown several times faster release than marketed tablet and co-crystals were characterized by using DSC, FTIR and SEM[87]

Chandrasekhar Patro et al have worked on Mouth Fast Dissolving Tablets of Cetirizine (MFDT's) have emerged as an alternative to conventional oral dosage forms to improve the patient compliance. The MFDT's are solid dosage forms that dissolve or disintegrate rapidly in the oral cavity, which results in solution or suspension without the need of water. The main objective of this work is to formulate and evaluate Cetirizine HCl MFDT's using different concentrations of super-disintegrants like croscarmellose sodium (CCS), sodium starch glycolate (SSG). FT-IR studies revealed that there was no interaction between Cetirizine HCl and the excipients used in the study. The results indicate that formulation prepared with 5% croscarmellose sodium was found to be optimized which provides maximum drug release (99%) and minimum disintegration time (less than 20sec). Stability studies of optimized formulation revealed that formulation is stable.[88]

K. P. R. Chowdary et al have worked on Fast dissolving tablets of Paracetamol (FDTs) are novel types of tablets that dissolve / disintegrate / disperse in saliva within few seconds without water. Paracetamol is a widely prescribed antipyretic and analgesic drug for all age groups. The objective of the study is to formulate and evaluate FDTs of paracetamol employing three known super-disintegrants namely crospovidone, croscarmellose sodium and primojel and one new co-processed excipient namely pre-gelatinized starch-PEG 1500- aerosil. The new co-processed excipient, pre-gelatinized starch- PEG-aerosil is comparable to the known super-disintegrants for formulation of FDTs.[89]

Ali MS et al have been worked on Formulation and Evaluation of Fast Dissolving Oral Films of Diazepam. Oral films dissolve rapidly along with drug in mouth and majority of the drug is absorbed through buccal/oral mucosa in to systemic circulation avoiding first pass metabolism. The aim of present investigation was to formulate the Fast dissolving oral films (FDOF) of Diazepam an anti-epileptic drug which is normally administered by intramuscular route or as rectal suppository in acute conditions of seizure emergencies.[90]

Shaikh Siraj Nawaj et al have worked on recent development in fast disintegrating technology of Ondansetron. Mainly works to improve the quality of these delicate dosage forms without affecting their integrity. Current investigations deal with the formulation of fast dissolving tablet of Ondansetron HCl with the effect of different co-processed excipients by using ball mill that disintegrates in oral cavity on contact with saliva & thereby improve therapeutic efficacy because the mannitol was stick to dies and punch therefore ball mill is used to prepare co ground mixtures of crospovidone and mannitol to improve the compatibility and stability of product. The Fast disintegrating tablets of Ondansetron HCl were prepared by direct compression method using different synthetic super-disintegrant such as crospovidone, and natural super-disintegrants such as Karaya gum and Fenugreek gum in different concentration. The result shows that co-processing of excipients is the most suitable approach for formulation of Fast dissolving tablet.[91]

Mahmoud Met al have worked on Tolmetin Sodium Fast Dissolving Tablets for Rheumatoid Arthritis Treatment. Tolmetin sodium (TLM) is a non-steroidal anti-inflammatory drug (NSAIDs). TLM is used to treat inflammation, skeletal muscle injuries, and discomfort associated with bone disorders. Because of the delayed absorption from the gastro intestinal tract (GIT), the currently available TLM dosage forms have a rather protracted start to the effect, according to pharmacokinetic studies. The aim of this study was

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to create a combination for TLM fast dissolving tablets(TLM-FDT) that would boost the drug's bioavailability by increasing pre-gastric absorption.[92]

CHAPTER-4

METHODOLOGY

Table-1: Materials used

Sl. No.	Material	Source
1	Minoxidil	CHEMLAND IND
2	Croscarmellose sodium	Evertozen Pharma Pvt. Ltd. Gadcharla
3	Sodium starch glycolate	Evertozen pharma Pvt Ltd Gadcharla
4	Crospovidone	Evertozen pharma Pvt Ltd Gadcharla
5	Microcrystalline cellulose (MCC)(PH102)	FDC Ltd., Goa
6	Pre-gelatinized starch	Evertozen pharma Pvt Ltd Gadcharla
7	Aspartame	Medrich Pharmaceuticals, Bangalore
8	Mannitol	Strides Arco Labs, Bangalore
9	Sodium bicarbonate	HD fine
10	Tartaric acid	HD fine
11	Flavor	Alkem Labs Pvt. Ltd., Mumbai
12	Magnesium stearate	Glenmark Ltd., Nashik
13	Talc	SD Fine Chem. Mumbai

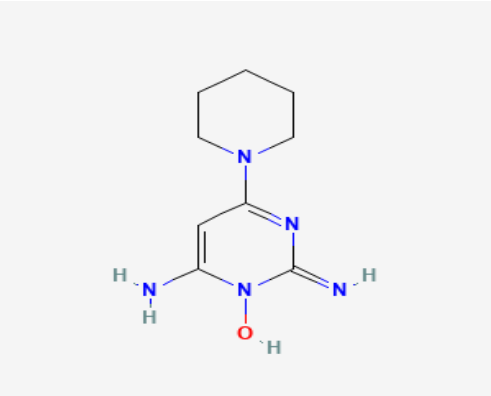
Table-2: Equipment's used

Sl. No.	Equipment	Model /Source
1	UV-spectrophotometer	1800 Pharmaspec, Shimadzu
2	Digital balance	BL-220H, Shimadzu
3	Digital pH meter	Systronic Electronics, Mumbai
4	Dissolution apparatus	DT-06 N, Electro lab USP XXIII
5	IR spectroscopy	Shimadzu
6	Hot air oven	Tempo Instruments &Equipment's, Mumbai
7	Hardness tester	Monsanto Hardness Tester
8	Friability test apparatus	Electrolab
9	Tablet punching machine	Clit, Ahmedabad
10	Stability chamber	Osworld JRIC-11, Mumbai

DRUGPROFILE
MINOXIDIL

Chemical Formula: $C_9H_{15}N_5O$
Drug Category: Antihypertensive
Chemical name: 2,4-pyrimidinediamine, 6-(1-piperidinyl)-, 3-oxide
IUPAC Name: 6-piperidin-1-ylpyrimidine-2,4-diamine 3-oxide

Chemical Structure:



Drug Category: Minoxidil is an antihypertensive vasodilating agent used for resistant hypertension
Molecular Weight: 209.251 g/mol

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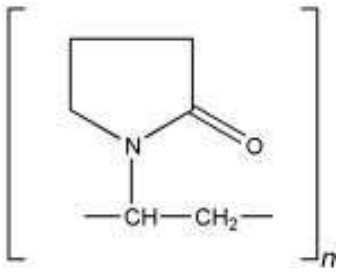
State: Solid
Dose: Adults and children over 12 years of age: 5 to 40 milligrams taken as a single dose
Solubility: Sparingly soluble in water and soluble in ethanol
Indication: Minoxidil is used as anti-hypertensive drug which is mainly used in the decreasing the blood pressure also used to stimulate hair growth and to slow balding. It is most effective for people under 40 years of age whose hair loss is recent. Minoxidil has no effect on receding hairlines. It does not cure baldness; most new hair is lost within a few months after the drug is stopped.
Mechanism of Action: Minoxidil. It is a powerful arteriolar dilator. It is effective orally. It causes reflex tachycardia, Na^+ and water retention. Hence, minoxidil is used with a B-blocker and diuretic.
Drug Interaction: Systemic cyclosporine may enhance side effects like hypertrichosis when used with topical minoxidil. The hypertrichosis symptoms improved drastically after stopping topical minoxidil for two months.
Side effects: Minoxidil may cause side-effects like increased hair growth, weight gain, fast heartbeat, and chest pain.
Contraindication: Minoxidil is relatively contraindicated in patients with renal disease, pre-existing pulmonary hypertension, or chronic congestive heart failure not secondary to hypertension because the drug can cause an increase in pulmonary artery pressure, which could be detrimental to these patients.
Storage:
Store in cool and dry place, Away from direct sun light.

EXCIPIENTS DATA

Crospovidone

Non-proprietary Names: BP: Crospovidone; PhEur: Crospovidonum; USPNF: Crospovidone
Synonyms: Crosslinked povidone, E1202,KollidonCL, KollidonCL-M, PolyplasdoneXL, PolyplasdoneXL-10, polyvinylpolypyrrolidone, PVPPand1-vinyl-2-pyrrolidinonehomopolymer.
Chemical name &CAS Registry number: 1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]
Empirical formula and molecular weight: $(C_6H_9NO)_n > 1000000$
An exact determination of the molecular weight has not been established because of the insolubility of the material.

Structural formula



Functional category: Tablet disintegrant

Applications in pharmaceutical formulation or technology:
Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2-5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of Crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, Crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to Crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.
Description: Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odourless, and hygroscopic powder.
Stability and storage conditions: Since Crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Croscarmellose Sodium

Non-proprietary name: USPNF: Croscarmellose sodium
Synonyms: Ac-Di-Sol, Cross-linked Carboxymethylcellulose Sodium, Modified Cellulose Gum, Nymcel ZSX, Primellose, Solutab
Functional category: Tablet and capsule disintegrant.
Chemical name: Cellulose, carboxymethyl ether, sodium salt, cross-linked.
CAS Registry number: 74811-65-7.
Description: Croscarmellose sodium occurs as an odourless, white-coloured powder.

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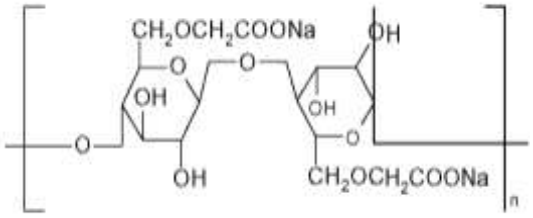
Structural formula:



Molecular weight: 90000-700000
pH (1% w/v dispersion): 5.0-7.0.
Solubility: Insoluble in water. Although croscarmellose sodium rapidly swells to 4-8 times of its original volume on contact with water.
Stability and storage condition: Croscarmellose sodium is a stable though hygroscopic material.

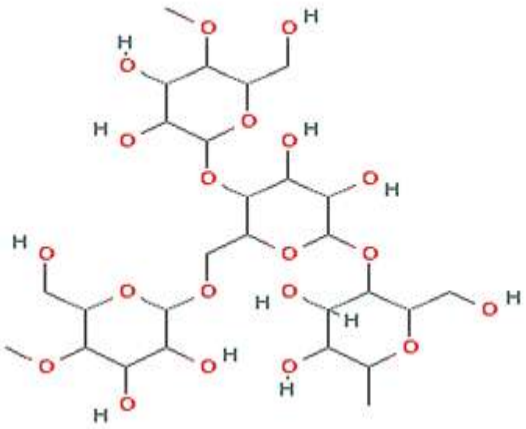
A model tablet formulation prepared by direct compression, with croscarmellose sodium as disintegrant, showed no significant difference in drug dissolution after storage at 30°C for 14 months.
Incompatibilities: The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by wet granulation or direct compression process which contain which contain hygroscopic material such as sorbitol.
Safety: Croscarmellose is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially non-toxic and non-irritant material. However, oral consumption of large amount of croscarmellose sodium may have a laxative effect although the quantities used in solid dosage formulations are unlikely to cause such problems.

Applications:
- Disintegrant in capsule –10-25%
- Disintegrant in tablets –0.5-5%

Pre-Gelatinized Starch
Non-proprietary name: Pre-gelatinized maize starch, USPNF: Pre-gelatinized starch
Functional category: Tablet and capsule diluent; tablet and capsule disintegrant; binder
Synonyms: Compressible starch; Instastarch; lycatab PGS; 78- 1551; Pharma gel.
Chemical names: pre-gelatinized starch
CAS Registry number: 9005-25-8

Empirical formula: $(C_6H_{10}O_5)_n$
Molecular weight: Where n = 300-100

Structural formula:



Description: Pre-gelatinized starch occurs as a moderately coarse to fine, white to off- white coloured powder, it is odourless has a slight characteristic taste.
Solubility: Practically insoluble in organic solvents. Slightly soluble to soluble in cold water, depending upon the degree of pre-gelatinization.
Stability and storage conditions: Stable, through hygroscopic material, which should be stored in well closed container.
Safety: pre-gelatinized starch and starch are widely used in oral solid regarded as nontoxic and non-irritant excipient.
Applications: Pre-gelatinized starch is a modified starch used in oral capsule and tablet formulation as a binder, diluent, and disintegrants.

Microcrystalline Cellulose (Avicel Ph 102)
Non-proprietary name: Microcrystalline cellulose, USP: Microcrystalline cellulose.
Functional category: Tablet and capsule diluent, tablet disintegrant, suspending and/or viscosity increasing agent.
Synonyms: Cellulose gel: Crystalline cellulose: Avicel PH101, 102,
Chemical names: Cellulose
CAS Registry number: 9004-34-6
Empirical formula: C6H1005) n-220
Molecular weight: 36,000(approx)

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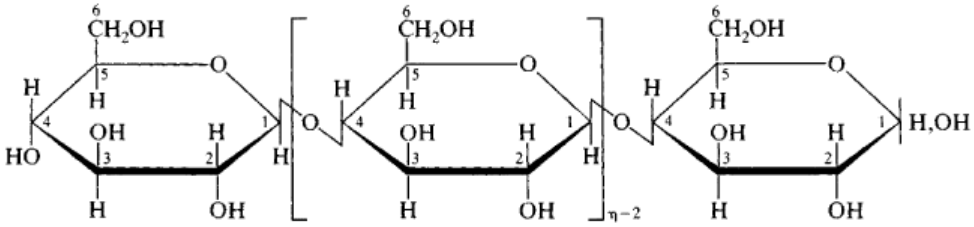
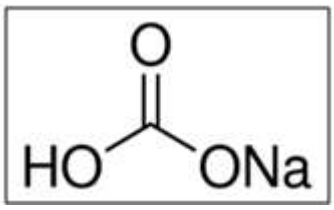
Structural formula:



Description: Purified, partially depolymerized cellulose occurs as a white, odourless, tasteless, crystalline powder composed of porous particles.
Density: Apparent density - 0.28g/cm'; Tap density - 0.43g/cm³
Solubility: Insoluble in water, dilute acids and most organic solvents, slightly soluble in 5% w/v NaOH solution.
Incompatibilities: None cited in the literature
Safety: Generally regarded as safe.
Applications: Tablet binder/diluent (wet ordry granulation)
Tablet disintegrant 5 to 15%
Tablet glidant 5 to 15%
Anti-adherent 5 to 20%

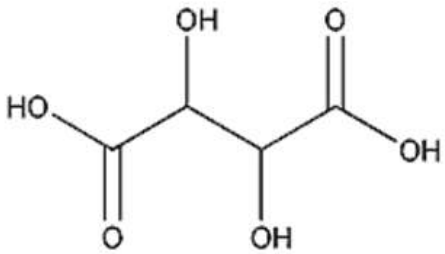


Sodium Bicarbonate
Non-proprietary name:
BP: sodium bicarbonate
JP: Sodium bicarbonate
PhEur: Natrii hydrogenocarbonas
Functional category: Alkalizing agent, Therapeutic agent
Synonyms: baking soda, E500, monosodium carbonate, sodium acid carbonate
Chemical names: Carbonic acid monosodium salt
CAS Registry number: 144-55-8

Empirical formula: $NaHCO_3$
Molecular weight: 84.01
Structural formula: $NaHCO_3$
Description: Sodium bicarbonate occurs as an odourless, white crystalline powder with saline, slightly alkaline taste
Density:2.159 g/cm
Solubility: Ethanol, Ether
Stability and storage conditions: Sodium bicarbonate is stable in dry air but slowly decomposes in moist air and should therefore be stored in well closed container in cool, dry, place.
Incompatibilities: Sodium bicarbonate reacts with acids, acidic salts and many alkaloidal salts, with evolution of carbon dioxide.
Safety: Administration of excessive amounts of sodium carbonate may thus disturb the body electrolyte balance to metabolic alkalosis or possibly sodium overload with potentially serious consequences.
Applications: sodium carbonate is generally used in pharmaceutical formulation as a source of carbon dioxide in effervescent tablets and granules.

Tartaric acid
Non-proprietary name: BP; tartaric acid PhEur; Acidum tartaricum USPNF; tartaric acid
Functional category: Acidifying agent; acidulant; flavour enhancer; sequencing agent.
Synonyms: L-(+)-2,3- dihydroxybutane dioic acid, E334; d- tartaric acid; L- (+)-tartaric acid.
Chemical names: [R-(R, R)]-2,3- dihydroxybutane dioic acid
CAS Registry number: 87-69-4
Empirical formula: $C_4H_6O_6$
Molecular weight: 150.9

Structural formula:



L-tartaric acid

Description: Tartaric acid occurs as a colourless monoclinic crystal, or a white or almost white crystalline powder. It is odourless, with an extremely tart

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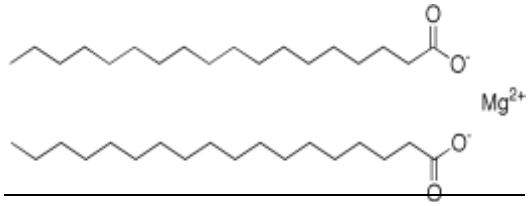
Density: 1.76 g/cm^3
Solubility: glycerine, methanol, water (1 in 75), propan-1-ol (1 in 0.75)
Stability and storage conditions: The bulk material is stable and should be stored in well closed container in cool, dry place.
Incompatibilities: Tartaric acid reacts with metal carbonates and bicarbonates.
Safety: An acceptable daily intake for L-(+) tartaric has not been act by the WHO although an acceptable daily intake of up to 30 mg/kg body weight for monosodium
Applications: Tartaric acid is used in the beverages, confectionery, food products and pharmaceutical formulation as an acidulant, it may also be used as an acidifying agent, a sequestering agent and as an antioxidant synergist.

Mannitol
Synonyms: Cordycepin acid, manita, manna sugar, mannite, Pearlitol.
Functional category: Tablet and capsule diluent, sweetening agent, tonicity agent, vehicle (bulking agent) for lyophilized preparations.
Applications: As a diluent in tablets (10-90% w/w). It is not hygroscopic and can be used with moisture sensitive active ingredients. In the manufacture chewable tablet formulation because of its negative heat of solution, sweetness, mouth feel.
Description: White, odourless, crystalline powder, or free flowing granules. It has a sweet taste.
Solubility: Freely soluble in water, practically insoluble in ether.
Storage conditions: The bulk material should be stored in a well-closed container, in a cool, dry, place.
Incompatibilities: Mannitol solution, 20 % w/v or stronger, may be salted out by potassium or sodium chloride. It is incompatible with xylitol infusion & may form complexes with metals like Fe, Al, and Cu.
Safety: When consumed orally in large amounts laxative effects may occur. Daily ingestion of over 20 g is foreseeable.

Magnesium Stearate
Non-proprietary name: NF: Magnesium stearate; BP/EP: Magnesium stearate.
Synonyms: Metallic stearic; magnesium salt.
Functional category: Tablet and capsule lubricant.
Chemical names: Octadecanoic acid; magnesium salt; magnesium stearate
CAS Registry number: 557-04-0
Empirical formula: $C_{36}H_{70}MgO_4$
Molecular weight: 591.3

Structural formula:



Description: It is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint characteristic odour and taste. The powder is greasy to touch and readily adheres to the skin.
Density (He):1.03-1.08 g/cm^3
Bulk volume:3.0-8.4 ml/g
Tapped volume: 2.5-6.2ml/g

Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in benzene and warm ethanol (95%).
Stability and storage conditions: Stable, non-self-polymerizable. Store in a cool, dry place in a well closed container.
Incompatibilities: Incompatible with strong acids, alkalis, iron salts and with strong oxidizing materials.
Safety: Described as inert or nuisance dust. OSHA has adopted limits of 15mg/m^3 for the total dust and 5mg/m^3 for the respirable fraction. Dust clouds of magnesium stearate may be explosive. However, oral consumption of large quantities may result in some laxative effect or mucosal irritation.
Applications: Tablet and capsule lubricant, glidant and anti-adherent in the concentration range of 0.25 to 2.0%.

Talc
Synonyms: Magsil Osmanthus, Magsil Star, Purtalc, Steatite
Functional category: Glidant, tablet and capsule lubricant, anti- cackling agent.
Applications: It is used as a lubricant in solid dosage forms (1-10%), in topical preparations as dusting powder (90-99 %).
Description: It is a very fine, white to greyish-white coloured, odourless, impalpable, unctuous powder. It adheres to the skin, is soft to touch, and free from grittiness.
Solubility: Practically insoluble in dilute acids and alkalis, organic solvents and water.
Stability: Talc is a stable material.

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Storage conditions: It should be stored in a well-closed container in a cool, dry, place.
Incompatibilities: Incompatible with quaternary ammonium compounds.

Sodium saccharin
Functional category: Sweetening agents
Synonyms: Sodium salt; britsol; crystallose; E954; soluble gluside; soluble saccharin. Sucromalt.
Description: saccharin sodium occurs as white, odourless, or faintly aromatic, efflorescent, crystalline powder. It has an intensely sweet taste, with a metallic aftertaste which at normal levels of use can be detected by approximately 25% of the population.
Solubility: Ethanol (1 in 102), Ethanol 90% (1 in 50), water (1 in 2).
Stability and storage conditions: Saccharin sodium is stable under the normal range of condition employed in formulation.
Safety: The WHO has set s temporary acceptable daily intake of up to 2.5 mg/kg body weight for saccharin, including its salt.
Applications: Saccharin sodium is an intense sweetening agent used in beverages, food products, table top sweeteners and pharmaceutical formulation such as tablets, powders, medicated confectionery, gels, suspension, and liquids.

Aspartame:
Functional category: Sweetening agent.
Synonyms: APM, Aspartyl phenylamine methylester, Equal, Canderel, Nutrasweet, Sanecta, Tri-sweet.
Description: it occurs as white, almost odourless crystalline powder.
Solubility: Slightly soluble in ethanol (95%), sparingly soluble in water. Solubility increases at higher temperature and at more acidic pH
Stability and storage conditions: It is stable in dry conditions. In presence of moisture, hydrolysis occurs. Degradation also occurs during prolonged heat treatment. Bulk material should be stored in a well-closed container, in a cool, dry place.
Incompatibilities: Incompatible with dibasic calcium phosphate.
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 flavour systems and can be used to mask some unpleasant taste and has sweetening power of 180-200 times that of sucrose.

DISINTEGRANTS MECHANISM OF ACTION

A disintegrant is an excipient, which is added to aid in the breakup of the compacted mass, when put into a fluid environment. This is especially important for immediate release product where rapid release of the product is required. Disintegration mechanisms are complex processes. They depend first on the excipients used, but also on the properties of the active material.

The proposed mechanism of action of disintegrants includes:
1. Water uptake through wicking.
2. Swelling.
3. Deformation (shape recovery).
4. Particle repulsion.
5. Heat of wetting.

Disintegrants usually work in following ways:
Wicking: Water transport into the tablet.
Swelling: Particles absorb water and expand like a dry sponge, pushing against the interior of a tablet or capsule causing it to fall apart or discharge its contents.
Elastic recovery: Stored potential energy is released from disintegrant particles after contact with a fluid environment.
Repulsion: Electrostatic forces separate the particles.

Wicking and Swelling:

A disintegrant must transport water into the tablet centre very quickly (capillary) and has to swell itself at the same moment. As soon as the water penetrates the tablet, it disrupts inter-articular matrix bonds causing the tablet to fall apart. To accelerate water transportation, very often powdered cellulose or microcrystalline cellulose is used.

In the disintegrating tablet, the disintegrant volume increases. During this process the space between matrix particles is filled and after very short time, the particles are separated by the force of the swelling disintegrant.

During swelling the disintegrant undergoes a deformation that means a force, which acts against the compressed particles.

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Elastic Recovery:

Most materials, which undergo a plastic deformation during compression, try to return to their initial shape as soon as possible (stored potential energy). In the tablet matrix, there is no means to recover the former shape. But as soon as water penetrates into the tablet matrix and the forces, which keep the particles together, are diminished, those particles have the ability to expand back.

In figure2 elastic particles are shown before compression (red). After compression, these particles are plastically deformed. After penetration of water into the tablet, these particles return back to their initial shape.

Repulsion:

The principle is that water molecules penetrate a tablet or capsule interior and generate partial positive and negative charges throughout the matrix. This results in the breakdown of particle-particle electrostatic forces of attraction contributing to matrix breakdown.

The latter two mechanisms are not well supported by research.

Water penetration is an indispensable pre-processing step for disintegration. The sorption properties of various disintegrants are found to be essential for efficient disintegration and dissolution. If the wetting of the super disintegrant is slow, for example by coating the disintegrant with a hydrophobic substance, disintegration of the mass is also slowed. The extensive research on super disintegrants has not only implicated the extent of water uptake is important but also have conclusively demonstrated that the rate of water uptake is of critical importance for number of disintegrants.

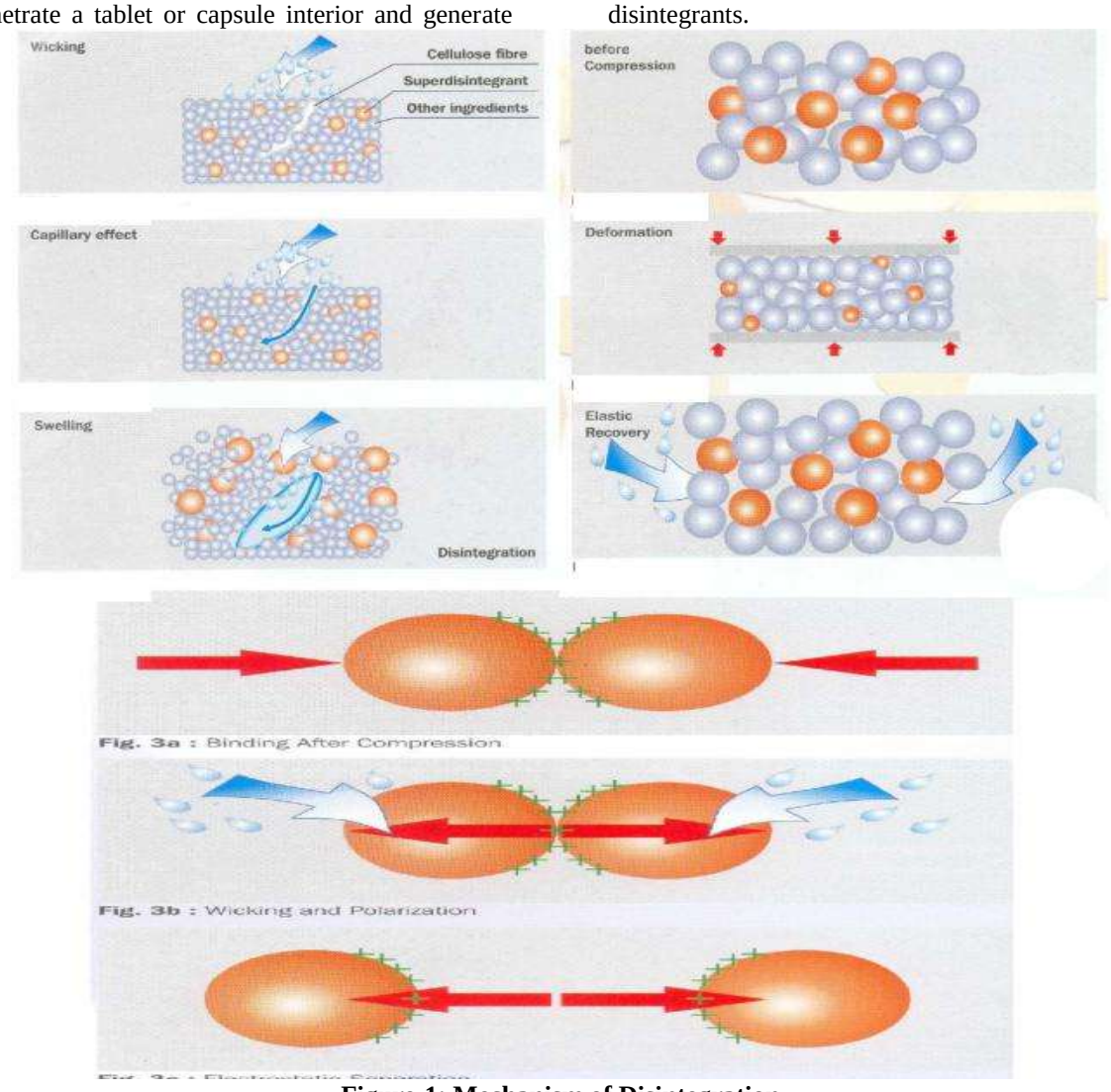

Figure-1: Mechanism of Disintegration

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PLAN OF THE RESEARCH WORK

Pre-formulation studies:

Selection of excipients and its combinations suitable for the immediate release tablet.

Drug-excipients compatibility study:

Preparation of standard calibration curve ofMinoxidil in alcohol.

Evaluation of pre-compression parameters of the formulations

a) Bulk density
b) Tapped density
c) Angle of repose
d) Carr's index
e) Hausner's ratio

Evaluation of post-compression parameters of the formulations

a) Weight variation
b) Hardness
c) Friability
d) Content uniformity
e) In-vitro dispersion time
f) Wetting time
g) Water absorption ratio
h) In-vitro dissolution study

Preparation of calibration curve

Preparation of standard calibration curve of Minoxidil in methanol (Alcohol):

5 mg of Minoxidil was dissolved in 50 ml of methanol by slight shaking, which gives 100 mcg/ml concentration (1st stock solution). 1 ml of this solution was taken and made up to 10 ml with methanol, which gives 10 mcg/ ml concentration (2nd stock solution).

From the 2nd stock solution, 0.2,0.4,0.6,0.8 and 1 ml was taken in another 10 ml volumetric flask and make up the volume up to 10 ml with methanol which gives a concentration of 02, 04, 06, 08 and 10 mcg/ml. The absorbance of diluted solutions was measured at 285nm using methanol as blank and a standard plot was drawn using the data obtained. The correlation coefficient was calculated. The absorbance data of the above concentrations are shown in table No.13.

Formulations of Minoxidil fast dissolving Tablets by Direct Compression Method[7]:

Fast dissolving tablets of Minoxidil were prepared by direct compression, using super disintegrants and directly compressible mannitol as diluent to enhance the mouth feel.

- All the ingredients were passed through # 44 mesh separately.
- The drug and mannitol were mixed in small portion each time and blending it to get a uniform mixture and kept aside.
- Then the ingredients were weighed and mixed in geometrical order and tablets were compressed at 7 mm size to get a tablet of desired weight using a (Clit pilot press 10 station compression machine). The tablets were prepared according to the formulae shown in table No.3&4.

The prepared formulations were studied for post-compression parameters like size, weight variation, drug content, hardness, friability, thickness, in-vitro dispersion time, water absorption and wetting time.

Formulations of Minoxidil fast dissolving Tablets by Effervescent Technique[20]:

Different formulations of Minoxidil were produced using different concentration of sodium bicarbonate and tartaric acid as effervescence producing agent by effervescent technique. All the ingredients (except purified talc) were accurately weighed and sifted through # 44mesh separately. The drug diluents were mixed in small proportion in geometric order. The ingredients after sifting through # 44mesh were thoroughly mixed. The tablets of 150 mg weight were prepared by direct compression method on 10-station rotary tablet machine using 7mm round flat punches. The tablets were prepared by using the formulae given in table No. 5 and 6.

Formulations of Minoxidil fast dissolving Tablets by sublimation method:

In this study fast-dissolving tablet were prepared by using camphor. Nine formulations of Minoxidil containing camphor in different proportions were prepared by using MCC (PH102) as a diluent. All the ingredients were passed through # 60 mesh separately. The drug and the diluents was mixed in small portion of both each time and blending it to get uniform mixture and set aside. The other ingredients were weighed and mixed in geometrical order. Flavouring agent was added at the end and then mixed thoroughly with lubricant. The tablets of weight 150 mg were prepared by direct compression method on 10-station rotary tablet machine using 7mm round flat punches. The tablets were prepared by using the formulae given in table No. 7 and 8.

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Table-3: Composition of fast dissolving tablet of Minoxidil by direct compression (for 01 tablet)

Ingredients (mg)		Formulation code								
	MDF_0	MDF_1	MDF_2	MDF_3	MDF_4	MDF_5	MDF_6	MDF_7	MDF_8	MDF_9
Minoxidil	5	5	5	5	5	5	5	5	5	5
Crospovidone (CP)	-	3	6	9	-	-	-	-	-	-
Croscarmellose sodium (CCS)	-	-	-	-	3	6	9	-	-	-
Pre-Gelatinized starch (PGS)	-	-	-	-	-	-	-	3	6	9
Micro crystalline cellulose (MCC)	30	30	30	30	30	30	30	30	30	30
Aspartame	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Flavour	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol SD 200	109	106	103	100	106	103	100	106	103	100
Total weight	150	150	150	150	150	150	150	150	150	150

Table-4: Composition of fast dissolving tablet of Minoxidil by direct compression (for 50 tablets)

Ingredients (mg)		Formulation code								
	MDF_0	MDF_1	MDF_2	MDF_3	MDF_4	MDF_5	MDF_6	MDF_7	MDF_8	MDF_9
Minoxidil	250	250	250	250	250	250	250	250	250	250
Crospovidone (CP)	-	150	300	450	-	-	-	-	-	-
Croscarmellose sodium (CCS)	-	-	-	-	150	300	450	-	-	-
Pre-Gelatinized starch (PGS)	-	-	-	-	-	-	-	150	300	450
Micro crystalline cellulose (MCC)	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500
Aspartame	75	75	75	75	75	75	75	75	75	75
Flavour	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talc	75	75	75	75	75	75	75	75	75	75
Magnesium stearate	75	75	75	75	75	75	75	75	75	75
Mannitol SD 200	5450	5300	5150	5000	5300	5150	5000	5300	5150	5000
Total weight	7500	7500	7500	7500	7500	7500	7500	7500	7500	7500

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Table-5: Composition of fast dissolving tablets of Minoxidil by effervescent method (for 01 tablet)

Ingredients (mg)		Formulation code								
	MEF_0	MEF_1	MEF_2	MEF_3	MEF_4	MEF_5	MEF_6	MEF_7	MEF_8	MEF_9
Minoxidil	5	5	5	5	5	5	5	5	5	5
Sodium bicarbonate	30.3	7.5	15.0	22.5	7.5	15.0	22.5	7.5	15.0	22.5
Tartaric acid	22.5	3.75	7.5	15.0	3.75	7.5	15.0	3.75	7.5	15.0
Crospovidone (CP)	-	3	6	9	-	-	-	-	-	-
Croscarmellose sodium (CCS)	-	-	-	-	3	6	9	-	-	-
Pre-gelatinized starch(PGS)	-	-	-	-	-	-	-	3	6	9
Micro crystalline cellulose (MCC)	30	30	30	30	30	30	30	30	30	30
Aspartame	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol SD 200	57.5	96.5	82	64	96.5	82	64	96.5	82	64
Total weight	150	150	150	150	150	150	150	150	150	150

Table-6: Composition of fast dissolving tablets of Minoxidil by effervescent method (for 50tablet)

Ingredients (mg)		Formulation code								
	MEF_0	MEF_1	MEF_2	MEF_3	MEF_4	MEF_5	MEF_6	MEF_7	MEF_8	MEF_9
Minoxidil	250	250	250	250	250	250	250	250	250	250
Sodium bicarbonate	1510	375	750	1125	375	750	1125	375	750	1125
Tartaric acid	1120	187.5	375	750	187.5	375	750	187.5	375	750
Crospovidone (CP)	-	150	300	450	-	-	-	-	-	-
Croscarmellose sodium (CCS)	-	-	-	-	150	300	450	-	-	-
Pre-gelatinized starch(PGS)	-	-	-	-	-	-	-	150	300	450
Micro crystalline cellulose (MCC)	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500
Aspartame	75	75	75	75	75	75	75	75	75	75
Talc	75	75	75	75	75	75	75	75	75	75
Magnesium stearate	75	75	75	75	75	75	75	75	75	75
Mannitol SD 200	2875	4810	4100	3200	4810	4100	3200	4810	4100	3200
Total weight	7500	7500	7500	7500	7500	7500	7500	7500	7500	7500

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Table-7: Composition of fast dissolving tablets of Minoxidil bysublimation method(for 01 tablet)

Ingredients (mg)		Formulation code								
	MSF_0	MSF_1	MSF_2	MSF_3	MSF_4	MSF_5	MSF_6	MSF_7	MSF_8	MSF_9
Minoxidil	5	5	5	5	5	5	5	5	5	5
Compour	6	3.75	7.5	15	3.75	7.5	15	3.75	7.5	15
Crospovidone (CP)	-	3	6	9	-	-	-	-	-	-
Croscarmellose sodium (CCS)	-	-	-	-	3	6	9	-	-	-
Pregelatin starch(PGS)	-	-	-	-	-	-	-	3	6	9
Micro crystalline cellulose (MCC)	30	30	30	30	30	30	30	30	30	30
Mannitol	105	104.25	97.5	87	104.25	97.5	87	104.25	97.5	87
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Sodium saccharin	1	1	1	1	1	1	1	1	1	1
Total weight	150	150	150	150	150	150	150	150	150	150

Table-8: Composition of fast dissolving tablets of Minoxidil bysublimation method(for 50tablet)

Ingredients (mg)		Formulation code								
	MSF_0	MSF_1	MSF_2	MSF_3	MSF_4	MSF_5	MSF_6	MSF_7	MSF_8	MSF_9
Minoxidil	250	250	250	250	250	250	250	250	250	250
Camphor	375	187.5	375	750	187.5	375	750	187.5	375	750
Crospovidone (CP)	-	150	300	450	-	-	-	-	-	-
Croscarmellose sodium (CCS)	-	-	-	-	150	300	450	-	-	-
Pre-gelatinized starch(PGS)	-	-	-	-	-	-	-	150	300	450
Micro crystalline cellulose (MCC)	1500	1500	1500	1500	1500	1500	1500	1500	1500	1500
Mannitol	5250	5212	4875	4350	5212	4875	4350	5212	4875	4350
Talc	75	75	75	75	75	75	75	75	75	75
Magnesium stearate	75	75	75	75	75	75	75	75	75	75
Aspartame	50	50	50	50	50	50	50	50	50	50
Total weight	7500	7500	7500	7500	7500	7500	7500	7500	7500	7500

PREFORMULATION STUDY

Determination of Bulk Density and Tapped Density[21,22,23.]

6 gm of the granules (W) from each formula were introduced into a 50 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted.

The bulk density, and tapped density were calculated using the following formulae:

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Bulk density = W / V_O
Tapped density = W / V_F
Where,
W = weight of the granules,
V_O = initial volume of the granules,
V_F = final volume of the granules.

Hausner's Ratio[24.]

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.
Hausner's ratio = Tapped density/Bulk density

Table-9: Hausner's Ratio

Sl. No.	Hausner's ratio	Property
1.	0-1.25	Free flowing
2.	1.25-1.6	Cohesive powder

Compressibility Index (Carr's Index)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material, the more flowable it is. A material having values of less than 20% has good flow property.

$$C_I = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Table-10: Grading of Powders according to Compressibility Index

Sl. No	% Compressibility Index	Properties
1	5-12	Free flowing
2	12-19	Good
3	19-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

Determination of Angle of Repose

Angle of repose is an indication of the frictional forces existing between the blend particles. It is the maximum angle possible between the surface of the pile of blend and the horizontal plane:

$\tan\theta = h / r$
Where, θis the angle of repose,
h is the height of the heap of powder,
r is the radius of the heap of the powder.
Therefore $\theta = \tan^{-1}(h/r)$.

Table-11: Grading of Powders according to Angle of Repose

Sl. No.	Angle of repose (θ)	Type of flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

Method

Weighed quantities of the blend were poured through the funnel from the fixed height onto the graph paper. The height of the heap was measured. The circumference of the heap was marked by pencil. The area of the circle formed was calculated based on large squares and small squares present inside the circle and angle of repose was then calculated on the parameter 'r' which was found out from the area of circle.

Evaluation of Tablets[25, 26.]

The prepared tablets were subjected to post compression studies.

Weight Variation

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The IP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the IP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit. IP official limits of percentage deviation of tablet are Weight variation (mg) (145-153) within the IP limits.

Table-12: Weight Variation Limits

Sl. No.	Average weight oftablet (mg)	Maximum %difference allowed
1	80mg or less	10
2	80-250mg	7.5
3	250mg or more	5

Tablet Hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Monsanto hardness

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tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness.

Friability

Friability generally refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. Friability generally reflects poor cohesion of tablet ingredients.

Method

10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.

Percentage friability was calculated by using the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \text{ X } 100$$

Tablet Thickness

Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Callipers. It was determined by checking the thickness of three tablets of each formulation.

Content Uniformity Test[27]

The tablets were tested for their drug content uniformity. Random 20 tablets were weighed and powdered. The powder equivalent to 50 mg was weighed accurately and dissolved in 50 ml of methanol. The solution was shaken thoroughly. The un-dissolved matter was removed by filtration through Whatman No.41 filter paper. Then dilute the solution to obtain 10 µg solution. The absorbance of the diluted solutions was measured at 285nm. The concentration of the drug was computed from the standard curve of the Minoxidil in methanol.

Wetting Time and Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured (figure-2). The wetted tablet was then weighed. The results are shown in table No. 17, 18 & 19.

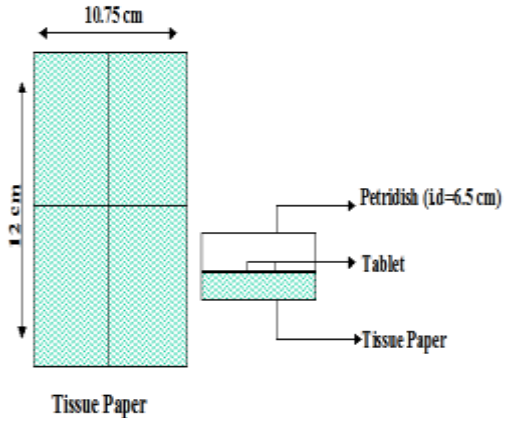

Figure-2: Schematic Representation of Wetting Time / Water Absorption Ratio Determination

Water absorption ratio 'R' was determined using following equation:

$$R = 100 \times \frac{Wa - Wb}{Wb}$$

Where,

W_a = weight of tablet before water absorption,

W_b = weight of tablet after water absorption.

In-vitroDispersion Time[28]

Tablet was added to 10 ml ofmethanol at 37±0.5°C. Time required for complete dispersion of a tablet was measured. The results are shown in table No. 17, 18 & 19.

In-vitro(Dissolution) study[29]

In-vitrodissolution of a Minoxidil fast dissolving tablets were studiedin Electrolab USP TDT-06T dissolution apparatus (Electrolab) employing a paddle stirrer. 900 ml of 6.8 phosphate buffer was used as dissolution medium. The stirrer was adjusted to rotate at 50 rpm. The temperature of dissolution media was previously warmed to 37±0.5°C and was maintained throughout the experiment. One tablet was used in each test, 5 ml of sample of dissolution medium were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analysed for drug release by measuring the absorbance at 285nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Percentage amount of Minoxidil released was calculated and plotted against time.

The results of in-vitro release data obtained for all formulations were fitted in two

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popular models of data treatments as follows:

1. Zero-order kinetic model (cumulative percent drug released versus time).
2. First-order kinetic model (log cumulative percent drug remaining versus time).

Zero-Order Kinetics

When the rate of release of drug is independent of the amount of the drug remaining in the dosage form and constant over a period of time, it is said to be zero-order release. This is expressed mathematically as follows:

$$\frac{dC}{dt} = K_t^0 \text{.....1}$$

where

C =Concentration of un-dissolved drug

K_t^0 = ero-order release rate constant

t = Time

Since C is constant, X the amount of drug release is identified as:

$$\frac{dC}{t} = K\text{.....2}$$

Integration of equation (2) yields:

X = Kt + constant.....3

If the data from a release study followed a zero-order release, a plot of X versus t, results in straight line plots with slope equal to K, the value of K would indicate the amount of drug that is releasing per unit time and intercept of the line at time zero is equal to the constant in the equation (3).

First-Order Kinetics:

When the rate of release is proportional to the first power of drug in the dosage form and is expressed mathematically in the form of equation (4). Then the release is said to be first-order with respect to drug in the dosage form.

$$\frac{dC}{C} = K_1\, dt \text{.....4}$$

Where K_1 is the first-order rate constant which on integration yields in natural logarithm form.

$I_nC = -K_1t$ + constant.....5

Or in common logarithm form

$$\log C = \left[\frac{K_1 t}{2.303}\right] + \text{constant.....6}$$

Both equation (5) and (6) will be recognized as producing straight lines if InC or log C is plotted against t, this is an identifying characteristic of a release in which the rate of release is proportional to the concentration of the drug present in the dosage form.

The log percent drug remaining was plotted against time to obtain first-order release patterns.

Stability Testing

Accelerated Stability Studies on Promising Minoxidil Formulations:

Stability studies on the promising formulations were carried out by storing 15 tablets in amber coloured screw-capped bottle at elevated temperature of 40±2ºC/75±5% RH (Stability chamber, Oswald) over a period 90 days (3 months). At interval of one month, the tablets were visually examined for any physical changes, in drug content and in-vitro dispersion time. The results are shown in tableNo.41& 42. Statistical analysis of the drug content data is shown in table no. 43 & 44.

Drug-Excipient Interaction Studies

While developing a new formulation, it is necessary to check the drug compatibility with the carrier or excipient used and that the drug has not undergone any degradation when it passes through the various processes. Suitable evidential experiments are conducted to justify and prove the intactness of the drug in the formulations.

Infrared Spectroscopy

Infrared spectroscopy is one of most powerful analytical technique when it comes to the determination of presence of various functional groups involved in making up the molecule. It provides very well accountable spectral data regarding any change in the functional group characteristics of a drug molecule occurring while in the processing of a formulation. IR spectra of Minoxidil and its formulations were obtained by KBr pellet method using (Shimadzu FTIR series model-8400S) spectrophotometer in order to rule out drug-carrier interaction occurring during the formulation process.

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CHAPER-5

RESULTS

Table-13: Standard Graph of fast dissolving tablet ofMinoxidil in methanol (Alcohol) (λ_{max}285nm)

Concentration (mcg/ml)	Absorbance			Mean±SD*
	I	II	III	
0	0.000	0.000	0.000	0.000±0.000
2	0.125	0.131	0.140	0.132±0.0015
4	0.271	0.256	0.255	0.260±0.0036
6	0.373	0.375	0.382	0.376±0.0574
8	0.504	0.497	0.506	0.502±0.0088
10	0.602	0.606	0.608	0.605±0.0132

***Average of three determinations**

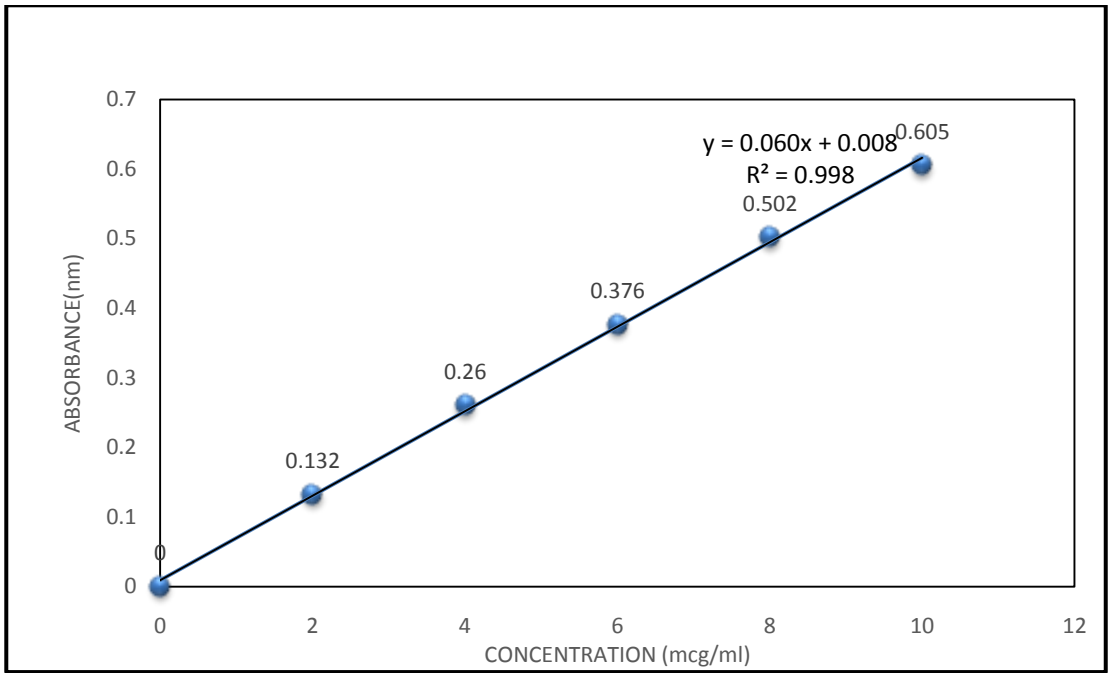

Figure-3: Standard Graph ofMinoxidil in methanol (Alcohol)

Table-14: Pre-compression parameters of fast dissolving tablet ofMinoxidilformulations by direct compression method

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (degree)	Carr's index (%)	Hausner's ratio
MDF_0	0.49±0.03	0.52±0.01	28.42±1.83	14.45±2.04	1.07±0.04
MDF_1	0.50±0.03	0.59±0.02	30.32±1.56	15.51±2.21	1.19±0.02
MDF_2	0.52±0.01	0.61±0.01	25.46±1.25	16.80±1.54	1.20±0.02
MDF_3	0.53±0.02	0.62±0.03	29.11±1.36	17.18±2.57	1.22±0.01
MDF_4	0.53±0.03	0.65±0.02	27.41±1.22	18.18±2.12	1.21±0.03
MDF_5	0.52±0.01	0.64±0.01	25.45±1.67	16.42±2.13	1.20±0.04
MDF_6	0.51±0.02	0.65±0.02	30.75±1.88	18.18±1.98	1.23±0.03
MDF_7	0.52±0.01	0.65±0.01	25.64±1.78	19.62±1.56	1.23±0.02
MDF_8	0.53±0.04	0.64±0.01	27.19±1.97	18.18±2.31	1.21±0.01
MDF_9	0.54±0.02	0.66±0.03	28.41±0.36	17.10±2.14	1.16±0.03

***Average of three determinations**

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Table-15: Pre-compression parameters of fast dissolving tablet ofMinoxidilformulations by Effervescent Method

Formulation Code	Bulk Density(g/cc)	Tap Density(g/cc)	Angle of Repose(degree)	Carr's index(%)	Hausner's Ratio
MEF_0	0.454±0.021	0.536±0.019	21.05±0.51	15.01±0.68	1.18± 0.31
MEF_1	0.458±0.032	0.592±0.021	26.05±0.48	15.61±0.74	1.18± 0.36
MEF_2	0.516±0.021	0.632±0.022	24.26±0.23	17.60±0.26	1.18± 0.45
MEF_3	0.521±0.033	0.621±0.072	25.24±0.44	17.51±0.42	1.21± 0.55
MEF_4	0.530±0.041	0.650±0.046	26.15±0.15	16.18±0.36	1.20± 0.64
MEF_5	0.503±0.052	0.630±0.035	24.45±0.15	15.21±0.24	1.21± 0.47
MEF_6	0.528±0.031	0.648±0.053	25.46±0.41	16.20±0.96	1.22± 0.25
MEF_7	0.511±0.021	0.631±0.073	23.93±0.82	17.60±0.48	1.22± 0.44
MEF_8	0.510±0.061	0.616±0.66	25.22±0.25	15.21±072	1.20± 0.54
MEF_9	0.530±0.030	0.650±0.56	24.98±0.32	16.18±0.45	1.23±0.32

***Average of three determination**

Table-16: Pre-compression parameters of fast dissolving tablet of Minoxidil formulations bysublimation method

Formulation Code	Bulk Density (g/cc)	Tap Density (g/cc)	Angle of Repose (degree)	Carr's index (%)	Hausner's Ratio
MSF_0	0.421±0.029	0.521±0.062	23.24±0.38	15.51±0.42	1.21± 0.55
MSF_1	0.458±0.032	0.592±0.021	25.05±0.38	15.78±0.54	1.18± 0.26
MSF_2	0.528±0.031	0.642±0.031	24.26±0.32	17.60±0.28	1.28± 0.45
MSF_3	0.521±0.039	0.631±0.062	26.22±0.54	16.46±0.32	1.23± 0.41
MSF_4	0.520±0.048	0.620±0.042	26.41±0.38	16.41±0.41	1.22± 0.58
MSF_5	0.535±0.058	0.650±0.028	23.55±0.25	16.28±0.34	1.20± 0.58
MSF_6	0.521±0.039	0.628±0.043	24.46±0.31	17.19±0.86	1.32± 0.45
MSF_7	0.521±0.031	0.621±0.053	24.83±0.92	16.51±0.45	1.28± 0.34
MSF_8	0.520±0.056	0.623±0.046	26.20±0.45	16.38±061	1.30± 0.67
MSF_9	0.523±0.030	0.642±0.42	25.98±0.52	17.08±0.55	1.25±0.57

***Average of three determination**

Table-17: post-compression parameters of fast dissolving tablet ofMinoxidil formulations by direct compression method

Parameters		Formulation code								
	MDF0	MDF1	MDF 2	MDF 3	MDF 4	MDF 5	MDF 6	MDF 7	MDF 8	MDF 9
Hardness(kg/cm²)	2.7±0.15	2.4±0.20	2.1±0.02	2.42±0.18	2.8±0.29	2.9±0.12	2.8±0.22	2.9±0.12	2.7±0.23	2.9±0.41
Thickness (mm)	3±0.08	3.1±0.01	3.0±0.02	3.1±0.25	3.1±0.09	3.2±0.08	3.1±0.32	3.0±0.08	3.1±0.21	3.0±0.18
Friability (%)	0.64	0.79	0.76	0.77	0.69	0.87	0.74	0.91	0.76	0.79
In-vitro dispersion time (sec)	76±1	36±1.2	26±1.6	20±1.2	64±1.1	62±1	61±1	64±1.2	65±1.5	66±1.6
Wetting time (sec)	147±1.22	19±1.52	16.17±1.0	14.85±1.35	36.88±1.18	35.32±1.43	34.17±1.15	36.88±1.05	35.3±1.02	35.17±1.03
Water absorption ratio (%)	43.02±0.02	61.5±0.02	73±0.005	93.32±0.505	60.10±0.37	76.23±0.22	92.15±0.79	60.10±1.37	76.23±0.58	83.15±0.02
Percent drug content (%)	94.33±0.42	95.87±0.40	97.08±0.382	95.01±0.33	94.66±1.13	94.64±0.81	97.64±0.56	96.69±0.32	98.12±0.41	94.33±0.42

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Weight variation(mg) (145-153.5mg) with in I.P limits of±7.5%
***Average of three determinations**

Table-18: Post-compression parameters of fast dissolving tablet ofMinoxidil formulations by effervescent method

Parameters		Formulation code								
	MEF0	MEF1	MEF 2	MEF 3	MEF 4	MEF 5	MEF 6	MEF 7	BEF 8	BEF 9
Hardness(kg/cm²)	2.6±0.02	2.7±0.12	2.8±0.01	2.7±0.04	2.6±0.08	2.7±0.22	2.8±0.12	2.8±0.08	2.8±0.02	2.9±0.01
Thickness (mm)	3.0±0.02	3.1±0.08	3.1±0.03	3.2±0.01	3.2±0.04	3.2±0.02	3.3±0.01	3.2±0.04	3.40±0.02	3.32±0.02
Friability (%)	0.89	0.74	0.81	0.85	0.76	0.69	0.65	0.64	0.85	0.89
In-vitro dispersion time (sec)	78±0.01	61±0.02	64±0.06	66±0.03	62±0.01	59±0.052	58±0.026	65±0.08	64±0.02	63±0.06
Wetting time (sec)	126±1.23	28±1.05	24.18±1.63	18±1.52	24.03±1.25	23.41±1.26	20.15±1.2	26±1.24	24.28±2.23	22.35±1.27
Water absorption ratio (%)	75.23±0.55	77.01±0.55	81.34±0.32	88.85±0.32	83.02±0.12	93.55±0.59	98.26±0.66	81.34±0.55	87.85±0.35	96.05±0.55
Percent drug content (%)	95.83±0.33	95.65±0.45	96.18±0.391	95.51±0.25	97.65±1.18	94.92±0.68	96±0.55	96.59±0.28	95.17±0.32	95.83±0.33

Weight variation(mg) (145-153.5mg) with in I.P limits of±7.5%
***Average of three determinations**

Table-19: Post-compression parameters of fast dissolving tablet ofMinoxidilformulations bysublimation method

Parameters		Formulation code								
	MSF0	MSF1	MSF 2	MSF 3	MSF 4	MSF 5	MSF 6	MSF 7	BSF 8	BSF 9
Hardness(kg/cm²)	2.2±0.06	2.1±0.01	2.1±0.08	3.3±0.18	3.1±0.02	3.2±0.01	3.1±0.08	2.8±0.02	2.7±0.12	2.7±0.21
Thickness (mm)	3.17±0.02	3.1±0.01	3.0±0.08	3.1±0.4	3.1±0.08	3.2±0.02	3.2±0.18	3.1±0.12	3.2±0.12	3.1±0.14
Friability (%)	0.86	0.81	0.84	0.75	0.81	0.71	0.72	0.68	0.75	0.79
In-vitro dispersion time (sec)	126±0.12	38±0.23	28±0.02	20.9±0.06	60±0.09	58±0.01	26±0.02	62±0.55	59±0.04	64±0.07
Wetting time (sec)	89±1.02	24±1.03	29.98±1.05	33±1.22	27.03±1.16	26.31±1.06	23.15±1.05	30±1.75	28.38±1.63	25.45±1.07
Water absorption ratio (%)	62.02±0.45	81.2±0.51	87.3±0.22	93.2±0.42	86.04±0.17	94.25±0.61	99.48±0.67	85.42±0.55	91.95±0.21	99.15±0.52
Percent drug content (%)	94.52±0.33	94.75±0.71	95.28±0.31	94.41±0.35	96.65±1.22	93.92±0.78	97.77±0.45	97.5±0.38	94.17±0.22	92.83±0.31

Weight variation(mg) (145-153.5mg) with in I.P limits of±7.5%
***Average of three determinations**

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Figure-4: In-vitro dispersion time of fast dissolving tablet of Minoxidil tablets by Direct Compression Method

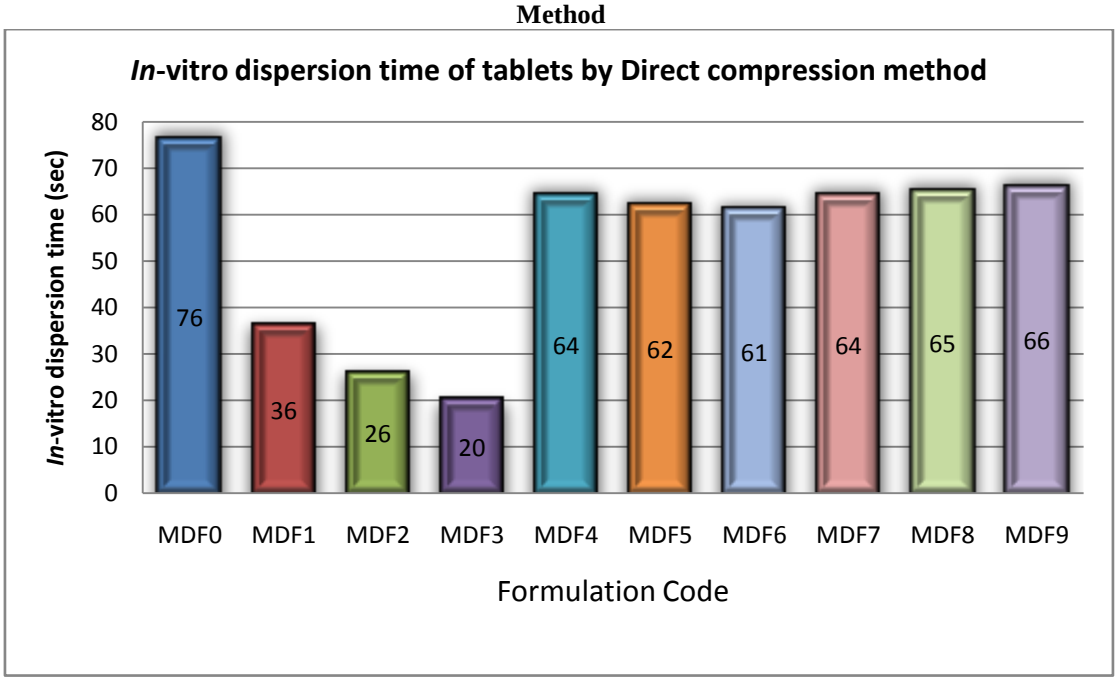

Figure-5: Wetting Time of fast dissolving tablets of Minoxidil tablets by Direct Compression Method

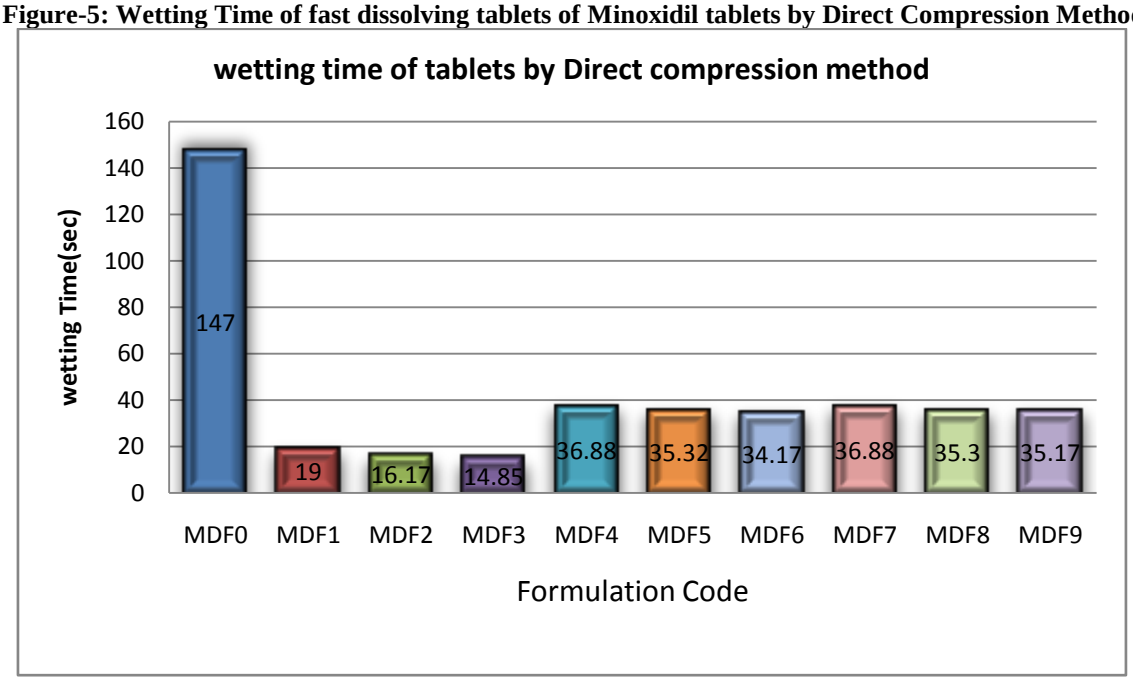

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Figure-6: In-vitro dispersion time of fast dissolving tablet of Minoxidil tablets by Effervescent Method

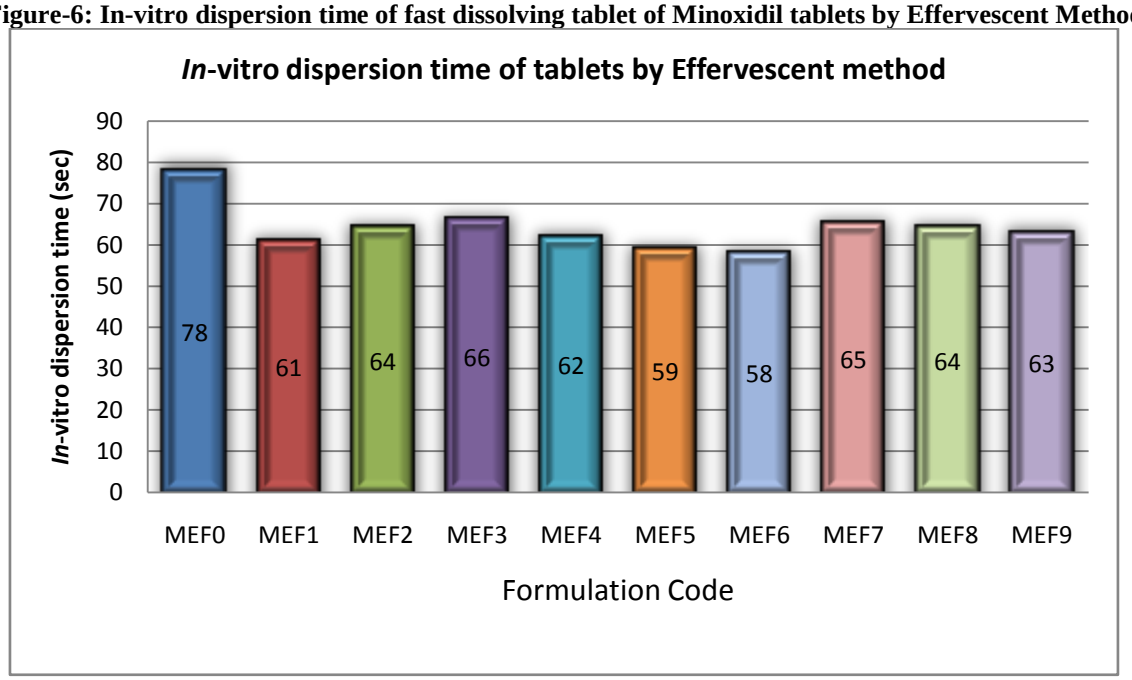

Figure-7: Wetting Time of fast dissolving tablets of Minoxidil tablets by Effervescent Method

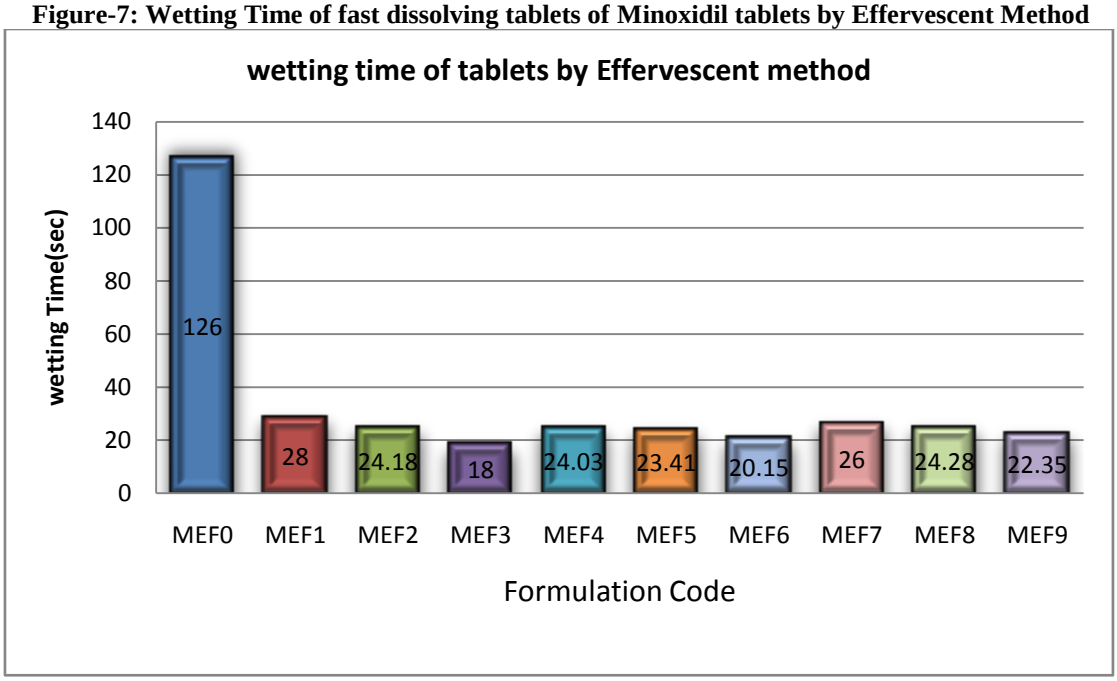

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Figure-8: In-vitro dispersion time of fast dissolving tablet of Minoxidil tablets by sublimation method

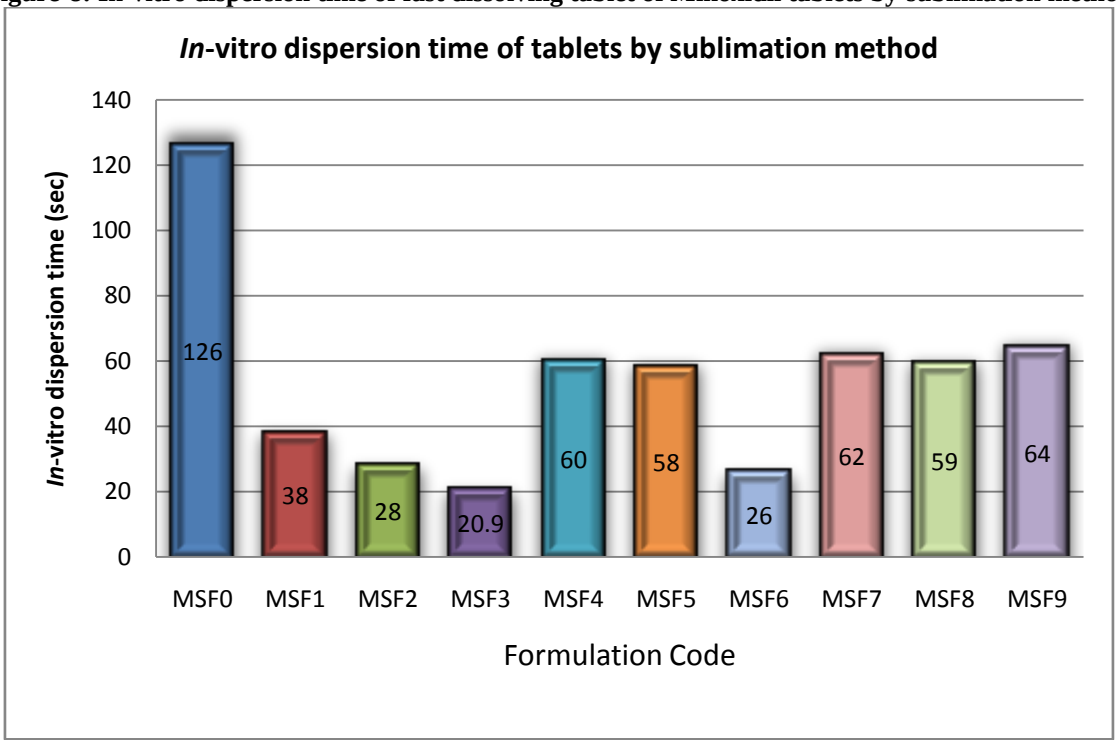

Figure-9: Wetting Time of fast dissolving tablets of Minoxidil tablets by sublimation method

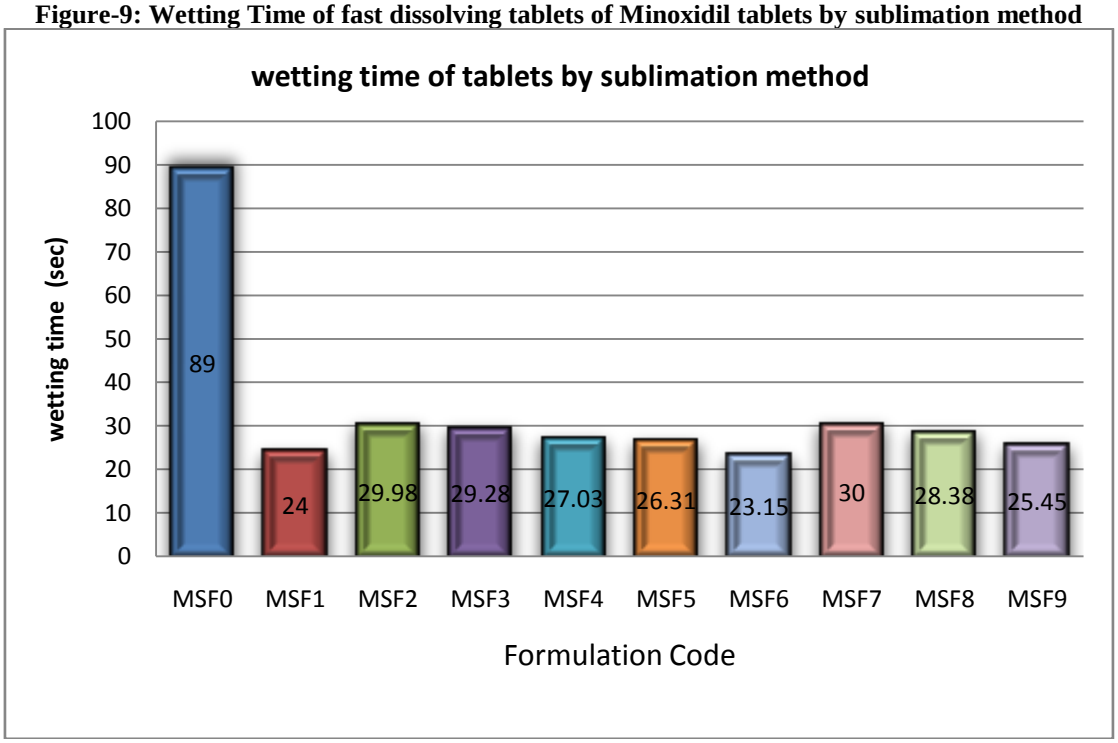

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Table-20: In-vitro Release Data of fast dissolving tablet ofMinoxidil by direct compression method of formulations MDF_0-MDF_3

(Zero order)

Sl. No.	Time (min)	MDF_0±SD*	MDF_1±SD*	MDF_2±SD*	MDF_3±SD*
1	0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
2	2	33.8±0.25	22.23±0.48	28.8±0.84	29.9±0.52
3	4	43.2±0.45	30.5±0.54	36±0.45	31.7±0.82
4	6	54.6±0.62	36.2±0.71	41.2±0.84	40.9±0.45
5	8	60.2±0.35	43.1±0.98	56.8±0.90	52.6±0.63
6	10	66.8±0.78	57.6±0.74	61.2±0.84	60.2±0.14
7	15	68.8±0.56	72.9±0.45	72.2±0.61	74.6±0.32
8	20	82±0.52	81.6±0.15	80.6±0.68	81.6±0.63
9	25	82.8±0.45	89.8±0.29	95.2±0.54	96.1±0.58
10	30	88.6±0.67	92.3±0.78	-	-

***Average of three determination**

Figure-10: Cumulative % Drug Release v/s Time (Zero order) Plots of Formulations MDF_0- MDF_3

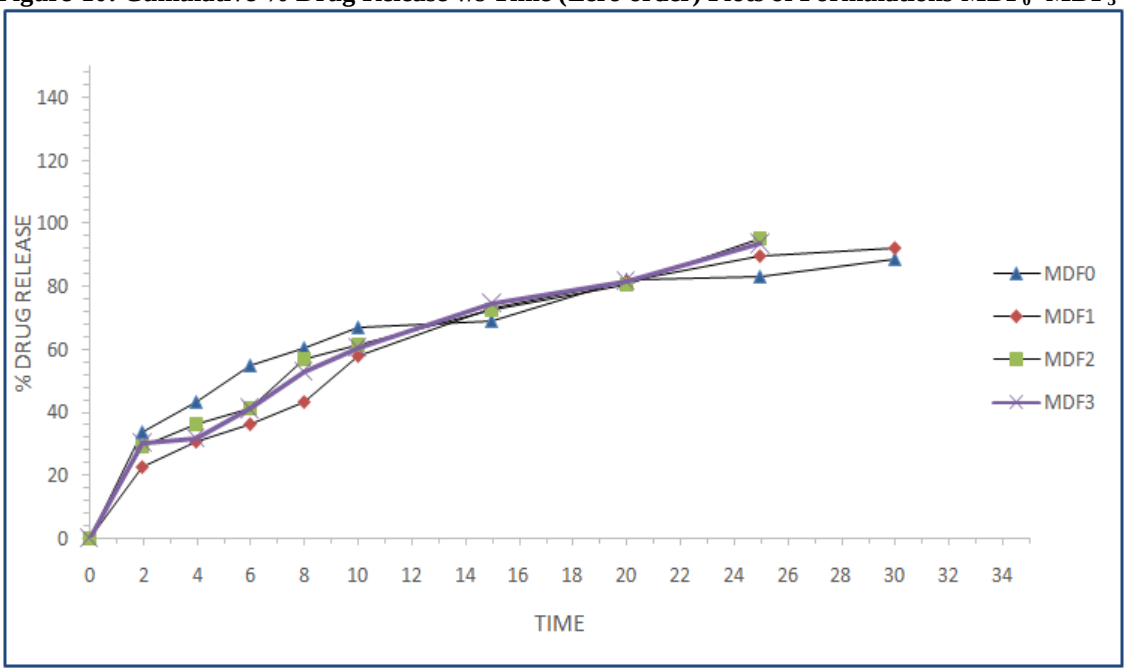

Table-21: In-vitro Release Data of fast dissolving tablet ofMinoxidilmethod of Formulations BDF_0-BDF_3 (First order)

Sl. No.	Time (min)	MDF_0	MDF_1	MDF_2	MDF_3
0	0	2.0000	2.0000	2.0000	2.0000
1	2	1.80	1.890	1.82	1.845
2	4	1.75	1.843	1.86	1.83
3	6	1.68	1.804	1.76	1.77
4	8	1.59	1.755	1.69	1.67
5	10	1.52	1.627	1.58	1.59
6	15	1.49	1.432	1.49	1.40
7	20	1.34	1.264	1.27	1.26
8	25	1.23	1.008	0.68	0.59
9	30	1.05	0.886	-	-

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Figure-11: Log Cumulative % Drug Remaining v/s Time (First order) Plots of Formulations MDF_0-MDF_3

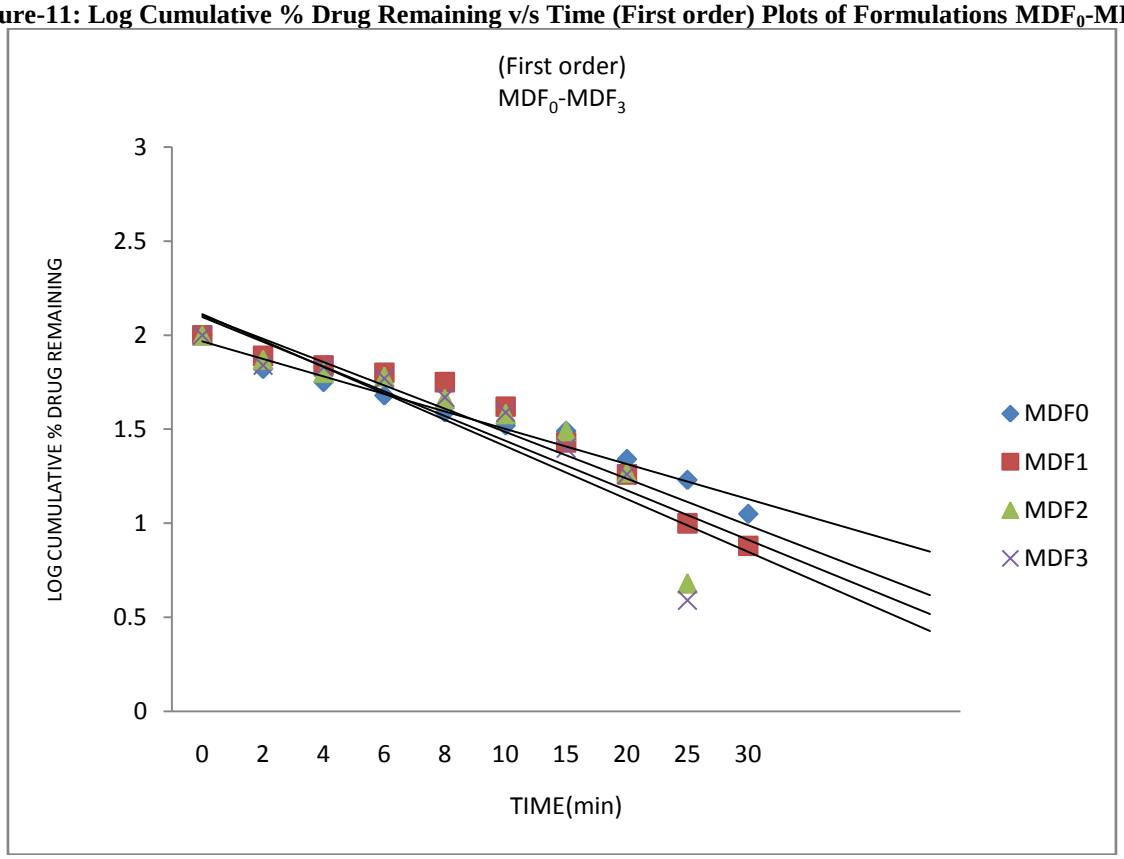

Table-22: In-vitro release Data of fast dissolving tablet of Minoxidilby direct compression method of formulations MDF_4-MDF_6

(Zero order)

Sl. No.	Time (min)	MDF_4±SD*	MDF_5±SD*	MDF_6±SD*
1	0	0.00±0.00	0.00±0.00	0.00±0.00
2	2	28.61±0.24	30.43±0.75	35.45±0.87
3	4	31.7±0.52	37.2±0.63	48.8±0.44
4	6	40.9±0.82	47.2±1.12	61.4±0.54
5	8	52.6±0.61	59.8±0.32	70.3±0.45
6	10	66.8±0.54	68.3±0.98	79.4±0.74
7	15	81.6±0.25	82.8±0.55	97.1±0.28
8	20	89.8±0.35	95.2±0.58	-
9	25	94.8±0.77	-	-
10	30	-	-	-

***Average of three determination**

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Figure-12: Cumulative % Drug Release v/s Time (Zero order) Plots of Formulations MDF_4- MDF_6

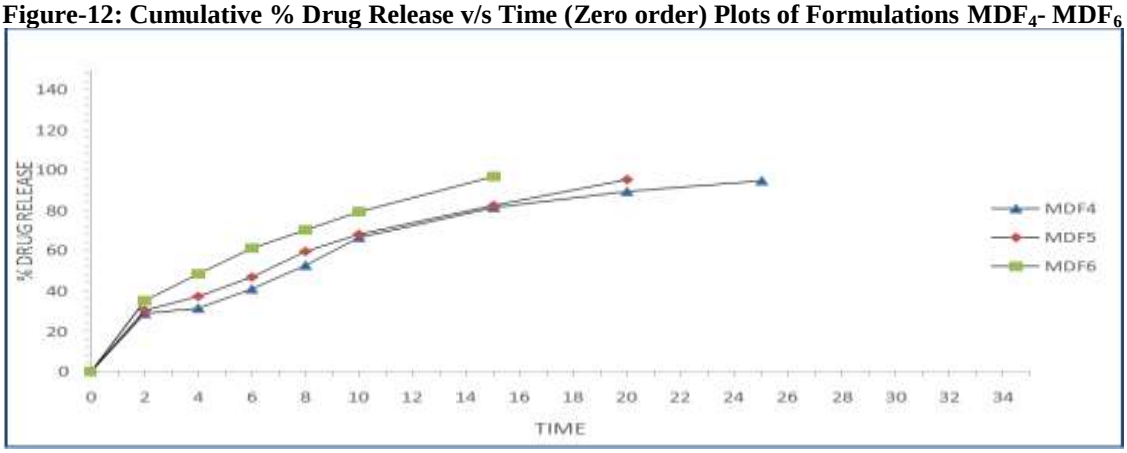

Table-23: In-vitro release Data of fast dissolving tablet of Minoxidil by direct compression method of formulations MDF_4-MDF_6

(First order)

Sl. No.	Time (min)	MDF_4	MDF_5	MDF_6
0	0	2.0000	2.0000	2.0000
1	2	1.853	1.842	1.809
2	4	1.834	1.797	1.709
3	6	1.771	1.722	1.586
4	8	1.675	1.604	1.472
5	10	1.521	1.501	1.313
6	15	1.264	1.235	0.447
7	20	0.963	0.681	-
8	25	0.716	-	-
9	30	-	-	-

Figure-13: Log Cumulative % Drug Remaining v/s Time (First order) Plots of Formulations MDF_4-MDF_6

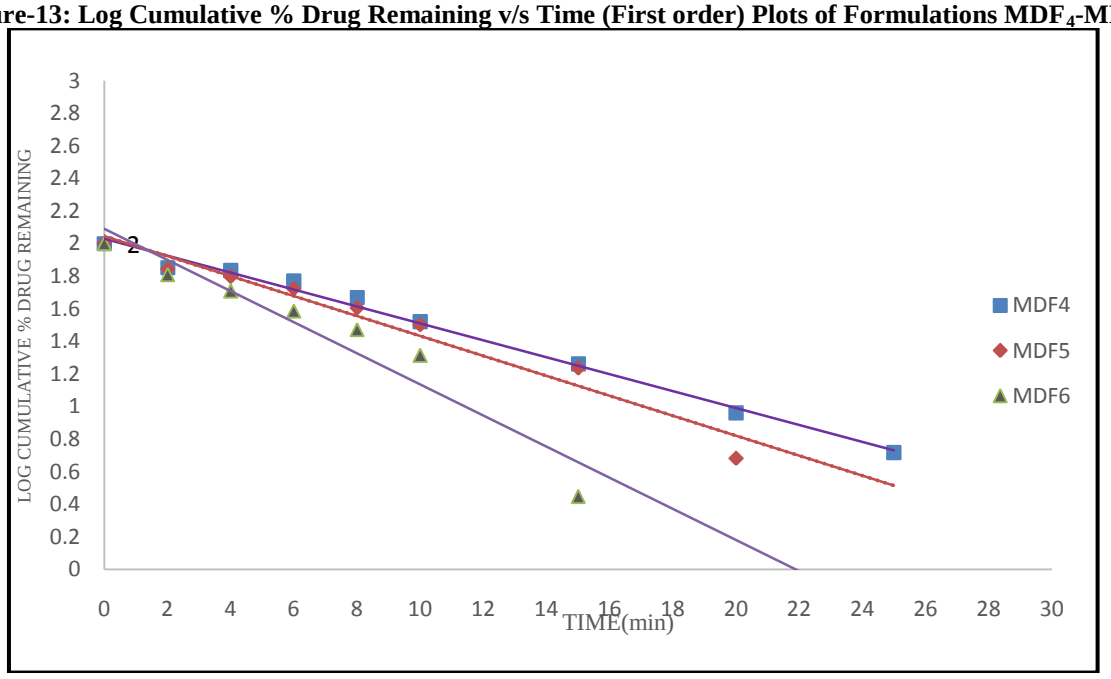

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Table-24: In-vitro Release Data of fast dissolving tablet of Minoxidil by direct compression method of formulations MDF_7-MDF_9

(Zero order)

Sl. No.	Time (min)	MDF_7±SD*	MDF_8±SD*	MDF_9±SD*
1	0	0.00±0.00	0.00±0.00	0.00±0.00
2	2	18.9±0.32	19.23±0.68	25.6±0.58
3	4	24.8±0.53	27.2±0.99	32.35±0.41
4	6	33.41±0.71	39.4±1.01	47.4±0.58
5	8	44.84±0.88	47.6±0.99	56.2±0.71
6	10	51.2±0.57	54.2±0.89	62.8±0.50
7	15	63.4±0.62	60.2±0.96	73.4±0.61
8	20	70.2±0.74	75.4±0.66	93.2±0.56
9	25	81.9±0.57	91.8±0.57	-
10	30	90.4±0.72	-	-

***Average of three determination**

Figure-14: Log Cumulative % Drug Remaining v/s Time (Zero order) Plots of Formulations MDF_7-MDF_9

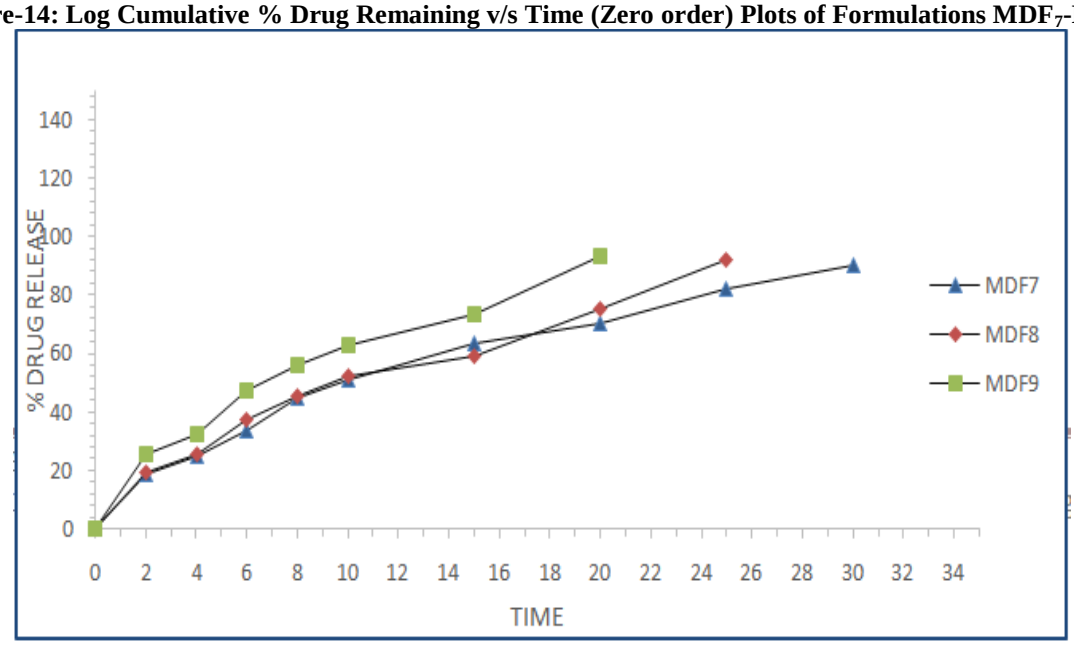

Table-25: In-vitro Release Data of fast dissolving tablet of Minoxidil by direct compression method of formulations MDF_7-MDF_9

(First order)

Sl. No.	Time (min)	MDF_7	MDF_8	MDF_9
0	0	2.0000	2.0000	2.0000
1	2	1.909	1.906	1.830
2	4	1.876	1.862	1.830
3	6	1.823	1.782	1.720
4	8	1.741	1.719	1.641
5	10	1.688	1.660	1.577
6	15	1.563	1.599	1.424
7	20	1.474	1.390	0.832
8	25	1.257	0.913	-
9	30	0.982	-	-

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Figure-15: Log Cumulative % Drug Remaining v/s Time (First order) Plots of Formulations MDF_7-MDF_9

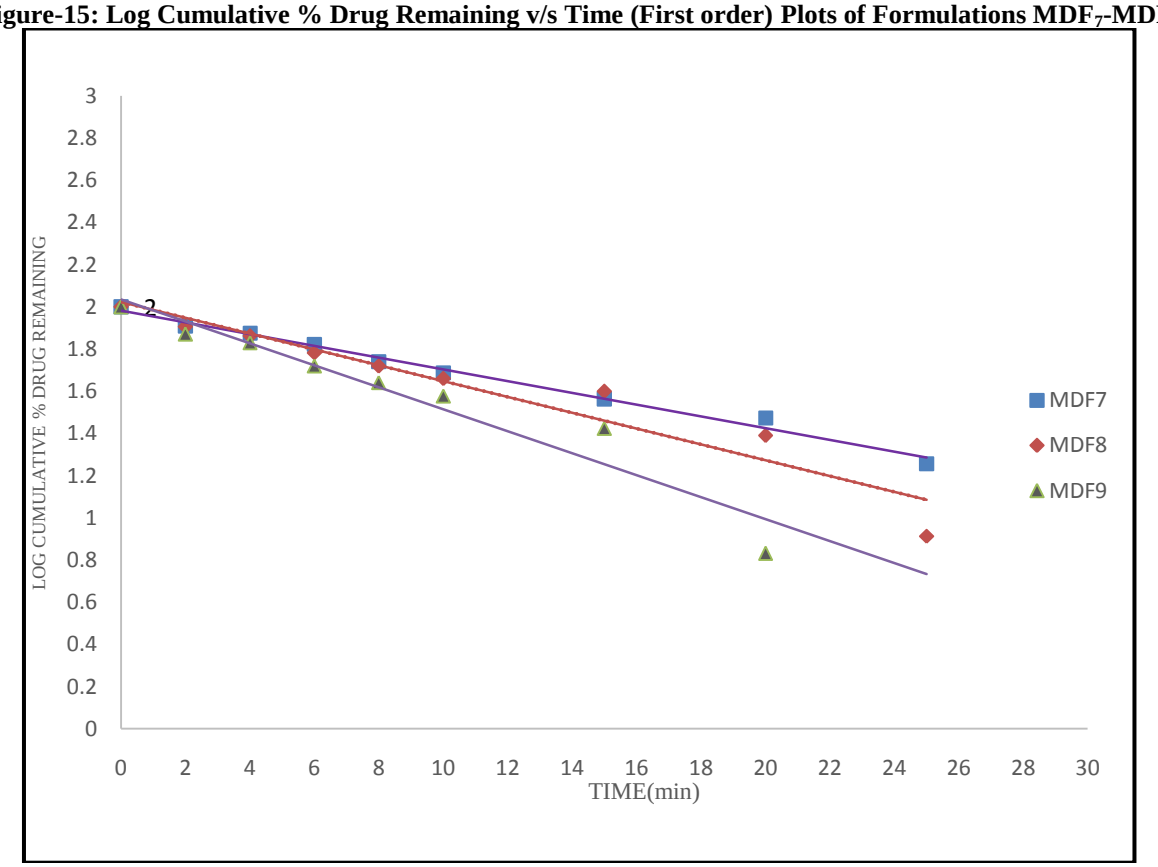

Table-26: In-vitro release Data of fast dissolving tablet Minoxidilby effervescent method of formulations MEF_0-MEF_3

(Zero order)

Sl. No.	Time (min)	MEF_0±SD*	MEF_1±SD*	MEF_2±SD*	MEF_3±SD*
1	0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
2	2	16.6±0.13	24.6±0.52	31.6±0.44	35.9±0.55
3	4	23.6±0.56	33.5±0.31	39.2±0.66	37.9±0.87
4	6	31.8±0.85	38.2±0.84	45±0.48	46.6±0.52
5	8	46.4±0.14	48.6±0.19	56.6±0.59	57.6±0.48
6	10	56.2±0.18	53.2±0.75	60±0.62	65.6±0.56
7	15	61.9±0.46	64.8±0.15	74.2±0.78	82.4±0.23
8	20	71.2±0.86	79±0.18	90.2±0.52	95.2±0.44
9	25	78.9±0.98	90.2±0.24	94.2±0.63	-
10	30	88.6±0.92	-	-	-

***Average of three determination**

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Figure-16: Cumulative % Drug Release v/s Time (Zero order) Plots of Formulations MEF_0- MEF_3

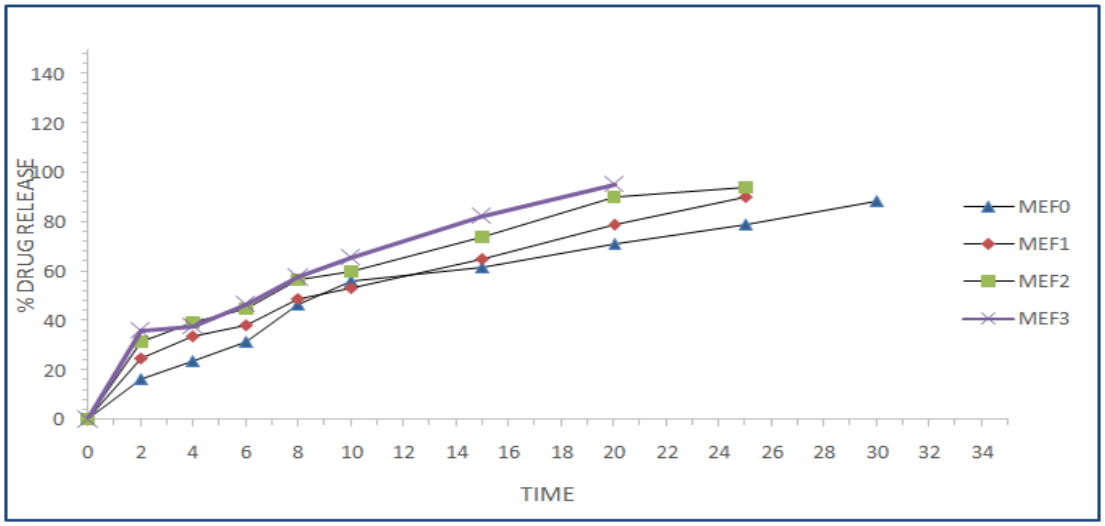

Table-27: In-vitro release Data of fast dissolving tablet of Minoxidil by effervescent method of formulations MEF_0-MEF_3

(First order)

Sl. No.	Time (min)	MEF_0	MEF_1	MEF_2	MEF_3
0	0	2.0000	2.0000	2.0000	2.0000
1	2	1.921	1.877	1.835	1.806
2	4	1.883	1.822	1.783	1.793
3	6	1.833	1.790	1.740	1.727
4	8	1.729	1.710	1.637	1.627
5	10	1.641	1.670	1.602	1.536
6	15	1.580	1.546	1.411	1.245
7	20	1.459	1.322	0.991	0.681
8	25	1.324	0.991	0.974	-
9	30	1.056	-	-	-

Figure-17: Log Cumulative % Drug Remaining v/s Time (First order) Plots of Formulations MEF_0-MEF_3

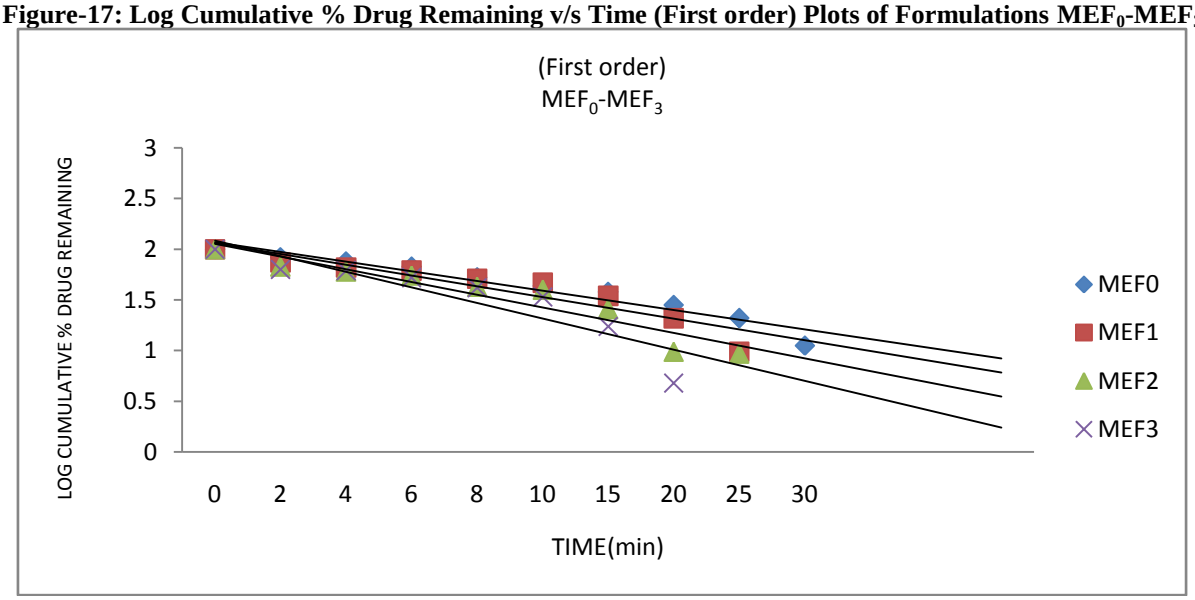

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Table-28: In-vitrorelease Data of fast dissolving tablet Minoxidil by effervescent method of formulations MEF_4-MEF_6

(Zero order)

Sl. No.	Time (min)	MEF_4±SD*	MEF_5±SD*	MEF_6±SD*
1	0	0.00±0.00	0.00±0.00	0.00±0.00
2	2	26.7±0.16	22.56±0.58	32.6±0.43
3	4	31.5±0.26	30±0.74	44.4±0.10
4	6	37.5±0.34	41±0.78	55.6±0.48
5	8	46.8±0.27	55.6±0.36	66.4±0.91
6	10	55.6±0.86	61.2±0.17	72.8±0.23
7	15	65.6±0.42	81.9±0.21	87.2±0.38
8	20	78.8±0.67	90.2±0.66	96.3±0.26
9	25	87.8±0.77	95.7±0.28	-
10	30	92.0±0.62	-	-

***Average of three determination**

Figure-18: Cumulative % Drug Release v/s Time (Zero order) Plots of Formulations MEF_4- MEF_6

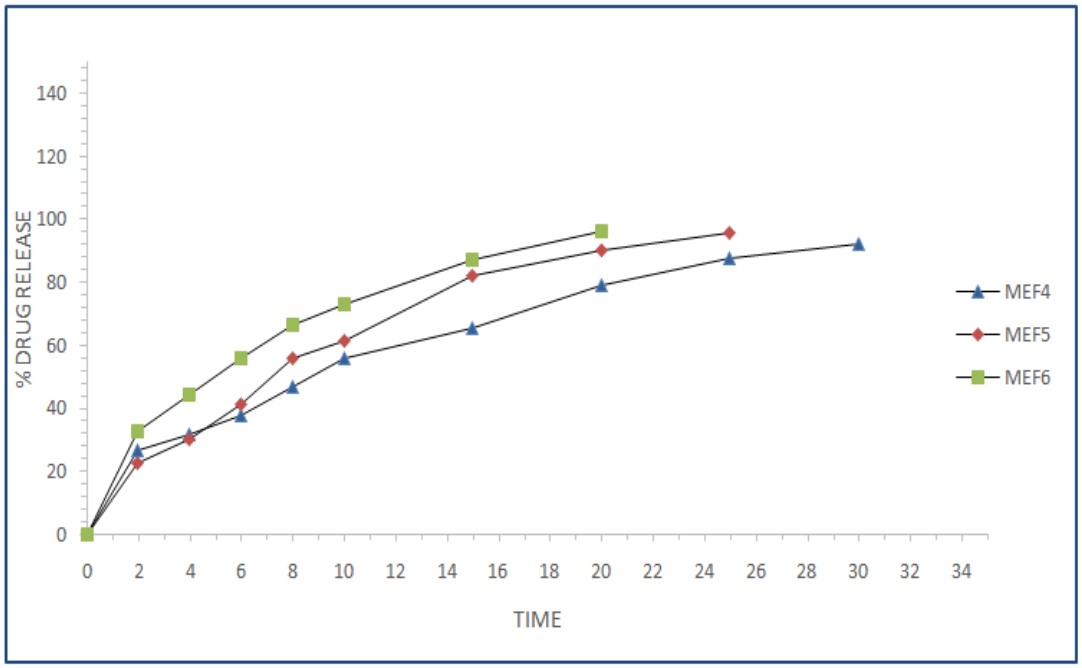

Table-29: In-vitrorelease Data of fast dissolving tablet of Minoxidilby Effervescent method of Formulations MEF_4-MEF_6

(First order)

Sl. No.	Time (min)	MEF_4	MEF_5	MEF_6
0	0	2.0000	2.0000	2.0000
1	2	1.865	1.888	1.828
2	4	1.835	1.845	1.745
3	6	1.795	1.770	1.647
4	8	1.725	1.647	1.526
5	10	1.647	1.588	1.434
6	15	1.536	1.257	1.107
7	20	1.326	0.991	0.556
8	25	1.086	0.633	-
9	30	0.857	-	-

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Figure-19: Log Cumulative % Drug Remaining v/s Time (First order) Plots of Formulations MEF_4-MEF_6

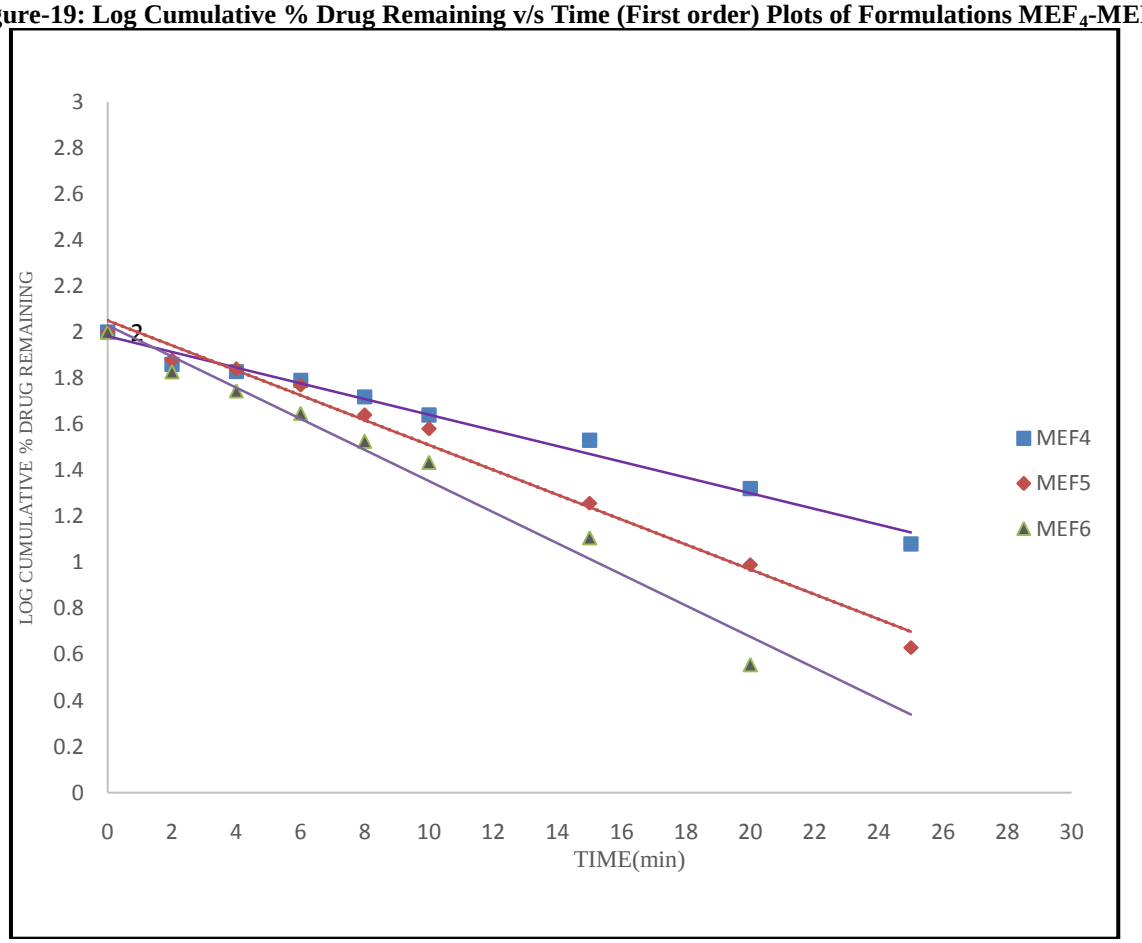

Table-30: In-vitrorelease Data of fast dissolving tablet of Minoxidil by effervescent method of formulations MEF_7-MEF_9

(Zero order)

Sl. No.	Time (min)	MEF_7±SD*	MEF_8±SD*	MEF_9±SD*
1	0	0.00±0.00	0.00±0.00	0.00±0.00
2	2	19.23±0.64	25.6±0.48	26.7±0.18
3	4	28.3±0.47	33.2±0.15	33.9±0.22
4	6	33.8±0.55	41.2±0.78	43.9±0.66
5	8	39.7±0.44	50.6±0.80	56.6±0.15
6	10	48.6±0.78	63.8±0.23	64.3±0.58
7	15	59.6±0.26	75.8±0.45	80.2±0.02
8	20	69.1±0.55	86.2±0.29	95.2±0.97
9	25	80.1±0.21	94.2±0.54	-
10	30	93.5±0.77	-	-

***Average of three determination**

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Figure-20: Cumulative % Drug Release v/s Time (Zero order) Plots of Formulations MEF_7- MEF_9

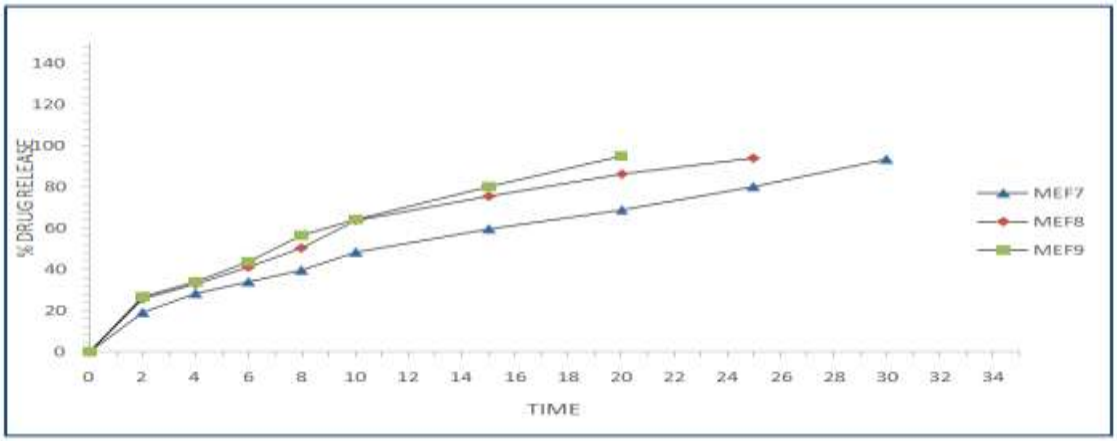

Table-31: In-vitrorelease Data of fast dissolving tablet of Minoxidil by effervescent method of formulations MEF_7-MEF_9

(First order)

Sl. No.	Time (min)	MEF_7	MEF_8	MEF_9
0	0	2.0000	2.0000	2.0000
1	2	1.907	1.871	1.865
2	4	1.855	1.824	1.820
3	6	1.820	1.7769	1.748
4	8	1.780	1.647	1.637
5	10	1.710	1.558	1.549
6	15	1.606	1.383	1.296
7	20	1.489	1.139	0.447
8	25	1.298	0.763	-
9	30	0.812	-	-

Figure-21: Log Cumulative % Drug Remaining v/s Time (First order) Plots of Formulations MEF_7-$MEF_9$of formulations

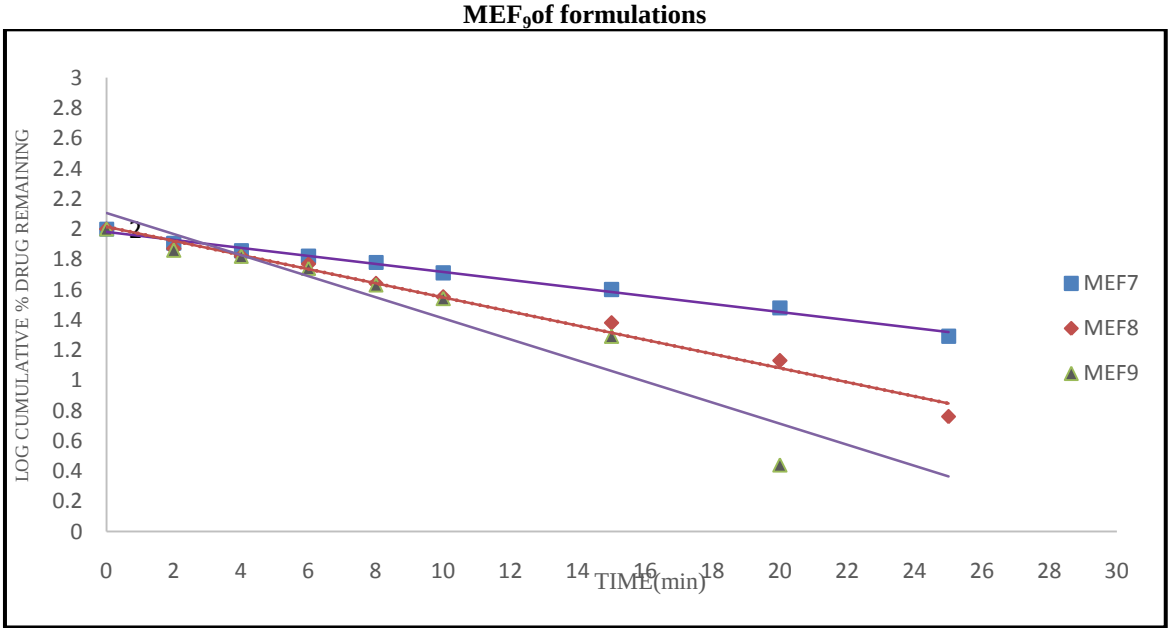

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Table-32: In-vitro release data of fast dissolving tablet of Minoxidil by sublimation methodof Formulations MSF_0-MSF_3

(zeroorder)

Sl. No.	Time (min)	MSF_0±SD*	MSF_1±SD*	MSF_2±SD*	MSF_3±SD*
1	0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
2	2	19.2±0.51	29.5±0.21	33.25±0.35	37.4±0.62
3	4	24.6±0.37	33.8±0.26	41.8±0.22	46.4±0.40
4	6	30±0.50	44.4±0.60	53±0.42	55.6±0.36
5	8	52.2±0.24	55.2±0.26	63.1±0.38	69±0.82
6	10	58.8±0.28	64.8±0.44	72.9±0.40	77.9±0.16
7	15	66±0.36	75.6±0.12	90.8±0.36	96.2±0.45
8	20	75.5±0.20	90.2±0.68	95.1±0.12	-
9	25	88.4±0.77	94.5±0.36	-	-
10	30	91.5±0.28	-	-	-

***Average of three determination**

Fig-22: In-vitro Release Data of fast dissolving tablet of Minoxidil by sublimation methodMSF_0-MSF_3(Zero order)

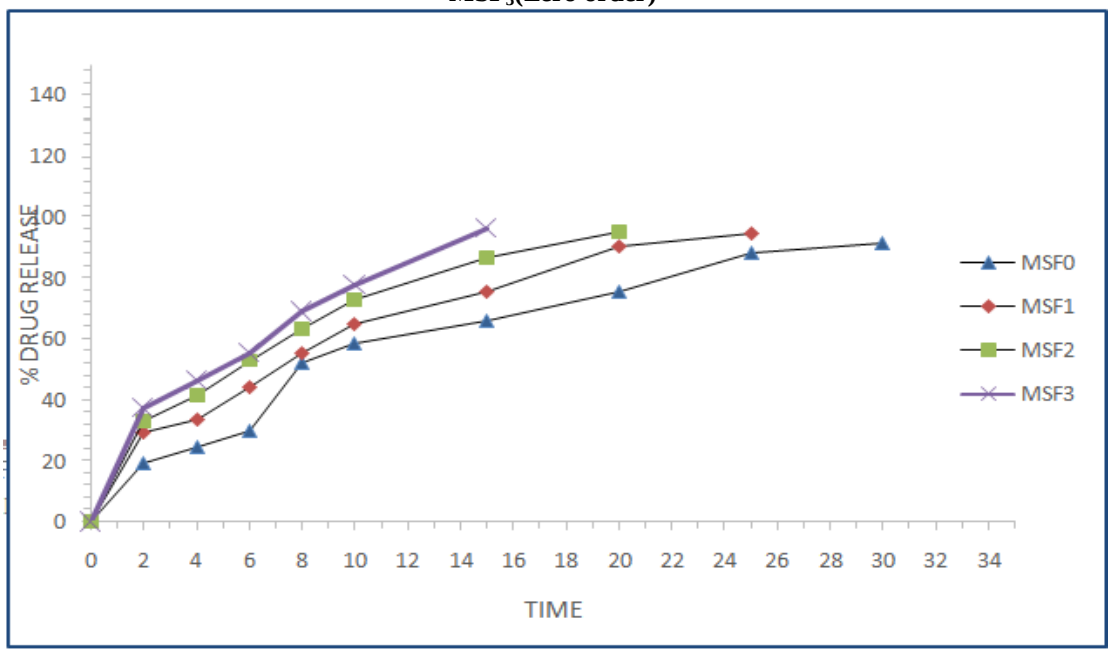

Table-33: In-vitro Release Data of fast dissolving tablet of Minoxidil by sublimation method of Formulations MSF_0-MSF_3

(First order)

Sl. No.	Time (min)	MSF_0	MSF_1	MSF_2	MSF_3
0	0	2.0000	2.0000	2.0000	2.0000
1	2	1.907	1.848	1.821	1.796
2	4	1.877	1.820	1.764	1.729
3	6	1.845	1.745	1.672	1.647
4	8	1.990	1.651	1.567	1.491
5	10	1.614	1.546	1.432	1.44
6	15	1.53	1.387	0.963	0.579
7	20	1.38	0.991	0.690	-
8	25	1.064	0.740	-	-
9	30	0.929	-	-	-

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Figure-23: Log Cumulative % Drug Remaining v/s Time (First order) Plots of formulations MSF_0-MSF_3

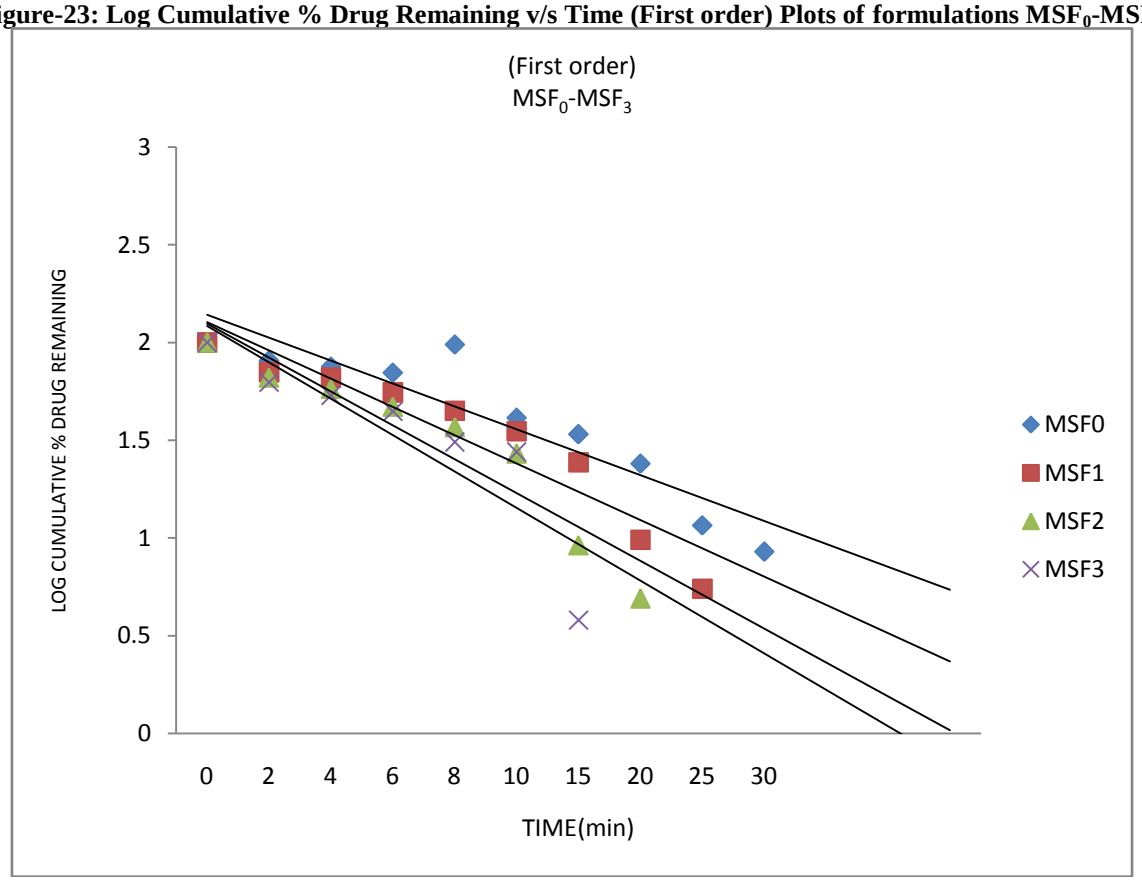

Table-34: In-vitro Release Data of fast dissolving tablet of Minoxidil by sublimation method of Formulations MSF_4-MSF_6

(zero order)

Sl. No.	Time (min)	MSF_4±SD*	MSF_5±SD*	MSF_6±SD
1	0	0.00±0.00	0.00±0.00	0.00±0.00
2	2	26.6±0.21	33.9±0.36	31.1±0.35
3	4	31.5±0.36	37.2±0.42	40.9±0.26
4	6	41.2±0.45	44.8±0.30	54.6±0.57
5	8	54.2±0.40	56.6±0.26	70.8±0.20
6	10	63.12±0.14	68.4±0.42	82.6±0.62
7	15	73.4±0.36	81±0.26	97.8±0.25
8	20	86.8±0.26	96.2±0.45	-
9	25	93.8±0.28	-	-
10	30	-	-	-

***Average of three determination**

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Figure-24: Cumulative % Drug Release v/s Time (Zero order) Plots of Formulations MSF_4- MSF_6

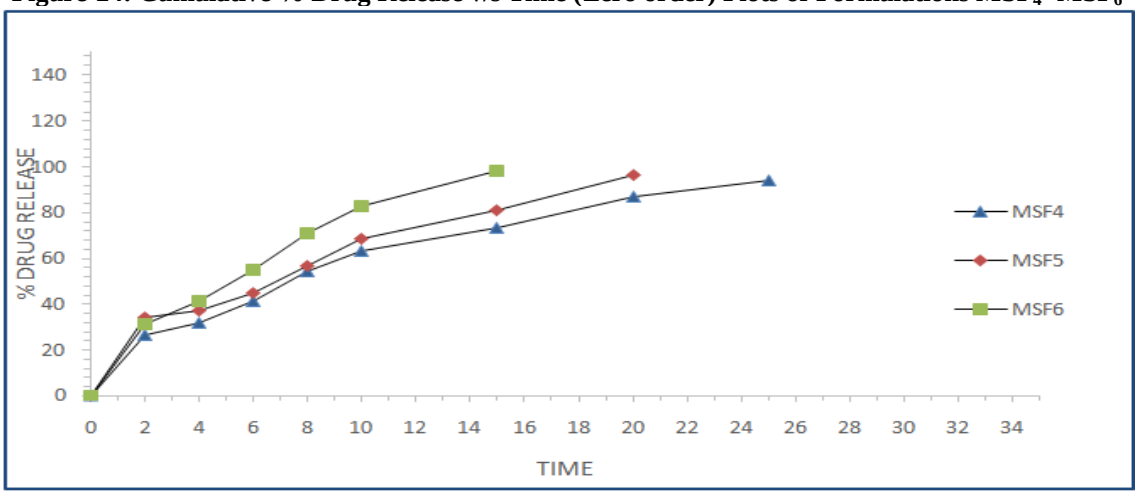

Table-35: In-vitro Release Data of fast dissolving tablet of Minoxidil by sublimation method of Formulations MSF_4-MSF_6

(First order)

Sl. No.	Time (min)	MSF_4	MSF_5	MSF_6
0	0	2.0000	2.0000	2.0000
1	2	1.865	1.820	1.838
2	4	1.835	1.797	1.771
3	6	1.769	1.741	1.657
4	8	1.661	1.637	1.465
5	10	1.566	1.499	1.240
6	15	1.424	1.278	0.342
7	20	1.120	0.579	-
8	25	0.792	-	-
9	30	-	-	-

Figure-25: Log Cumulative % Drug Remaining v/s Time (First order) Plots of Formulations MSF_4-MSF_6

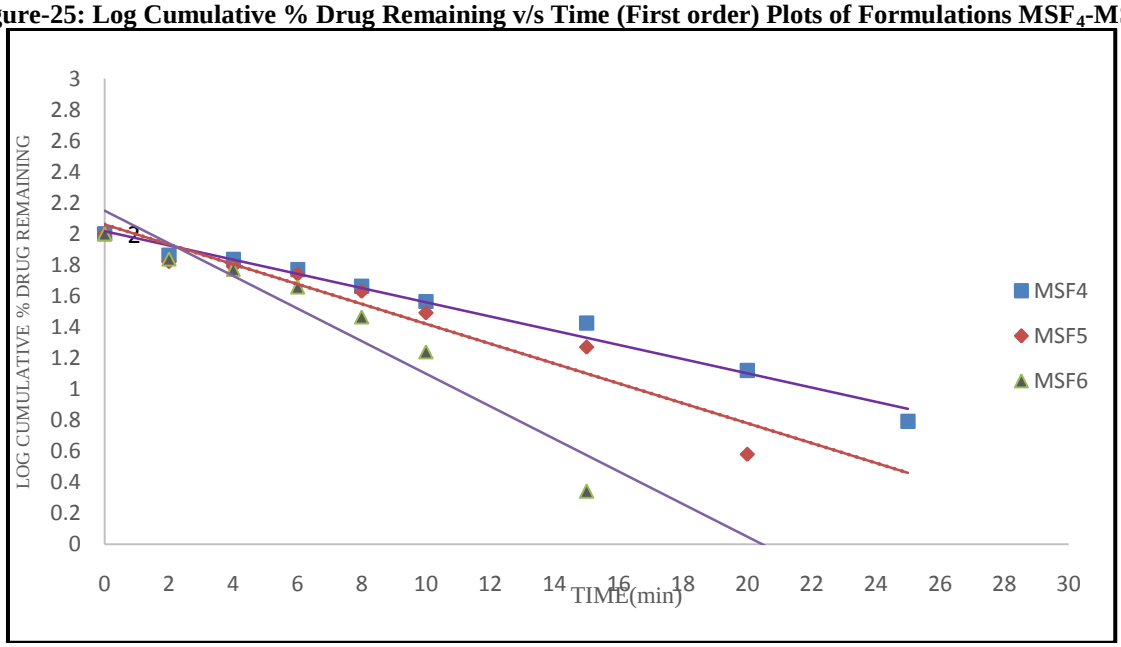

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Table-36: In-vitro Release Data of fast dissolving tablet of Minoxidil by sublimation method of Formulations MSF_7-MSF_9

(Zero order)

Sl. No.	Time (min)	MSF_7±SD*	MSF_8±SD*	MSF_9±SD*
1	0	0.00±0.00	0.00±0.00	0.00±0.00
2	2	18.9±0.72	19.23±0.56	26.8±0.27
3	4	29.6±0.15	29.9±0.12	35.5±0.25
4	6	33.9±0.38	38.4±0.36	43.2±0.27
5	8	42.6±0.20	45.6±0.26	56.6±0.36
6	10	54.6±0.36	54.6±0.32	72.5±0.24
7	15	64.4±0.45	67±0.66	80.8±0.38
8	20	75.8±0.42	77.9±0.18	95.4±0.66
9	25	88.9±0.22	93.8±0.38	-
10	30	92.8±0.78	-	-

***Average of three determination**

Figure-26: Cumulative % Drug Release v/s Time (Zero order) Plots of Formulations MSF_7- MSF_9

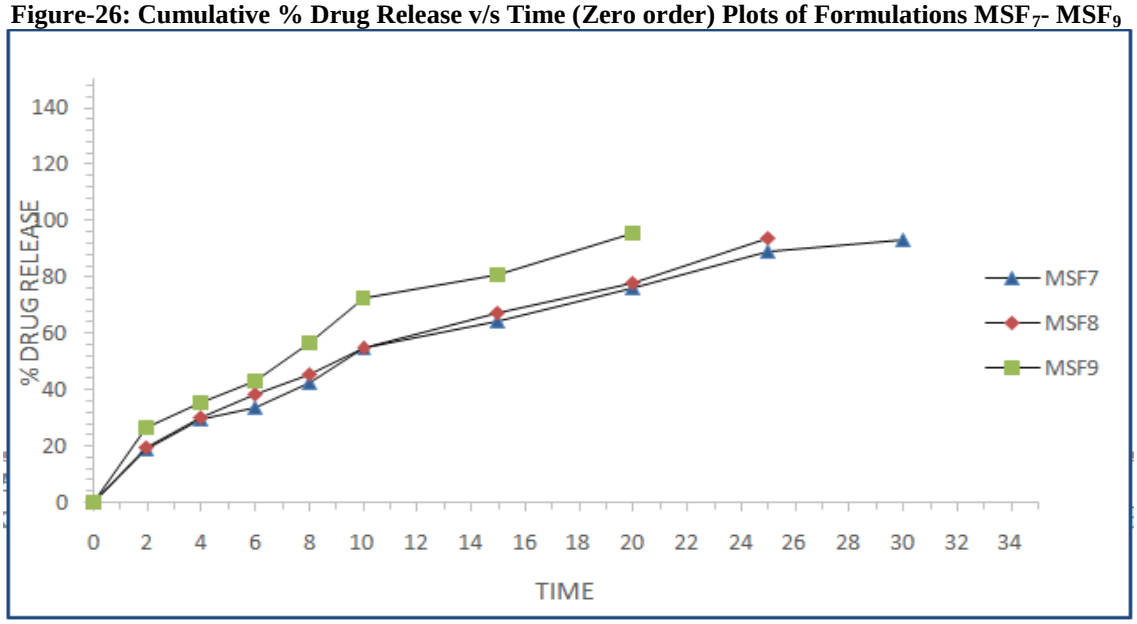

Table-37: In-vitro Release Data of fast dissolving tablet of Minoxidil by sublimation method of Formulations MSF_7-MSF_9

(First order)

Sl. No.	Time (min)	MSF_7	MSF_8	MSF_9
0	0	2.0000	2.0000	2.0000
1	2	1.909	1.907	1.864
2	4	1.847	1.845	1.809
3	6	1.820	1.789	1.754
4	8	1.758	1.735	1.637
5	10	1.657	1.657	1.439
6	15	1.551	1.518	1.283
7	20	1.383	1.344	0.662
8	25	1.045	0.792	-
9	30	0.857	-	-

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Figure-27: Log Cumulative % Drug Remaining v/s Time (First order) Plots of Formulations MSF_7-MSF_9

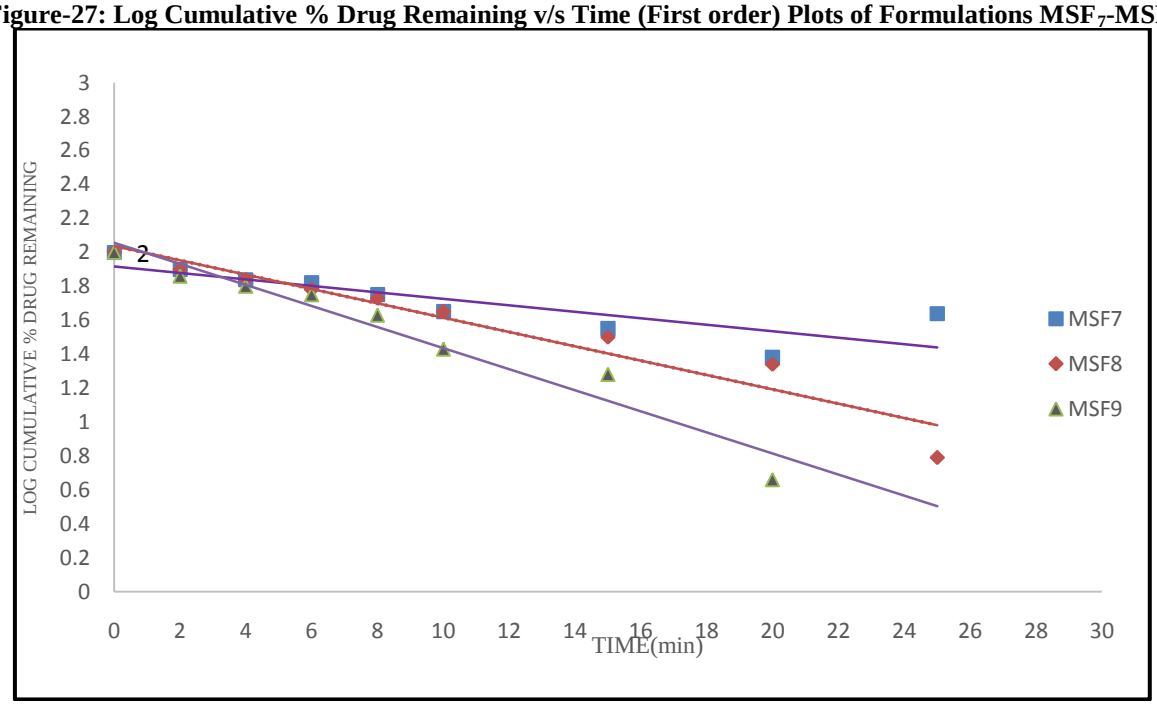

Table-38: Kinetic data of promising fast dissolving tablet formulations by Direct Compression method

Formulation Code		Zero-Order	First-Order
	B	2.09136	-0.02510
MDF_0	A	38.7721	1.82922
	r	0.93921	-0.99106
MDF_1	B	2.63319	2.93257
	A	23.3607	17.1090
	r	0.96799	0.93715
MDF_2	B	2.79825	-0.04582
	A	27.2196	2.03459
	r	0.98147	-0.95048
MDF_3	B	2.94601	-0.04941
	A	25.3073	2.04967
	r	0.98527	-0.95310
MDF_4	B	3.12939	-0.05270
	A	25.6442	2.03918
	r	0.96487	-0.99494
MDF_5	B	3.67483	-0.06291
	A	25.9011	2.06423
	r	0.98634	-0.97731
MDF_6	B	4.69813	-0.10148
	A	30.1806	2.14449
	r	0.98962	-0.95449
MDF_7	B	2.51343	-0.03103
	A	19.7152	1.99935
	r	0.98153	-0.98730
MDF_8	B	2.93693	-0.03803
	A	18.8344	2.02786
	r	0.98436	-0.95474

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MDF_9	B	3.63508	-0.05182
	A	22.6884	2.02912
	r	0.98434	-0.98086

Table-39: Kinetic data of promising fast dissolving tablet formulations by Effervescent Method:

Formulation Code		Zero-Order	First-Order
	B	2.46571	1.75056
MEF_0	A	19.9238	-5.37194
	r	0.90369	0.52974
	B	2.79579	-0.04148
MEF_1	A	22.5598	1.99688
	r	0.99443	-0.97959
	B	2.80557	-0.04148
MEF_2	A	30.5622	1.96040
	r	0.97877	-0.97944
	B	3.51514	-0.06149
MEF_3	A	27.5307	2.05384
	r	0.99281	-0.96725
	B	2.94909	-0.03611
MEF_4	A	25.3787	1.99489
	r	0.98421	-0.99174
	B	3.30967	-0.05533
MEF_5	A	22.5286	2.07
	r	0.96750	-0.99448
	B	3.48680	-0.06875
MEF_6	A	32.6653	2.03846
	r	0.97340	-0.98458
	B	2.53137	-0.03409
MEF_7	A	18.6849	2.03688
	r	0.99438	0.95722
	B	3.05081	-0.04708
MEF_8	A	24.5032	2.01967
	r	0.97793	-0.99111
	B	3.86650	-0.07372
MEF_9	A	21.3538	2.15884
	r	0.99111	0.99440

Table-40: Kinetic data of promising fast dissolving tablet formulations by sublimation method

Formulation Code		Zero-Order	First-Order
	B	2.63385	-0.03767
MSF_0	A	21.1264	2.06900
	R	0.95734	-0.96651
	B	2.97420	-0.04945
MSF_1	A	27.5401	2.01885
	R	0.97654	0.99045
	B	3.60931	-0.06691
MSF_2	A	30.7634	2.03423
	R	0.97267	-0.99049
	B	4.96976	-0.09027
MSF_3	A	24.8100	2.11875

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	R	0.97852	-0.93590
MSF_4	B	3.01360	-0.04605
	A	24.9244	2.01811
	R	0.97688	-0.98993
MSF_5	B	3.62485	-0.06671
	A	26.1692	2.09230
	R	0.99040	-0.95675
MSF_6	B	5.34	-0.11930
	A	22.8	2.24364
	R	0.981163	-0.96177
MSF_7	B	2.95743	-0.03740
	A	17.8163	2.02987
	R	0.98848	-0.98732
MSF_8	B	3.08179	-0.04304
	A	18.6335	2.05180
	R	0.99099	-0.95855
MSF_9	B	3.88532	-0.06421
	A	22.6076	2.08346
	R	0.97596	-0.97067

Table-41: Stability Data of MDF6 Formulation at 40·C/75% RH

Sl. No.	Time in days	Physical changes	Percent drug content±SD*	In-vitrodispersion time*
1.	1st day (initial)	--	96.12±0.41	61.26±1.15
2.	30th day (1 month)	No changes	97.08±0.12	60.28±0.16
3.	60th day (2 month)	No changes	97.01±0.08	61.06±0.09
4.	90th day (3 month)	No changes	97.94±0.02	61.47±0.07

***Average of three determinations**

Table-42: Statistical Analysis for Drug Content Data of MDF_6 Formulation

Sl. No.	Trials	1st day (A)	90th day (B)	A – B
1.	1	97.12	96.94	0.18
2.	2	96.08	96.02	0.06
3.	3	97.66	97.01	0.6
4.	Percent drug content (Mean±SD)	96.95±0.382	96.65±0.578	0.3±0.196

Table-43: Stability Data of MEF_6 Formulation at 40ºC/ 75% RH

Sl. No.	Time in days	Physical changes	Percent drug content±SD*	In-vitrodispersion time*
1.	1st day(initial)	---	96.17±0.391	60.00±1.00
2.	30th day (1month)	No changes	95.09±0.121	61.96±0.12
3.	60th day (2 month)	No changes	96.01±0.138	63.72±0.38
4.	90th day (3 month)	No changes	94.96±0.155	64.43±0.41

***Average of three determinations**

Table-44: Statistical Analysis for Drug Content Data

Sl. No.	Trials	1st day (A)	90th day (B)	A – B
1.	1	96	95.36	0.64
2.	2	94.19	94.07	0.12
3.	3	95.22	94.99	0.23

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4.	Percent drug content(Mean±SD)	95.13±0.391	94.80±92	0.33±0.236

Table-45: Stability Data of MSF_6 Formulation at 40ºC/ 75% RH

Sl. No.	Time in days	Physical changes	Percent drug content ±SD*	In-vitro dispersion time*
1.	1st day (initial)	---	97.56±0.353	27.00±1.00
2.	30th day (1 month)	No changes	96.09±0.138	26.96±0.14
3.	60th day (2 month)	No changes	95.53±0.127	27.68±0.26
4.	90th day (3 month)	No changes	95.89±0.166	26.53±0.31

***Average of three determinations**

Table-46: Statistical Analysis for Drug Content Data

Sl. No.	Trials	1st day (A)	90th day (B)	A – B
1.	1	97.56	96.36	1.20
2.	2	95.19	95.28	0.17
3.	3	96.22	96.02	0.2
4.	Percent drug content (Mean±SD)	96.32±0.29	95.86±16	0.52±0.224

IR INTERPRINTATION

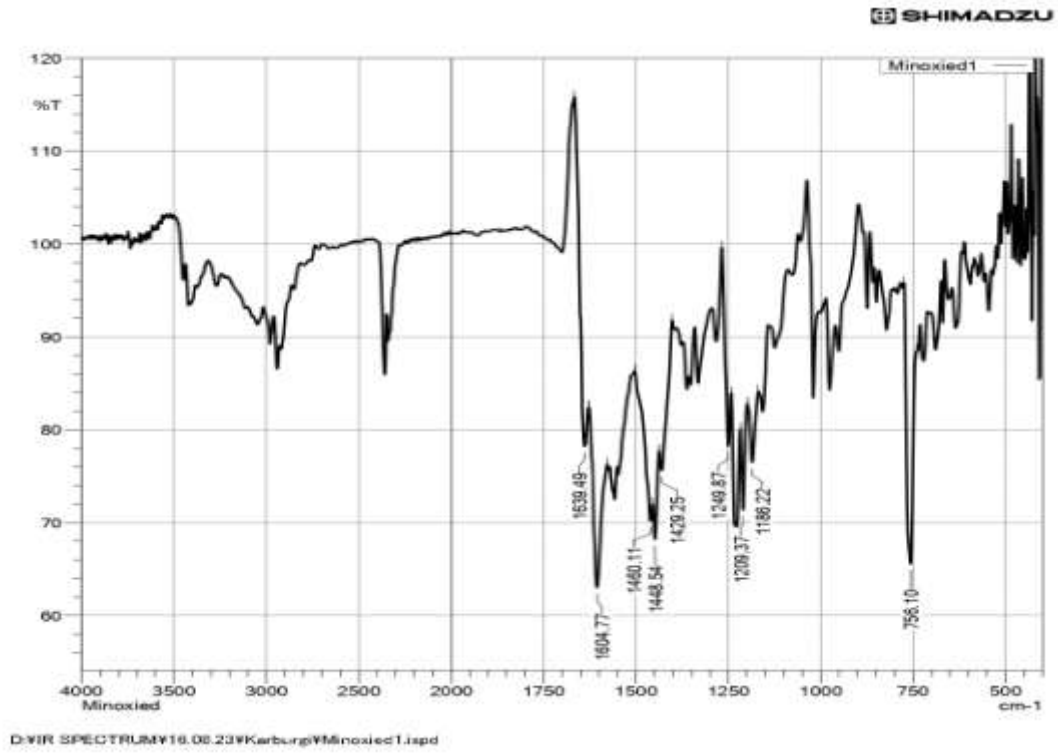

Figure- 28: IR Spectrum of pure drug Minoxidil

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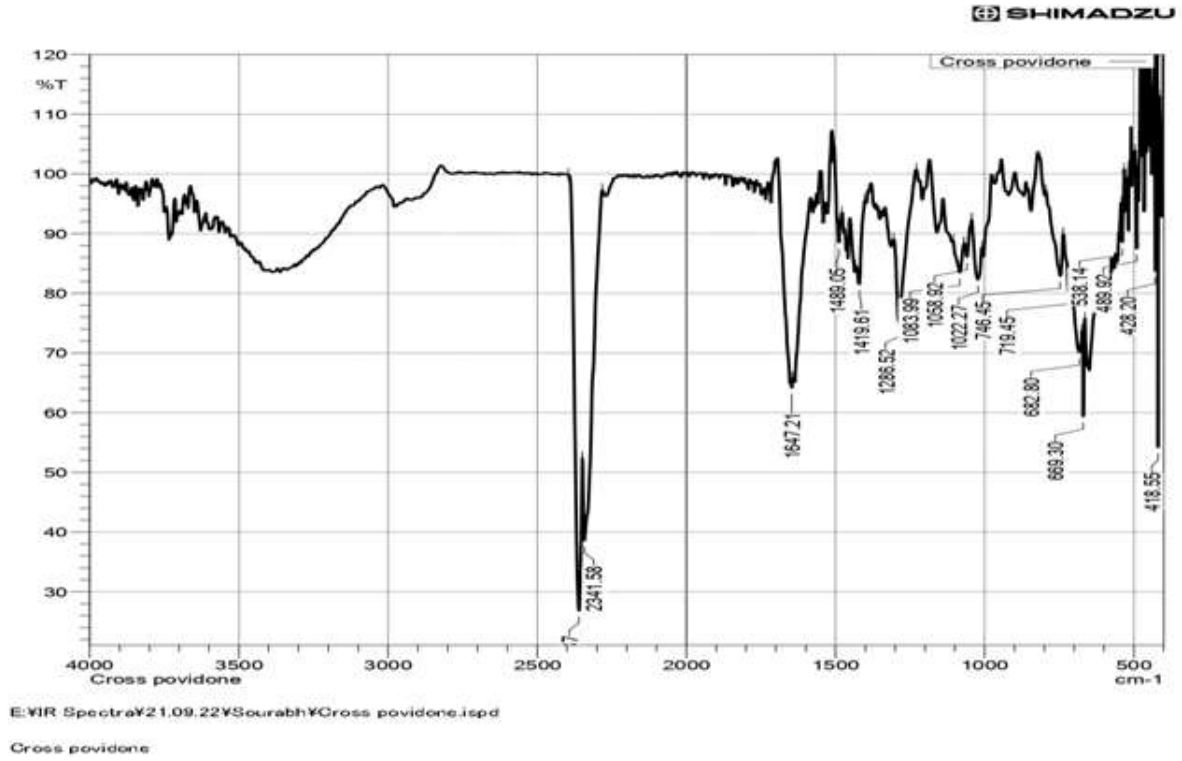

Figure-29: IR Spectrum of Crospovidone

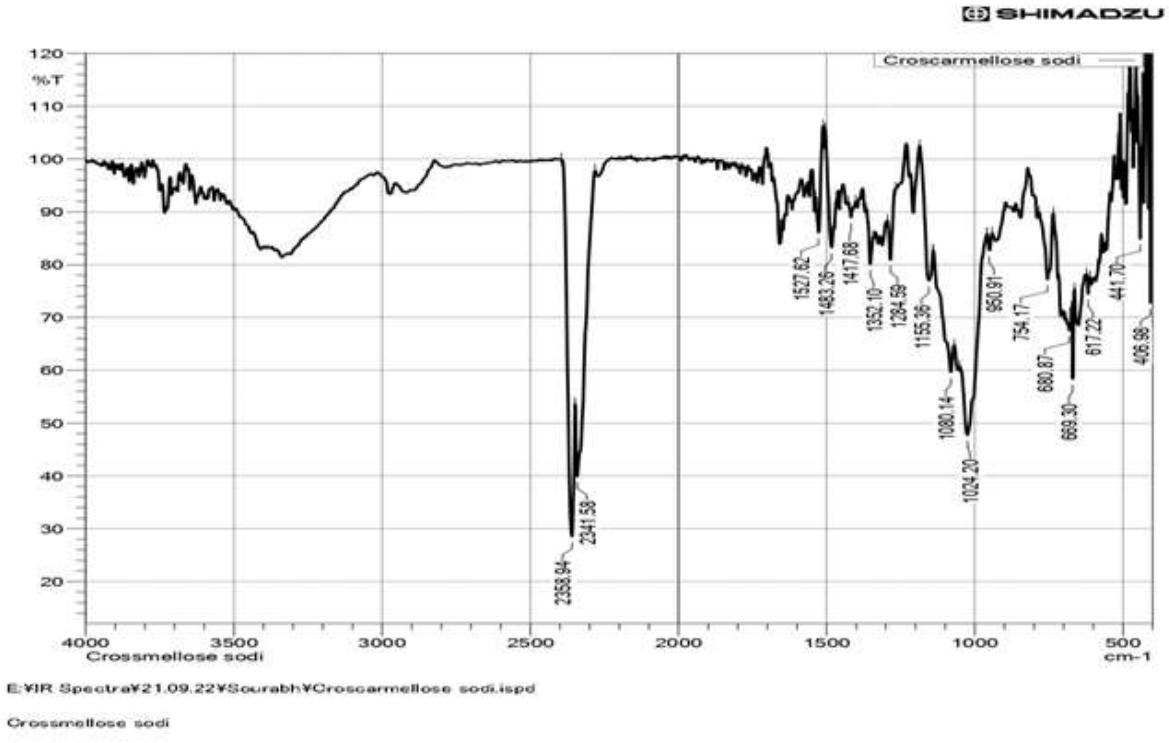

Figure-30: IR Spectrum of Croscarmellose Sodium

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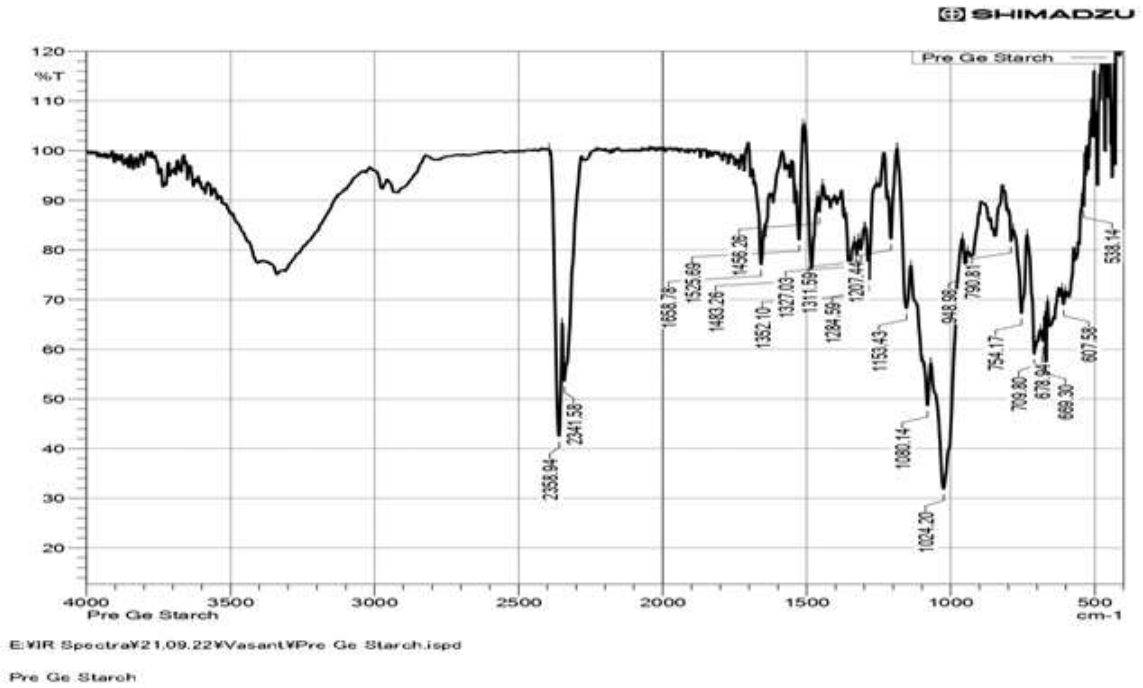

Figure-31: IR Spectrum of Pre-Gelatinized Starch

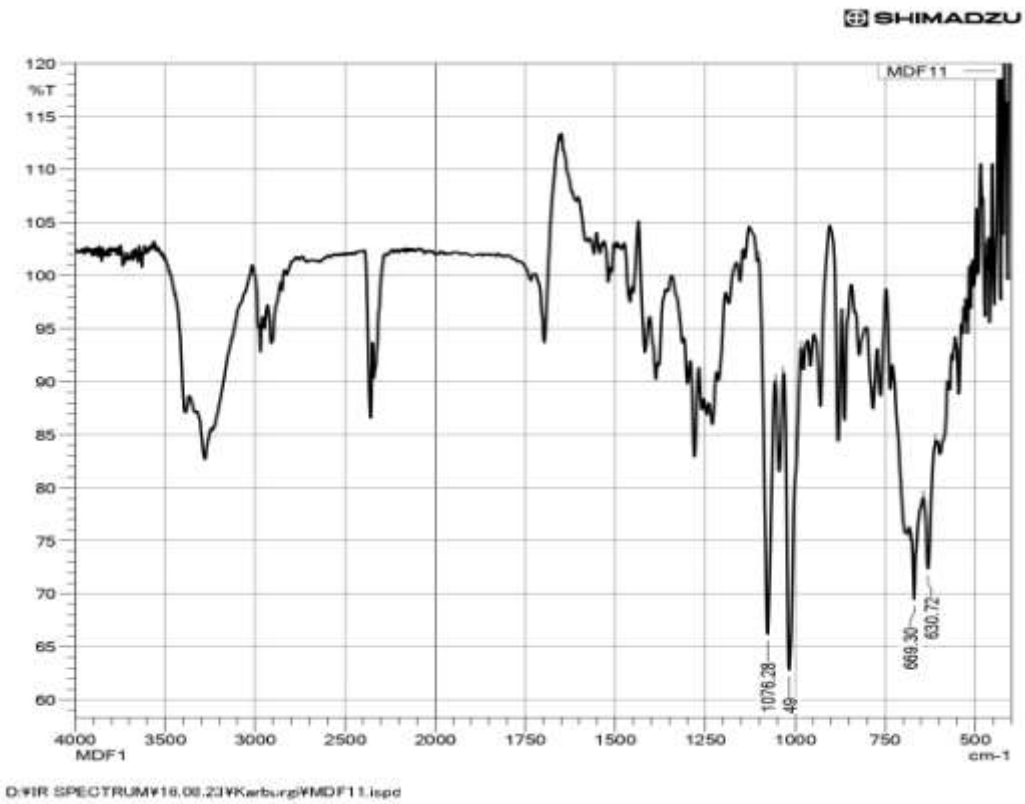

Figure-32: IR Spectrum of Formulation of MDF6

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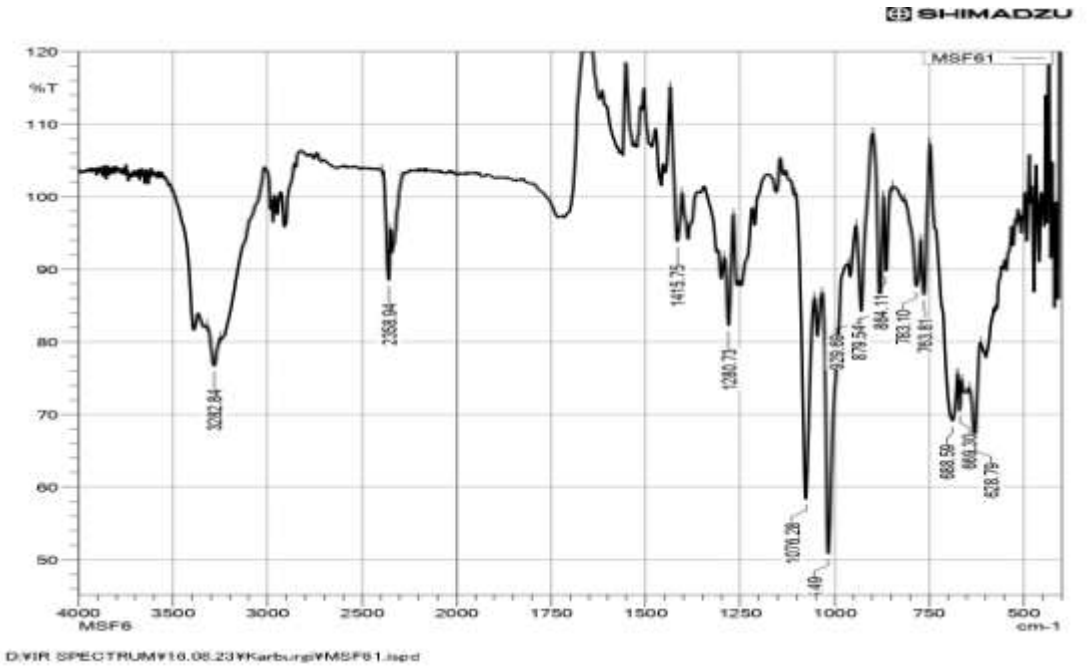

Figure-33 IR Spectrum of Formulation of MEF6

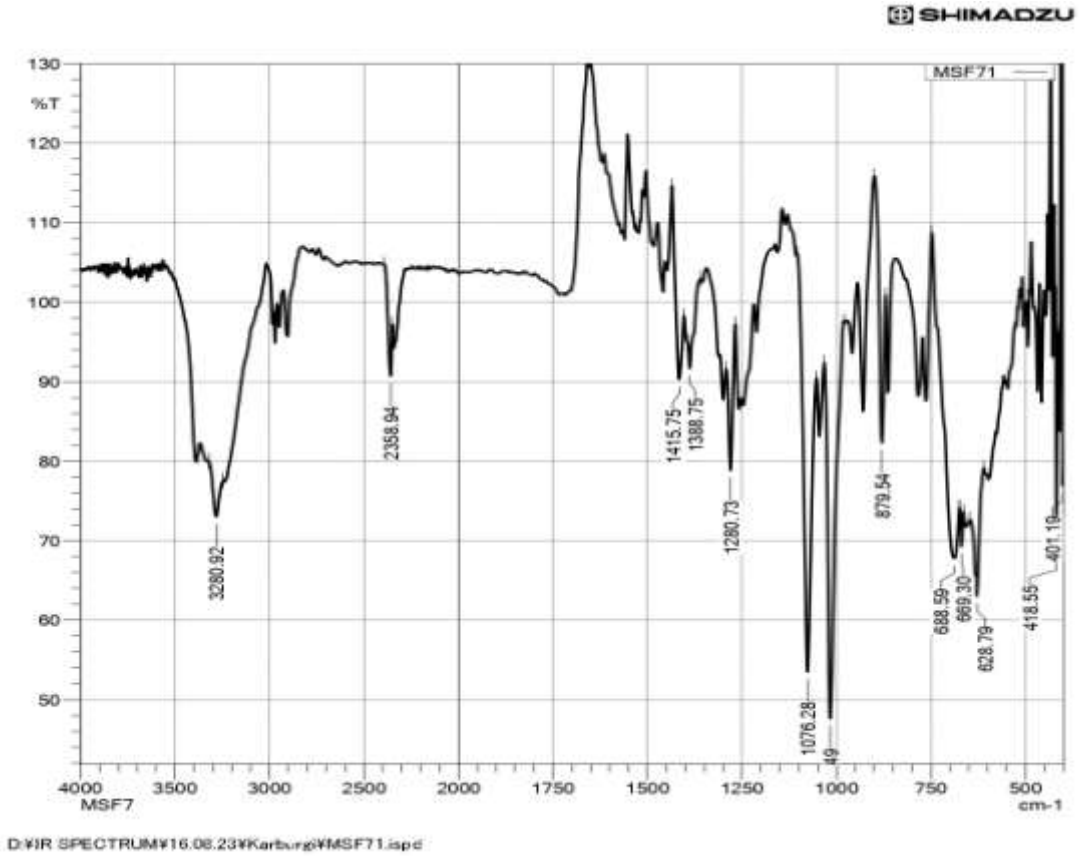

Figure-34: IR Spectrum of Formulation of MSF6

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CHAPTER-6

DISCUSSION

In the present study an attempt has been made to design and evaluate fast dissolving tablets of Minoxidil by direct compression, effervescent and sublimation method. In this method the formulations were prepared by using super-disintegrants such as Crospovidone, croscarmellose sodium and pre-gelatinized starch in different ratios, directly compressible MCC as a diluent and Aspartame as a sweetening agent and helps in masking slight bitter taste of the drug

All the prepared formulation (powder blend) were evaluated for various pre-compression parameters like bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio. The results are given in table No. 14,15& 16.

Pre-compression parameters of the all the prepared formulation (powder blend) by direct compression method the results are given in table No. 14, the tablets prepared by Effervescent method are given in the table No. 15 & the tablets prepared by sublimation method are given in table No.16.

The prepared Minoxidil tablet formulations were evaluated for various quality control parameters like weight variation, hardness, friability, disintegration time &drug content uniformity along with in-vitro dissolution studies were also performed the results are given in table No. 17,18 & 19 and table No. 17,18 & 19 for weight variation test & other parameters respectively.

The in vitro- dissolution profile of all the prepared Minoxidil formulation are given in table No. 20-37.

All the prepared formulation were evaluated for in-vitro dispersion time, wetting time water absorption ratio the results are given in table No. 17,18& 19.

Weight Variation:

The weight of all the tablets was found to be within the pharmaceutical limits of ±7.5 %. The weight of all the tablets was found to be uniform with low value of standard deviation.

All the formulation were evaluated for hardness. The hardness range for the tablet prepared by direct compression method was in the range of 2.1- 2.9 kg/cm^2 and the tablets prepared by the effervescent method was in the range of 2.6-2.9 kg/cm^2 and the tablets prepared by the sublimation method was in the range of 2.1–3.3kg/cm^{2}were well within the accepted pharmacopoeial limit.

Friability of all the prepared tablet formulations was according to pharmacopoeial limit of below 1%.the friability value of formulation prepared by Direct compression method was in the range 0.64%-0.91% and the tablets prepared by effervescent method was in the range 0.64-0.89%and the tablets prepared by sublimation method was in the range friability less than 1%.

The in- vitro dispersion time of prepared formulation by Direct compression method was in the range of 20.66sec to 76.26sec and the tablets prepared by effervescent method was in the range of 59.66 to 78.33sec and the tablets prepared by sublimation method was in the range of 20to 64sec.

Wetting time of all the prepared formulation by direct compression method was in the range of 14sec-36.88sec and the tablet prepared Effervescent method was in the range 18sec-28sec and the tablet prepared Sublimation method was in the range of 24.49 to 33 sec.

Water absorption ratio of prepared formulation by Direct compression method was in the range of 60.10%-93.32% and the tablets prepared by Effervescent method was in the range of 77.01%-96.05% and the tablets prepared by sublimation method was in the range of 81.2-99.48%.

The % drug content of all the formulation prepared by Direct compression method was in the range of 94.33%-98.12% and the tablets prepared by the Effervescent was in the range of 95.17%-97.65% and the tablets prepared by the sublimation method was in the range of 92.83%-97.5% and was well within the acceptable pharmacopoeial limits.

Among the tablets prepared by direct compression method, formulation (MDF_6) containing Micro crystalline cellulose (MCC) diluent as directly compressible vehicle, croscarmellose sodium(CCS) as superdisintegrant along with sodium Aspartame as sweeteners and talc and magnesium stearate as glidant & lubricant has shown in-vitro dispersion time of 62 sec, wetting time of 34.00 sec and water absorption ratio of 97.64%.

The tablets prepared by effervescent method, formulation (MEF_6) containing mannitol as diluent, micro crystalline cellulose (MCC) as binder, croscarmellose sodium (CCS) as superdisintegrant along with sodium bicarbonate and tartaric acid as bursting agent, talc and magnesium stearate as glidant and lubricant has shown in-vitro dispersion time of 58 sec, wetting time of 23.41 sec and water absorption ratio of 96%.

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The tablets prepared by Sublimation method, formulation (MSF_6) containing camphor as sublimating agent, micro crystalline cellulose (MCC) as binder, croscarmellose sodium (CCS)as super-disintegrant along with talc and magnesium stearate as glidant and lubricant has shown in-vitro dispersion time of 26 sec, wetting time of 23.15 sec and water absorption ratio of 97.77%.

In-vitro Dissolution Study:

In-vitro dissolution studies were performed in Methyl alcohol, on the all-prepared formulations prepared by direct compression method MDF_1.MDF_9, formulations prepared by Effervescent method MEF_1- MEF_9 And also, formulations prepared by Sublimation method MSF_1-MSF_9 The results are shown in table No. 20-37.

From the data obtained, formulation MDF_1 has released 92.3% in 30 min, MDF_2 has released 95.2% in 25 min, MDF_3 has released 96.1% in 25 min, MDF_4 has released 94.8% in 25 min, MDF_5 has released 95.2% in 20 min, MDF_6 has released 97.2% in 15 min, MDF_7 has released 90.4% in 30 min, MDF_8 has released 91.8% in 25 min and MDF_9 has released 93.2% in 20 min.

Formulations prepared by Effervescent method MEF_1 has released 90.2% in 25 min,MEF_2 has released 94.2% in 25 min, MEF_3 has released 95.2% in 20 min,MEF_4 has released 92.1% in 30 min,MEF_5 has released 95.7% in 25 min, MEF_6 has released 96.3% in 20 min,MEF_7 has released 93.5% in 30 min,MEF_8 has released 94.2% in 25 min, and MEF_9 has released 95.2% in 20 min.

Formulations prepared by Sublimation method MSF_1 has released 94.5% in 25 min,MSF_2 has released 95.1% in 20 min, MSF_3 has released 96.2% in 15 min,MSF_4 has released 93.8% in 25 min,MSF_5 has released 96.2% in 20 min, MSF_6 has released 97.1% in 15 min,MSF_7 has released 92.8% in 30 min,MSF_8 has released 93.8% in 25 min, and MSF_9 has released 95.4% in 20 min.

Drug-Excipient Interaction Studies (by FT-IR):

Among all the formulation the MDF_6 shows maximum release 97.2% in 15 min prepared by the a direct compression method, formulation MEF_6 shows maximum release 96.3 in 15 min prepared by effervescent method and formulation MSF_6 Shows maximum release 97.1 in 15 min.

The first order plots of formulation prepared by direct compression method are shown in figure No.21,23&25. The first order plots of formulation prepared by effervescent method is shown in figure No.27,29&31 and the first order plots of formulation prepared by sublimation method is shown in figure No.33,35&37

Drug Release Kinetics:

The in-vitro drug release data obtained from all the prepared tablet formulation prepared by direct compression method & effervescent method and sublimation method were fitted into two popular models of data treatment.

- Cumulative percent drug release versus time plot (Zero order).
- Log cumulative percent drug remaining versus time plot (first order).

The in-vitro drug release data was subjected to goodness of fitness by linear regression analysis according to zero order, first order kinetic equation. The results of linear regression analysis of data including regression coefficient are summarised in the table No. 38.

The regression coefficient ‘r’ value of zero order plots were compared to be in the range of 0.90369- 0.99099 indicating release from formulation were found follow zero order kinetics.

The regression equation ‘r’ value of first order plot were found to be in the range of 0.90713-0.99106 indicating drug release from the formulation were found to follow first order kinetics.

Assignments	**Minoxidil**	**MDF6**	**MSF6**	**MSF6**
NH(Stretching)	3472, 3444, 3422, 3367	3478, 3454, 3434, 3376	3475, 3455, 3433, 3378	347, 3444, 3422, 3367
H-Bonded N-H	3282, 3044	3282,3045	3282,3046	3280,3047

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CH(Stretching Aromatic &Aliphatic	2976, 2956, 2845	2976, 2956, 2845	2976, 2956, 2845	2976, 2956, 2845
C=N(Stretching Aromatic)	1639,1604	1645,1608	1637,1610	1647, 1611
Aromatic C=C (Stretching N-H Bending)	1548, 1460, 1448, 1429, 1455	1550,1465,1450,1432,1458	1548,1460,1448,1433, 1459	1548, 1460, 1448, 1432, 1462
N-O (Stretching Aromatic C-N Stretching)	1266, 1249, 1209	1266, 1255, 1212	1266, 1252, 1213	1266, 1251, 1215

Table-46:FT-IR peaks of minoxidil and excipients

FTIR Spectrum of the pure drug Minoxidil showed the presence of principal peaks at wave numbers 3472,3282,2976,1639,1548,1266 and 1348 cm^{-1}in complete FTIR region. Especially the fingerprint region peaks are intact and this indicates there is nodrug-excipientinteraction. The complete finger print region (3060-1020 cm^{-1}) indicates that the given drug is pure and matches all the peaks of the slandered FTIR graph. IR spectra of the physical mixture formulations contains almost all the peaks with negligible sift signifies there is no drug-drug interaction with the excipients used in the formulation.

IR spectroscopic studies indicated that the drug is compatible with all the excipients. The IR spectrum of all the prepared tablet formulation showed all the characteristic peaks of Minoxidil thus confirming that no interaction of drug occurred with the components of the formulation. The IR spectrum of pure drug Minoxidil &all the polymer used along with IR spectrum of all the prepared formulation by both methods are shown in figure No.28-34.

CHAPTER-7

CONCLUSION

In the present work an attempt has been made to design an evaluated fast dissolving tablet of Minoxidil by Direct compression, Effervescent Method and sublimation method.

By using MCC as directly compressible vehicle, pre-gelatinized starch and crospovidone as superdisintegrant, Aspartame as sweetening agent and help in masking bitter taste of drug. In case of effervescent method Magnesium stearate was used as binding agent, crospovidone, croscarmellose sodium, pre-gelatinized starch as superdisintegrant, mannitol as diluent sodium bicarbonate and tartaric acid as effervescence producing agent and camphor as sublimating agent, aspartame as flavouring agent.

The pre-compression parameters of the prepared tablet formulation (powder Blend) like bulk density, tapped density, angle of repose Carr's index and Hausners' ratio were performed and results indicated that the prepared powder blend was flowing with good angle of repose and Carr's index.

The weight of all the prepared tablets was within the pharmacopoeial limits the hardness range of prepared tablet formulation was in the range of 2.1-3.55 kg/cm^2 and for sublimation method all tablets had hardness in the range 5.0–5.4 $kg/cm^2$and were within pharmacopoeial limits

Friability of all prepared tablet formulation was in the range of 0.64-0.92% and for sublimation method friability less than 1% was in the pharmacopoeial limit.

The percent drug content of all the prepared tablet formulation was is in the range of 95.87-97.5% and is in the acceptable pharmacopoeial limits.

The in-vitro dispersion time of all the tablet formulation was in the range of 26.66-66.33 sec, wetting time was in the 33-65 sec and water absorption ratio was in the range of 50.79-86.06%.

Among the tablets prepared by direct compression method formulation MDF_6containing MCC as directly compressible vehicle, croscarmellose sodium as superdisintegrant along with aspartame as sweeteners and talc and magnesium stearate as glidant and lubricant as shown into dispersion time of 61.26sec, wetting time of 34.17sec and water absorption ratio of 92.15%.

The tablet prepared by effervescent method formulation MEF_6 containing mannitol as diluent, magnesium stearate as binder, croscarmellose sodium as superdisintegrant along with sodium bicarbonate and tartaric acid as effervescence producing agent, talc and magnesium stearate as glidant and lubricant. Shown in in- vitro

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dispersion 58sec, wetting time 20.15sec and water absorption ratio of 98.26%

The tablet prepared by sublimation method formulation MSF_6 containing mannitol as diluent, magnesium stearate as binder, croscarmellose sodium as superdisintegrant along with camphor as sublimation producing agent, talc and magnesium stearate as glidant and lubricant. Shown in in-vitro dispersion 26sec, wetting time 23.15sec and water absorption ratio of 99.48%

In-vitro dissolution study

In- vitro dissolution studies were performed in methyl alcohol, on the prepared formulation prepared by direct compression method MDF_1-MDF_9,for formulations prepared by effervescent method MEF_1-MEF_9 andalsoformulations prepared by sublimation method MSF_1-MSF_9.

Among all the formulation MDF_6 shows maximum release 97.2% in 15min. prepared by direct compression method, MEF_6 shows maximum release 96.3% in 20min prepared by effervescent method andMSF_6 shows maximum release 97.8% in 15min prepared by sublimation method.

Drug Release Kinetics:

The in-vitro drug release data obtained from all the prepared tablet formulation prepared by direct compression method, Effervescent method & Sublimation method.

- ❖ Cumulative percent drug release versus time plot (Zero order).
- ❖ Log cumulative percent drug remaining versus time plot (first order)

The regression coefficient 'r' value of zero order plots were compared to be in the range of 0.90369- 0.99443 indicating release from formulation were found follow zero order kinetics.

The regression equation 'r' value of first order plot were found to be in the range of 0.93798-0.99106 indicating drug release from the formulation were found to follow first order kinetics.

IR spectroscopic studies were conducted on pure drug Minoxidil and disintegrants used in the preparation of tablet formulation and IR spectroscopic studies of MDF6, MEF6 & MSF6 prepared formulation was performed. IR spectroscopic studies indicated there was no drug-excipients interaction.

Stability studies on promising formulation were performed as per ICH guidelines and these studies indicated that there were no significant changes in drug content and in vitro-dissolution studies.

CHAPTER-8

SUMMARY

Minoxidil is an antihypertensive vasodilating agent used for resistant hypertension. Minoxidil is a potent and long-lasting drug indicating for the treatment cardiovascular disease such as hypertension. The minoxidil is given as orally in minimum dose 2.5-5mg per day to maximum dose 40mg per day once respectively.

Minoxidil, a direct vasodilator, was first discovered in 1965 as a potent antihypertensive agent. Minoxidil acts on adenosine triphosphate–modulated potassium channels, which results in relaxation of smooth muscles. This lowers peripheral resistance and results in a decrease in both systolic and diastolic BP.

Geriatric and paediatric patients may have difficulties to swallowing and chewing tablets resulting in patients' non-compliance and ineffective therapy. The concept of formulating fast dissolving tablet containing minoxidil, since patients must strictly follow the doses regimen for preventing sub-therapeutic concentration, FDT will avoid missing out of a dose even during travelling or other situation, were there is no access to water.

The concept of formulating FDT containing Minoxidil offers suitable and practical approach in serving desired objective of fast disintegration and dissolution characteristics with increased bioavailability.

In the present research work Minoxidil FDT were prepared by three method i.e., direct compression method and effervescent method and sublimation method using micro crystalline cellulose (MCC) as DCV and mannitol as diluent respectively along with pre-gelatinized starch, crospovidone, croscarmellose sodium as superdisintegrants and sodium bicarbonate, tartaric acid as effervescence producing agent and camphor as sublimating agent with aspartame as sweetening agent.

The pre-compression parameters of the prepared tablet formulation (powder Blend) like bulk density, tapped density, angle of repose Carr's index and Hausners' ratio were performed and results indicated that the prepared powder blend was flowing with good angle of repose and Carr's index.

The prepared batches of tablet were subjected to quality control test like weight variation, hardness, friability, drug content

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uniformity, in-vitro dispersion, wetting time and water absorption ratio.

Along with in-vitro release studies estimation of Minoxidil in the prepared FDT's was carried out by extracting drug in methanol and measuring absorbance 285nm. in-vitro drug release studies were performed in electrolab-USP DTD-06T tablet dissolution test apparatus employing basket stirrer at 50 rpm using 900 ml of 6.8 buffer maintained 37±.5 ·C as dissolution medium.

The formulation MDF_6 prepared by direct compression method shows maximum release 97.2% in 15min and formulation MEF_6 shows maximum release 96.3% in 20min prepared by effervescent method and MSF_6shows maximum release 97.8% in 15min prepared by Sublimation method.

IR spectroscopic studies indicated that there is no drug- excipient interaction.

Stability studies on promising formulation indicated that there are no significant changes in drug content, in-vitro dispersion, and in-vitro drug release rate.

CHAPTER-9

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