EFFECT OF SUPER DISINTEGRATING AGENT AND LUBRICANT ON OPTIMIZED FAST DISINTEGRATING TABLETS OF VERAPAMIL HYDROCHLORIDE

A Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

Chennai-600032

In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

REG. NO: 26105403

Under the Guidance of

Mr. K. MOHAN KUMAR, M. Pharm.

DEPARTMENT OF PHARMACEUTICS

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

Signature of the Guide
K.MOHAN KUMAR, M. Pharm.

DEDICATED TO

MY PARENTS

&

FRIENDS

ACKNOWLEDGEMENT

ACKNOWLEDGEMENT

The Joyness, Satisfaction and euphoria that comes along with successful completion of any work would be incomplete unless we mention names of the people who made it possible, whose constant guidance and encouragement served as a beam of light crowned out effects.

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INTRODUCTION

1. INTRODUCTION

Drug delivery systems are a magic tool for existing drug to enhance the safety and efficacy of the drug molecule by formulating a dosage form being for the administration. Due to impaired swallowing ability, (dysphasia) it is common among all age groups, especially in elderly, mainly it is seen in swallowing conventional tablets and capsules. [1] In recent years, in accordance with changes in lifestyle, a demand has arisen for the development of dosage forms that can be readily handled and taken by many patients. [2] The oral fast-disintegrating tablets is also known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets, however the function and concept of all these dosage forms are similar. [3]

By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast disintegrating dosage form. [4] According to European Pharmacopoeia, the ODT should disintegrate in less than three minutes. [5]Rapid disintegration of the drug will produce quick onset of action. Tablet dosage form is mainly composed of the drug and excipients such as a diluent, binder, lubricant, disintegrant, and a glidant. [6]

Lubricants are pharmaceutical excipients that improve the fluidity, filling properties, adhesiveness and plasticity of powders and are indispensable for improving the quality and manufacturing efficiency of solid preparations. [7] Lubricants help in reducing the friction between the powder bed and the die wall during compression and ejection by interposing a film of low shear strength between them. Some lubricants can also act as anti adherent, which prevents sticking of the powder to the punches and die. Lubricant also has profound influence on disintegration time, hardness and drug dissolution therefore, it is important to optimize the concentration of lubricant in the formulation.[8] In solid pharmaceutical formulations, magnesium stearate (Mg-St) is widely used as a hydrophobic lubricant. The tensile strength of the tablet did not change when up to 3% of Mg stearate was mixed into the formulation. [9]

Short disintegration time with good dispersibility is the most important characteristics of fast disintegrating tablets. The necessity of an oral disintegrating

tablet is to disintegrate within seconds, in limited amount of the water available in the form of saliva. This demands the use of special type of disintegrants called as Super disintegrants. [10] The Super disintegrants provide quick disintegration due to combined effect of swelling and water absorption by the formulation. As an effect of swelling properties of super disintegrant, the wetted surface of the carrier increases, which promote wettability and dispensability of the system and there by enhance the disintegration and dissolution. In solid pharmaceutical formulations crosscarmellose sodium is widely used as a super disintegrant. [11] Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. [12]

Direct compression is the easiest way to manufacture tablets with low cost, conventional equipments, commonly available excipients and a limited number of processing steps leading to this technique is a preferable one. [13] This technique can now be applied to preparation of fast disintegrating tablets because of the availability of improved excipients especially super disintegrants. In many oral disintegrating tablet technologies are based on direct compression, the addition of super disintegrants affects the rate of disintegration and there by affects dissolution also. [14]

Traditional experimental methods involves significant amount of time and efforts to get meaningful results for a complex system. It is very much desirable to obtain an acceptable formulation using minimum amount of time and material. Factorial design is an efficient method of finding the relative significance of number of variables. Optimization procedure involving factorial designs and analysis of response surfaces are powerful, efficient and also a systematic tool and has been used in developing different oral dosage formulations. [15]

Hypertension is a chronic illness that affects-50 million people in the United States and 20% of the adult population in most countries. [16] Hypertensive patients are at great risk for other cardiovascular diseases, including stroke, myocardial infarction, and coronary artery disease, and congestive heart disease, renal insufficiency. [17] The goal of antihypertensive therapy is to “reduce the morbidity and mortality by the least intrusive means possible”. Calcium channel blockers are a diverse group of drugs used to manage many different cardiovascular diseases. [18] Over the last two decades,

calcium channel blockers have been widely prescribed for the treatment of Hypertension, angina and supra ventricular arrythmiasis. [19]

Verapamil hydrochloride (VRP) is a phenyl alkyl amine derivative and first clinically available and well known calcium antagonist. [20] Calcium antagonists are drugs which cause coronary and peripheral vasodilatation by reducing calcium influx through the slow channels of vascular smooth muscle and cardiac cell membranes. [21]

REVIEW OF LITERATURE

2. REVIEW OF LITERATURE

Sameer G. Late *et al*, [6] investigated the Effects of calcium silicate (disintegration-promoting agent) and various lubricants on an optimized β cyclodextrin-based **fast-disintegrating tablet** formulation and effects of moisture treatment were also evaluated at 75, 85 and 95% relative humilities. A two factor, three levels (32) full factorial design was used to optimize concentrations of calcium silicate and lubricant and reported that hardness was not affected at 75% moisture treatment. At 85 and 95% moisture it increased hardness of the tablets; however at the same time it negatively affected the disintegration time.

Syed Azeem *et al*, [22] Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however in many cases immediate onset of action is required than conventional therapy. To overcome these drawbacks, **immediate release** pharmaceutical dosage form has emerged as alternative oral dosage forms. There are novel types of dosage forms that act very quickly after administration. The basic approach used in development of tablets is by the use of super disintegrants like Cross linked carboxy methyl cellulose (Croscarmeliose), Sodium starch glycolate (Primogel, Explotab), Poly vinyl pyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after administration and also suggested that immediate release formulations are similar to many sustained release formulations that are now commonly available.

Simone Schiermeier *et al*, [23] Investigate to check whether the **fast disintegrating tablets** disintegrate either rapidly in water, to form a stabilized suspension, or disperse instantaneously in the mouth to be swallowed without the aid of water. A direct compression method was used to prepare these two types of tablets containing coated ibuprofen as a high dosed model drug. The properties of the water dispersible tablet, such as porosity, hardness, disintegration time and increase in viscosity after dispersion, were investigated. And concluded, fast dispersible tablets with acceptable hardness and desirable taste could be prepared within the optimum region.

Nadia Passerinia *et al,* [24] studied the potential of waxes by preparing with the ultrasonic spray congealing technique micro particles for controlling the in vitro release of **Verapamil HCl** was investigated. The results of this study show that by selecting the type and the amount of the carriers, micro particles with a spherical shape and good encapsulation efficiency were observed. These particles showed a zero-order release for 8 h, without modifying the solid state properties of the drug. Therefore, waxy micro particles prepared by the ultrasonic spray congealing technique are promising solvent-free devices for controlling the release of Verapamil HCl.

Tamara Gonc¸ alves-Araújoa *et al*, [25] the objective of the present paper was to study the existence of critical points governing the water and drug transport inside HPMC hydrophilic matrix systems obtained with different polymer viscosity grades. For this purpose, extended release formulations of **Verapamil HCl**, have been prepared and studied. In order to estimate the percolation threshold, the behavior of the kinetic parameters with respect to the volumetric fraction of each component at time zero, was studied. From the point of the percolation theory, the optimum concentration for all the studied polymers, to obtain a hydrophilic matrix system for the controlled release of Verapamil HCl is higher than 20% (v/v) HPMC. Above 20% (v/v) HPMC, an infinite cluster of excipients would be formed, ensuring uniform hydration, maintaining integrity of the system and controlling the drug release.

L. Maggi *et al*, [26] Studied the evaluation of the stereo selective dissolution of (±) **Verapamil HCl**, a model racemic drug and, for this purpose, different matrix compositions, a commercial product and a particular delivery device have been considered. The delivery device, recently proposed for the delayed release of drugs, consists of an active core containing the drug, coated by compression with different types of chiral polymeric materials. The quantitative determination of Verapamil enantiomers released by these systems was carried out using a stereo specific HPLC method. Hydroxypropylmethylcellulose, [cyclodextrin, hydroxypropyl] - cyclodextrin and cross-linked amylose did not show any stereo selective dissolution properties while pectin, galactomannan and scleroglucan seemed to give a slightly higher dissolution rate of the R, compared with the S enantiomer. It is, however, to be

verified whether these small differences in the release rate of the two enantiomers detected 'in vitro' could lead to real *in-vivo* effects.

Müge Kılıçarslan *et al*, [27] prepared the microspheres containing **Verapamil hydrochloride** with Eudragit RS 100 by solvent evaporation method. And also with solvent evaporation method where one of the parameters which affects the formation and properties of the microspheres by the variations of drug/polymer ratios. And also the effects of this parameter on the VRP loaded microspheres. And reported that the variation in drug/polymer ratios might have an influence on the physical characteristics of the microspheres and the increasing amount of polymer might be result in decreased drug dissolve.

Emami J *et al,* [35] Studied about the controlled-release bucco adhesive tablets of **Verapamil hydrochloride** which were prepared in order to achieve constant plasma concentrations, to improve the bioavailability by the avoidance of hepatic first-pass metabolism, and to prevent frequent administration. The maximum bio adhesive strength was observed in tablets formulated with a combination of CP-Na CMC followed by CP-HPMC and Na CMC-HPMC. Decreasing the content of CP in CP-HPMC tablets or Na CMC in CP-Na CMC or Na CMC, HPMC systems resulted in decrease in detachment forces. Lower release rates were observed by lowering the content of CP in CP-HPMC containing formulations or Na CMC in tablets which contained CP-Na CMC or Na CMC-HPMC. The release behavior was non- Fickian controlled by a combination of diffusion and chain relaxation mechanisms and best fitted zero-order kinetics and concluded that the bucco adhesive VPH tablets containing 53% CP and 13.3% HPMC showed suitable release kinetics (n = 0.78, K_0 zero order release = 4.11 mg/h, MDT = 5.66 h) and adhesive properties and did not show any interaction between polymers and drug based on DCS scanning. This bucco adhesive system may be useful for buccal administration of VPH.

C. Ferrero *et al*, [11] Evaluated the efficiency of **croscarmellose sodium** (Ac-Di-Sol) in a direct compression formulation containing a poorly water soluble drug (albumin tan ate) at high dosage. Tablet properties evaluated were affected by both variables, while compression parameters were essentially dependent on applied pressure. The disintegration process was correlated with the densification behavior, analyzed by means of Heckel plots and force-displacement curves, and tablet

microstructure, measured by using a mercury porosimeter. The shortest disintegration time was found for mixtures more prone to plastic deformation and densification at same level of applied pressure. These mixtures also revealed a finer pore structure. However, mixtures with higher yield pressures (i.e. less prone to plastic deformation) showed longer disintegration times and coarse pore structure. The different rearrangement of disintegrant particles in powder mixture is suggested to explain the dominant effect of the disintegrant bonding mechanism presented at a given mixture composition. According to our results, consolidation mechanism and microstructure analysis should be performed while optimizing disintegration response in tablets formulated with a disintegrant mainly acting by swelling mechanism.

C. Patil *et al*, [12] developed an ODT of Lamotrigine which is a recognized drug for epilepsy, and evaluated the **effect of various super disintegrants** on its disintegration time and release profile was the prime objective of this research work. Tablets were prepared by direct compression technique using 3 different super disintegrants. Sodium starch glycolate, Croscarmellose sodium and Crosspovidone XL-10 were used as super disintegrants in combinations to achieve optimum release profile, disintegration time and hardness. The results of *in-vitro* disintegration time indicated that the tablets dispersed rapidly in mouth within 8 s. Dissolution study revealed release rate of drug from the tablets was comparable with marketed tablet formulation of Lamotrigine. It was concluded that super disintegrants addition technique is a useful method for preparing orally disintegrating tablets by direct compression method.

Kuno Y,Kojima M *et al,* [28] Carried a study to evaluate the **effect of lubricants** on the characteristics of orally disintegrating (OD) tablets manufactured using the phase transition of sugar alcohol. OD tablets were produced by direct compression method. The effect of the type of lubricant on the tablet characteristics was evaluated using magnesium stearate (Mg-St), sodium stearyl fumarate (SSF), and talc as lubricants and concluded that consequently, talc was demonstrated to be the most desirable lubricant for the preparation of OD tablets based on the principle of the phase transition of sugar alcohol.

Jennifer Wang *et al*, [8] reviewed the theoretical aspects and practical considerations of **lubrication in tablet compression**. Properties of the materials that

are often used as lubricants, such as magnesium stearate, in tablet dosage form were summarized. The manufacturing process factors that may affect tablet lubrication were discussed. As important as the lubricants in tablet formulations are, their presence can cause some changes to the tablet physical and chemical properties. Furthermore, a detailed review is provided on the methodologies used to characterize lubrication process during tablet compression with relevant process analytical technologies. Finally, the Quality-by-Design considerations for tablet formulation and process development in terms of lubrication are discussed.

Takeaki Uchimoto *et al*, [9] Studied the effect of glycerin fatty acid ester (Poem TR-FB) concentrations on the dissolution rate of acetaminophen (APAP), the dissolution and disintegration behaviors of APAP tablets formulated using various lubricants were examined. The change over time in the available surface area of APAP (S(t)), which is in direct contact with solvent, was also analyzed using these dissolution data. In the dissolution tests, a retarded dissolution of APAP was not observed with TR-FB, whereas **magnesium stearate** (Mg-St), which is widely used as a lubricant, retarded the dissolution. However, no significant difference in the disintegration time between the two lubricants was observed. With regard to the time course of the S(t), Mg-St at 0.1% gave a maximum surface area value at 9.19 min (peak time); however, the profiles for APAP with Mg-St at greater than 0.5% showed downward curvature indicating a gradual decrease in surface area over time. Conversely, with TR-FB, even when its concentration was increased, the S(t) profile for APAP had a maximum value that was more than twice that of APAP with that of 0.5–3.0% of Mg-St. Scanning electron microscopy (SEM) observations showed that the differences in the dissolution rate and S(t) patterns between Mg-St and TR-FB could be explained by differences in extensibility deriving from their morphology. Therefore, it was concluded that TR-FB does not cause retardation of drug dissolution and may prove to be a superior alternative lubricant to Mg-St.

Chandrasekhar R *et al,* [29] Made an attempt to **optimize FDT**s using a progressive three-stage approach. Which includes hardness; friability and disintegration time tests were performed on the formulations at each stage with concentrations between 2% and 5% w/w, and were formulated at each concentration as single and combination bloom strength gelatin using 75 and 225 BSGs. And

reported that the addition of carbopol 974P-NF resulted in the enhancement of viscosity with a compromise of the hardness of the tablet, whereas Pluronic F127 (6%) showed an increase in disintegration time and viscosity with retention of mechanical properties.

Rai V.K *et al,* [30] Developed a Raloxifene Hydrochloride **immediate release tablet** by wet granulation technique. In order to obtain the best, optimized product six different formulations with different filler, binder, disintegrant and lubricant were taken as variables. Weight variation, thickness, hardness, friability, disintegration time, in-vitro release and pharmaceutical assay were also studied as response variables. Andreported that sticking was observed when the formulation containing stearic acid and sodium stearyl fumerate. However in the remaining four formulation containing magnesium sterate, no sticking was observed. The formulation NP061 was selected as an optimized product because different physical properties and in-vitro release profile showed best comparable with reference product. Optimization has proven as an effective tool in product development.

AIM AND OBJECTIVE

3. AIM AND OBJECTIVE

Verapamil hydrochloride is a selective calcium channel blocker and is widely used as an anti hypertensive drug. An attempt was made to prepare a fast disintegraing tablet of Verapamil hydrochloride to reduce the lag time and provide faster onset of action to get quick relief from hypertension. A fast disintegrating tablet form would thus be advantageous as Verapamil hydrochloride is water soluble and its preparation into fast disintegrating form would render it to disintegrate rapidly and there by result in rapid absorption without any lag time.

The objective of the present work is to prepare fast disintegrating tablet of Verapamil hydrochloride by employing 2 factor 3 level (3^2) full factorial design with nine experimental runs. And also to derive a statistical models and evaluate the influence of crosscarmellose sodium (X1) as a super disintegrant and magnesium stearate (X2) as a lubricant and also to determine the disintegration time (Y1) and hardness (Y2) is affected by adjusting two parameters namely crosscarmellose sodium at concentration of 0, 15, 30 and magnesium stearate at concentration of 0, 10, 20 respectively in a fast disintegrating tablets.

PLAN OF WORK

4. PLAN OF WORK

The scheme of the proposed work is as follows:

- Construction of standard curve of Verapamil Hydrochloride.
- Compatibility studies of drug and excipients by FT-IR spectral studies.
- Preformulation studies
  - Angle of repose.
  - Determination of bulk density.
  - Determination of tapped density.
  - Compressibility index.
  - Hauser's ratio.
  - Drug content uniformity test.
- Fabrication of fast disintegrating tablets of Verapamil Hydrochloride.
- Evaluation of physical parameters of fast disintegrating tablets.
  - Thickness.
  - Hardness.
  - Friability.
  - Weight variation.
  - Drug content uniformity test.
- In-vitro drug release studies for fast disintegrating tablets of Verapamil hydro chloride.
  - In-vitro disintegration time.

- In-vitro dissolution studies.

- Optimization of the best formulation using 3^2 factorial design.

- Evaluation of optimized fast disintegrating tablets by using ANOVA.

PROFILES

5. PROFILES

5.1. DRUG PROFILE

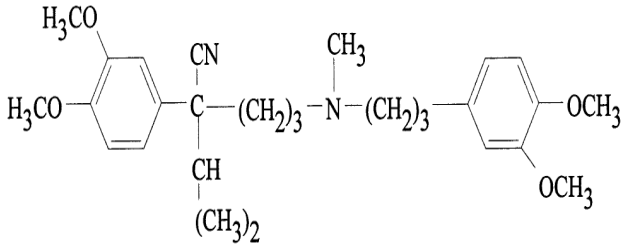
Verapamil hydrochloride

Category : Phenyl alkyl amine calcium channel blocking agent.

Empirical formula : $C_{27}H_{38}N_2O_4$ HCl

Molecular weight : 491.08

Chemical structure :



Chemical name : Benzeneacetonitrile, α [3-[[2(3,4dimethoxyphenyl) ethyl]methylamino]propyl]-3,4-dimethoxy-α-(1methylethyl) hydrochloride.

Melting point : 171ºC
pH : 5.0 - 6.5

Dosage and administration : Oral administration and contain 80mg of Verapamil Hydrochloride. [31]

Dosage form : Tablets, capsules
Description : White crystalline powder, practically odorless.
Solubility : Soluble in water, freely soluble in chloroform, sparingly Soluble in alcohol, Practically insoluble in ether.
Brands Available : Isoptin, Calaptin, Veramil.

Mechanism of action [32]

Verapamil hydrochloride exerts antihypertensive effects by inducing peripheral vasodilation and reducing peripheral vascular resistance usually without reflex tachycardia.

It is a calcium ion influx inhibitor that experts its pharmacological effects by modulating the influx of ionic calcium across the cell membrane of the arterial smooth muscle as well as in conductile and contractile myocardial cells.

Clinical uses [33]

- Verapamil hydrochloride is used to treat problems related to the heart and circulation. It is a calcium channel blocker.
- It works by relaxing and opening up the blood vessels, enabling blood to flow more freely around the body.

- Benefits of being on this drug include reduced blood pressure, a more regular heart rhythm and decreased likelihood of heart attack myocardial infarction in patients who had a previous heart attack.
- Mainly it is used for the treatment of hypertension and angina.
- It is used to control irregular heartbeats (arrhythmias).

Pharmacokinetics [34]

Absorption

The extent of oral absorption of Verapamil hydrochloride is more than 90%. Due to the rapid biotransformation of Verapamil hydrochloride during its first pass through the portal circulation, bioavailability ranges from 10 to 20%. Verapamil hydrochloride has non-linear pharmacokinetics because of its saturation kinetics (first pass metabolism) which leads to non-linear absorption.

Distribution

Verapamil HCl is widely distributed throughout body tissues; animal studies suggest that drug distribution to target organs and tissues is different with parenteral administration from that found after oral administration.

Metabolism

Verapamil undergoes extensive metabolism in the liver. Twelve metabolites have been identified in plasma, out of which only Nor verapamil was found in significant amount whereas other metabolites were in trace amounts. Nor Verapamil can reach steady-state plasma concentrations approximately equal to those of Verapamil HCl itself. The cardiovascular activity of nor Verapamil HCl appears to be approximately 20% that of Verapamil HCl.

Elimination [35]

Approximately 70 to 80% of an administered dose is excreted as metabolites in the urine and 16% or more in the feces. About 3 to 4% is excreted in the urine as unchanged drug.

Bioavailability **:** 10 to 20%.
Peak plasma concentration **:** 1-2 hours.
Biological half life : 4-6 hours.
Elimination half life **:** 2.8to 7.4 hours
Excretion **:** Urine
Volume of distribution **:** 2.4-6.2 L/Kg.

Drug interactions [36]

- **Aspirin:** In a few reported cases, co-administration of Verapamil HCl with aspirin has led to increased bleeding time greater than observed with aspirin alone.

- **Grapefruit juice**: The intake of grapefruit juice may increase drug levels of Verapamil HCl.

- **Digitalis**: Chronic Verapamil HCl treatment can increase serum digoxin levels by 50 to 75% during the first week of therapy, and this can result in digitalis toxicity. Maintenance and digitalization doses should be reduced when Verapamil HCl is administered, and the patient should be carefully monitored to avoid over or under digitalization.

- **Antihypertensive Agents**: Verapamil HCl administered concomitantly with oral antihypertensive agents (e.g., vasodilators, angiotensin-converting enzyme inhibitors, diuretics, beta blockers) will usually have an additive effect on lowering the blood pressure.

- **Quinidine:** concomitant use of Verapamil HCl and quinidine resulted in significant hypotension.

Adverse reactions [37]

- **Cardiovascular:** angina pectoris, atrio-ventricular dissociation, chest pain, myocardial infarction.

- **Digestive System:** diarrhea, dry mouth, gastrointestinal distress.

- **Nervous System**: cerebro vascular accident, confusion, insomnia, muscle cramps, psychotic symptoms,

- **Skin:** Arthralgia and rash, hair loss hyperkeratosis, sweating, urticaria.

- **Special Senses:** blurred vision, tinnitus.

- **Urogenital:** Gynecomastia, impotence, increased urination, spotty menstruation.

5.2. EXCIPIENT PROFILE

5.2.1. CROSSCARMELLOSE SODIUM

Non proprietary names

Bp : Carmellose sodium

Jp : Carmellose sodium

Ph Eur : Carmellose sodium

Usp : Carboxy methyl cellulose sodium

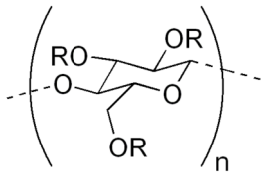
Synonyms : Sodium carboxy methyl cellulose; sodium CMC; ECG 505; Nymcel ZSC.

Chemical name : Cellulose, carboxy methyl ether.

Empirical formula : $C_4H_{12}NNao_7P_2 \bullet 3H_2O$

Molecular weight : 570.49 gms

Structural Formula :



R = H or CH_2CO_2H

Functional Category : Tablet and capsule disintegrant, stabilizing agent, suspending agent, viscosity Increasing agent and water absorbing agent.

Applications in Pharmaceutical Formulations

The main use of carboxy methyl cellulose sodium is in tablet formulations where it is used as a binder, diluent and disintegrant. Although carboxy methyl cellulose sodium is insoluble in water, it is an effective tablet disintegrant as it swells to several times its original bulk on contact with water. Concentration up to 15%w/w may be used in tablet formulations; above this concentration, tablet hardness is reduced.

Description : Carboxy methyl cellulose sodium occurs as a white to yellowish-white, hygroscopic, fine powder.

Typical Properties

Acidity/Alkalinity : pH =4.5-6.0 for a 1%w/w aqueous dispersion.

Solubility

Practically insoluble in acetone, chloroform, ethanol (95%), and ether. Insoluble in water, but swells to twice its volume to form a suspension. Insoluble in 0.1 mol/ Lit hydrochloric acid, but slightly soluble in 0.1mol/Lit sodium hydroxide.

Stability and Storage conditions : Carboxy methyl cellulose sodium is a stable, though hygroscopic material. It should be stored in a well closed container in a cool, dry place.

5.2.2. MAGNESIUM STERATE

Non proprietary names

Bp : Magnesium sterate

Jp : Magnesium sterate

Ph Eur : Magnesii stearas

Usp : Magnesium sterate

Synonyms : Magnesium octadecanote ; stearic acid Magnesium salt; octadecanoic acid, Magnesium salt.

Chemical name : Octadecanoic acid, magnesium salt

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

Molecular weight : 591.34

Structural Formula : $[CH_3 (CH_2)_{16}COO]_2 Mg$.

Functional Category : Tablet and Capsule lubricant.

Description

Magnesium sterate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste .The powder is greasy to the touch and readily adheres to the skin.

Typical Properties

Density (bulk) : 0.159 g/cm^3

Density (tapped) : 0.286g/cm^3

Density (true) : 1.092 g/cm^3

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

Applications in Pharmaceutical Formulations

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations .It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25-5.0%.It is also used in barrier creams.

Stability and Storage conditions **:** Magnesium stearate is stable and should Be Stored in a well-closed container in a cool and dry place.

Safety

Magnesium stearate is widely used as a pharmaceutical excipient and is generally regarded as being non toxic following oral administration. However oral consumption of large quantities may result in some laxative effect or mucosal irritation.

5.2.3. LACTOSE MONOHYDRATE

Non proprietary names

Bp **:** Lactose monohydrate

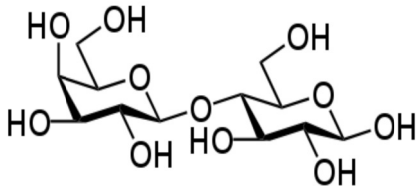
Jp **:** Lactose

Ph Eur **:** Lactose monohydricum

Usp **:** Lactose monohydrate

Chemical name **:** O-β-D-Galactopyranosyl-(1-4)-α-D-glucopyranose monohydrate

Structural Formula **:**



Empirical formula : $C_{12}H_{22}O_{11}.H_2O$
Molecular weight : 360.31
Functional Category : Binding agent, diluent for dry-powder Inhale tablet binder; tablet and capsule diluent.

Applications in Pharmaceutical Formulations

Lactose is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. Lactose is also used as a diluent in dry powder inhalation. Various lactose grades are commercially available that have different physical properties such as particle size distribution and flow characteristics.

Other applications of lactose include use in lyophilized products, where lactose is added to Freeze-dried solutions to increase plug size and aid cohesion. Lactose is also used in combination with sucrose (approximately 1:3) to prepare sugar coating solutions.

Direct compression grades of lactose monohydrate are available as granulated/agglomerated α-lactose mono hydrate, containing small amounts of anhydrous lactose.

Description

In the solid state ,Lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e.-Lactose mono hydrate-Lactose anhydrous, and stable α-Lactose anhydrous.

Typical Properties

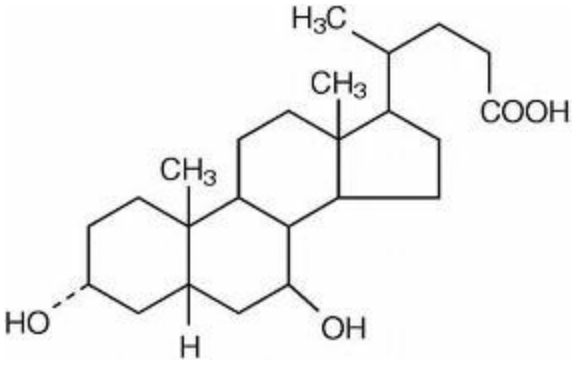
Angle of repose : 33^0 for pharmatose DCL 15; 32^0 for tablettose 70 and T tablettose 80.
Density (true) : 1.545 g/cm^3 (α-Lactose mono hydrate)
Melting point : 201-202^0c (for dehydrated α-Lactose mono hydrate)
Moisture content : Lactose mono hydrate contains approximately 5%w/w water of crystallization and range of 4.5-5.5% w/w water content.

5.2.4. MICROCRYSTALLINE CELLULOSE

Nonproprietary names

BP : Microcrystalline cellulose

USP : Microcrystalline cellulose
Synonyms : Avicel; cellulose gel; crystalline cellulose; E460; Emocel; Fibrocel; Tabulose; Vivacel.
Chemical Name : Cellulose
Chemical structure :



Empirical Formula : $(C_6H_{10}O_5)_n$
Molecular Weight : 36000
Functional category : Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant

Description

Micro crystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sized and moisture grades which have different properties and applications.

Applications in Pharmaceutical Formulations

Micro crystalline cellulose is widely used in pharmaceuticals, primarily as binder/diluents in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. In addition to its use as binder/diluents, micro crystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

5.2.5. MANNITOL

Non proprietary names

Bp : Mannitol

Jp : Mannitol

Ph Eur : Mannidex

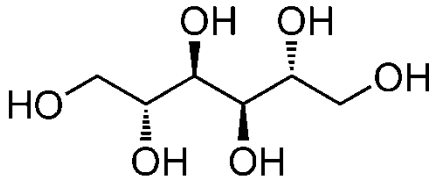
Usp : Manicol

Synonyms : Cordycepic Acid; E421; NCI-C50362; Manita; Manitol; Manna Sugar; Mannite; d-Mannitol; Mannitolum.

Empirical formula : $C_6H_{14}O_6$

Molecular weight : 182.2

Structural Formula :



Functional Category : Diluent for lyophilized preparations; Sweetening agent; tablet and capsule diluent; tonicity agent.

Description

A white odorless crystalline powder or granules with a sweet taste approximately as sweet as glucose and half as sweet as sucrose and imparts a cooling sensation in the mouth.

Typical Properties

Density (bulk)	**:** 0.7g/cm^3
Density (tapped)	**:** 0.8g/cm^3
Melting point	**:** 166° to 168°.
Solubility	**:** It is soluble in alkali and ethanol (95%) 1 in 83, and glycerin 1 in 18.Insoluble in ether.
Pharmaceutical Applications	**:** Tablet diluent-10-90%

Stability and Storage conditions

It is stable in the dry state and in aqueous solutions. The bulk material must be stored in well closed containers in a cool and dry place.

MATERIALS

6. MATERIALS

6.1. INGREDIENTS USED

Table 1: Ingredients used for the experiment

S. No	Name of the ingredient	Manufacturer/Suppliers
1.	Verapamil HCl	Micro labs, Hosur.
2.	Crosscarmellose Sodium	National chemie, Gujarath.
3.	Magnesium Sterate	Loba chemie pvt.ltd, Mumbai.
4.	Micro crystalline cellulose	E.Merck (India) limited, Mumbai.
5.	Lactose	Loba chemie pvt.ltd, Mumbai.
6.	Mannitol	Spectrum chemie, Cochin.

6.2. INSTRUMENTS USED

Table 2: Instruments used for the experiment

S.No	Name of the instrument	Manufacturing company
1.	Digital balance	Shimadzu ELB 300
2.	Tablet hardness tester	Monsanto tablet hardness tester
3.	Friability tester	Electro lab ET-2 friability test apparatus, India.
4.	Dissolution apparatus USP XXIII	veego tablet dissolution apparatus, Chennai.
5.	Double beam UV spectrophotometer	Perkin Elmer Lambda-25 UV/VIS spectrometer.
6.	Rotary tablet punching machine	Chamunda pharma machinery Pvt.ltd, Ahmadabad
7.	FT-IR spectrophotometer	Perkin Elmer spectrum RX1 FT-IR spectrophotometer.

METHODOLOGY

7. METHODOLOGY

7.1. PRE FORMULATION STUDIES

Pre formulation testing is an investigation of physical and chemical properties of drug substance alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form.

7.1.1. Compatibility studies (Fourier transform infrared spectroscopic studies)[38]

One of the requirement for the selection of suitable excipients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work a study was carried out by using FT-IR spectrophotometer to find out if there is any possible chemical interaction of Verapamil hydrochloride with magnesium stearate and crosscarmellose sodium.

Procedure

To study the compatibility of various formulation excipients with Verapamil hydrochloride solid admixtures were prepared by mixing the drug with each formulation excipients separately in the ratio of 1:1 and stored in air tight containers at 30 ± 2^0 /65±5% RH. The solid admixtures were characterized using Fourier transform infrared spectroscopy (FT-IR).

7.1.2. Construction of standard curve for Verapamil hydrochloride

Verapamil hydrochloride can be estimated spectrophotometrically at 279 nm as it obeys Beer's-Lambert's law limit in the range of 5-30 µg/ml.

Preparation of reagents

Preparation of 0.1 N HCl

Dissolve 8.5 ml of concentrated HCl in 1000 ml of distilled water.

Preparation of standard drug solution

Stock solution

100 mg of Verapamil hydrochloride was dissolved in 100 ml of 0.1 N HCl, to get a solution of 1000 µg/ml concentration.

Standard solution

10 ml of stock solution was made to 100 ml with 0.1 N HCl thus giving a concentration of 100 µg/ml. Aliquot of standard drug solution ranging from 0.5 ml, 1 ml, 1.5 ml, 2 ml and 2.5 ml were transferred into 10 ml volumetric flask and were diluted up to the mark with 0.1 N HCl. Thus the final concentration ranges from 5-25 µg/ml. Absorbance of each solution was measured at 279 nm against 0.1 N HCl as a blank. A plot of concentrations of drug versus absorbance was plotted.

7.1.3. Characterization of Powder [39]

Prior to compression, blend was evaluated for their characteristic parameters such as:

i. Angle of repose
ii. Bulk density
iii. Hauser's Factor
iv. Compressibility Index

i). Angle of repose

The angle of repose of granules, was determined by the fixed funnel and freestanding cone method, where by accurately weighed blend (5gm) were carefully poured through the funnel with its tip at 2 cm height (h) until the apex of the conical heap so formed just reached the tip of the funnel. The mean diameter (r), of the base for powder cone was measured and angle of repose (θ) was calculated using the following equation.

$$\mathbf{Tan\ \theta = h/r}$$

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

Where, θ =Angle of repose

h=Height

r=Radius

Table 3: USP official limits of angle of repose

Angle of repose (degrees)	Flow
25-30	Excellent
31-35	Good
36-40	Fair
41-45	Passable
46-55	Poor
56-65	Very poor
>66	Very, very poor

ii). Bulk density

Both loose bulk density and tapped bulk density were determined, where by a quantity (20gm) of blend from each formula, previously lightly shaken to break any agglomerates in cylinder. After the initial volume was observed, the cylinder was allowed to full under its own weight onto have a surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in the volume was noted loose bulk density (LBD) and tapped bulk density (TBD) were calculated using the following formulas.

LBW=Weight of the powder/volume of the packing

TBW=Weight of the powder/tapped volume of the packing

iii). Hauser's Ratio

It indicates the flow properties of the powder and it measured by the ratio of TD to the BD

Hauser's Ratio=TD/BD

Table 4: USP official limits of Hauser's ratio

Hauser's Ratio	property
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very very poor

1v). Compressibility index

To analyze flow ability, the Carr's index was calculated on the basis of the LBD and TBD. The compressibility index of the blend was determined by Carr's index.

Carr's index (%) = 100 [TD-BD/TBD]

Table 5: USP official limits of compressibility index

% Carr 's index	properties
<10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very very poor

7.2. FABRICATION OF FAST DISINTEGRATING TABLETS

Direct compression method [40]

The composition of fast disintegrating tablet of Verapamil hydrochloride is showed in table no-6. Weighed quantities of Verapamil hydrochloride along with appropriate concentration of Crosscarmellose sodium, Lactose, Micro crystalline cellulose, and Mannitol were weighed and sieved through sieve no:40 and mixed in geometric proportion in a dry and clean mortar for about 25 minutes. Then Magnesium stearate was added after passing the above blend through sieve no: 60 and mixed well for 2 minutes.

The above lubricated blend was compressed into tablets using 8 mm single tablet punching machine. Then the fabricated tablets were evaluated for thickness, hardness, friability, weight variation test, drug content uniformity, *In-vitro* disintegration time and *In-vitro* dissolution studies.

Table 6: Composition of Fast Disintegrating Tablet

Formulation code	Drug (mg)	Crosscarmellose sodium(mg)	Magnesium sterate(mg)	Lactose (mg)	Micro crystalline cellulose(mg)	Mannitol (mg)
F1	80	0	0	10	20	90
F2	80	5	5	10	20	80
F3	80	10	10	10	20	70
F4	80	20	15	10	20	65
F5	80	30	20	10	20	40
F6	80	10	0	10	20	80
F7	80	15	10	10	20	65
F8	80	0	5	10	20	85
F9	80	30	10	10	20	50

7.3. PHYSICOCHEMICAL EVALUATION OF FAST DISINTEGRATING TABLETS

The properties of the fast disintegrating-tablets such as Hardness, Friability, Weight variation & drug content uniformity were studied.

7.3.1. Thickness

The thickness of the tablets was determined by using a Vernier calipers, mean and SD was calculated.

7.3.2. Hardness test

For each formulation, the hardness of 3 tablets were determined by using a Monsanto hardness tester, mean and SD were calculated.

7.3.3. Friability test

For each formulation, 6 tablets were weighed. The tablets were placed in a friabilator (Roche friabilator) and subjected to 25 rpm in 4 minutes. The tablets were

de dusted and reweighed. The friability was calculated as the percentage of weight loss.

$$F=100(1-W_o/W_t)$$

Where,

W_o = Weight of tablets before friability test

W_t = Weight of tablets after friability test

7.3.4. Weight variation test

To study weight variation, of tablet of each formulation were weighed using an electronic balance and the test was performed according to the USP official limits of percentage deviation of tablet are presented in the table no 7.

$$\%\text{Maximum positive deviation} = (W_H - A/A) \times 100$$

$$\%\text{Minimum negative deviation} = (A - W_L/A) \times 100$$

Where, W_H= Highest weight in mg

W_L= Lowest weight in mg

A= Average weight of tablet in mg

Table 7: USP official limits of weight variation test

Average weight of tablet (mg)	**Maximum percentage difference allowed**
130 or less	10
130-324	7.5
More than 324	5

7.3.5. Drug content uniformity

Standard preparation

An accurately weighed amount of pure Verapamil hydrochloride (100 mg) was taken and transferred into 100 ml volumetric flask. It was dissolved and made up to volume with 0.1 N HCl and absorbance was measured at 279 nm.

Sample preparation

Tablets were weighed individually then placed in a mortar and powdered with a pestle. An amount of powdered Verapamil hydrochloride (100 mg) was extracted in 0.1 N HCl. The absorbance was measured at 279 nm after suitable dilution.

Calculation

The amount of Verapamil hydrochloride present in tablet can be calculated using the formula

$$\mathbf{A_t/A_sXS_w/100X100/S_tXA_v}$$

Where,

A_t=Absorbance of sample preparation

A_s=Absorbance of standard preparation

S_w=Weight of Verapamil hydrochloride working standard

S_t=Weight of Verapamil hydrochloride tablet (mg)

A_v=Average weight of tablet (mg)

7.4. *IN-VITRO* DRUG RELEASE STUDIES

In-Vitro disintegration time [41]

The disintegration time of the tablets was determined as per Indian pharmacopoeial monograph. The test was carried out using tablet disintegration apparatus.

Six tablets from each batch were placed and one liter of distilled water was used as the disintegration medium. The time required to obtain complete disintegration of all the six tablets were noted.

In-Vitro Dissolution time [42]

Medium : 0.1 N HCl (pH 1.2)

Apparatus : USP, XXIII-type 2 (Paddle)

RPM : 30

Temperature: 37° ±0.5° C

Volume : 900 ml

Procedure

The release of Verapamil hydrochloride from the compressed fast disintegrating tablets were studied up to 20 minutes in 900 ml of 0.1 N HCl (pH 1.2) as dissolution medium using a USP dissolution paddle assembly at 30 rpm and 37° ±0.5° C. An aliquot (1 ml) was withdrawn at periodic intervals of 1st, 2nd, 4th, 6th, 8th, 10th, 15th and 20th minutes and diluted to 10 ml with the dissolution medium, and drug content was determined by UV-Visible spectrophotometer at 279 nm. An equal volume of fresh dissolution medium was replaced to maintain the dissolution volume.

Dissolution studies were performed 3 times for a period of 20 minutes and the mean value was taken. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

7.5 Statistical Optimization Technique [43]

The optimization was designed statistically using 3^2 factorial design. A 3-level full-factorial design consists of 9 full-factorial design points; according to the model, 9 experiments were conducted in total. This design generally involves dependent variable Y and independent or controlled variable X. The 2 independent formulation variables are Y1, Y2 and the 2 dependent formulation variables are X1, X2 are selected.

For this study X_1, crosscarmellose sodium and X_2 magnesium stearate were selected. The levels of independent variables are shown in Table 8. The dependent variables were Y_1, disintegration time andY2, hardness was shown in Table 9.

The results obtained from the experiment were statistically analyzed for response variables by using Design Expert 8.07 version (Stat-Ease Inc., Minneapolis, Minnesota). The statistical model incorporating interactive and polynomial terms was used to evaluate the response. [44]

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1X1 + b_{22}X_2X$$

Thus the optimized formulation is prepared and evaluated for its disintegration time and hardness characteristics.

STATISTICAL OPTIMIZATION

Table 8: Independent Variables [45]

Code	**Variables**	**Low level (-1)**	**Medium Level (0)**	**High Level (+1)**
X_1	Crosscarmellose sodium	0	15	30
X_2	Magnesium Stearate	0	10	20

Table 9: Dependant / Response Variables [6]

Code	Dependent Variables
Y1	Disintegration Time
Y2	Hardness

Table 10: Composition of Fast Disintegrating Tablet of Verapamil HCl as Per 3^2 Factorial Design

Formulation code	Drug (mg)	Crosscarmellose sodium(mg)	Magnesium sterate(mg)	Lactose (mg)	Micro crystalline cellulose(mg)	Mannitol (mg)
Ff1	80	0	0	10	20	90
Ff2	80	0	10	10	20	80
Ff3	80	0	20	10	20	70
Ff4	80	15	0	10	20	75
Ff5	80	15	10	10	20	65
Ff6	80	15	20	10	20	55
Ff7	80	30	0	10	20	60
Ff8	80	30	10	10	20	50
Ff9	80	30	20	10	20	40

RESULTS

8. RESULTS

8.1. PREFORMULATION STUDIES

8.1.1. Compatibility studies (Fourier transform infrared spectroscopic studies)

Compatibility studies were performed using FTIR spectrophotometer. The spectrum of pure drug and physical mixture of drug and excipients were studied.

The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components. The spectra for all formulations were shown in Fig 1 to Fig 4.

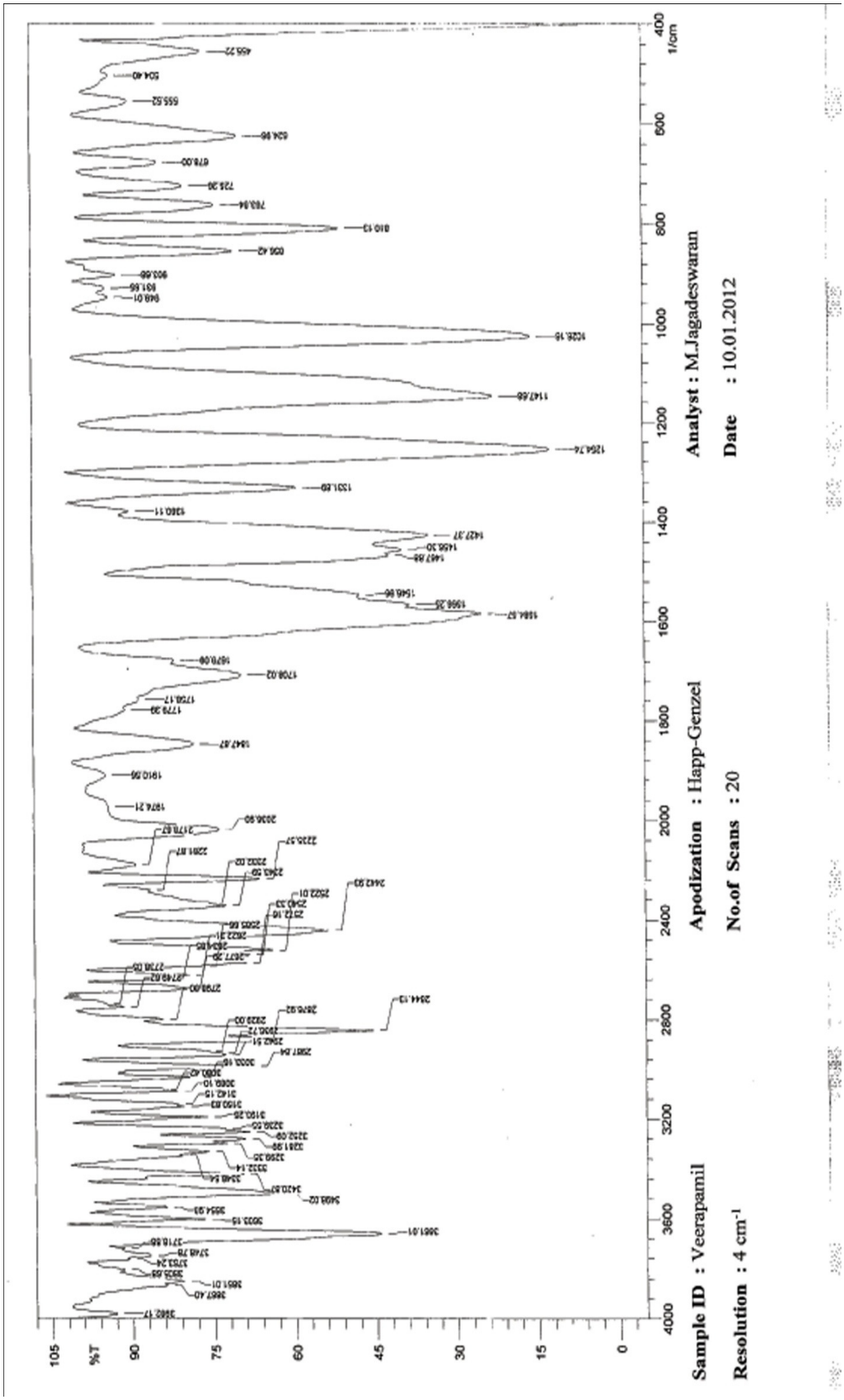


Fig 1: FT-IR Spectrum of Verapamil HCL

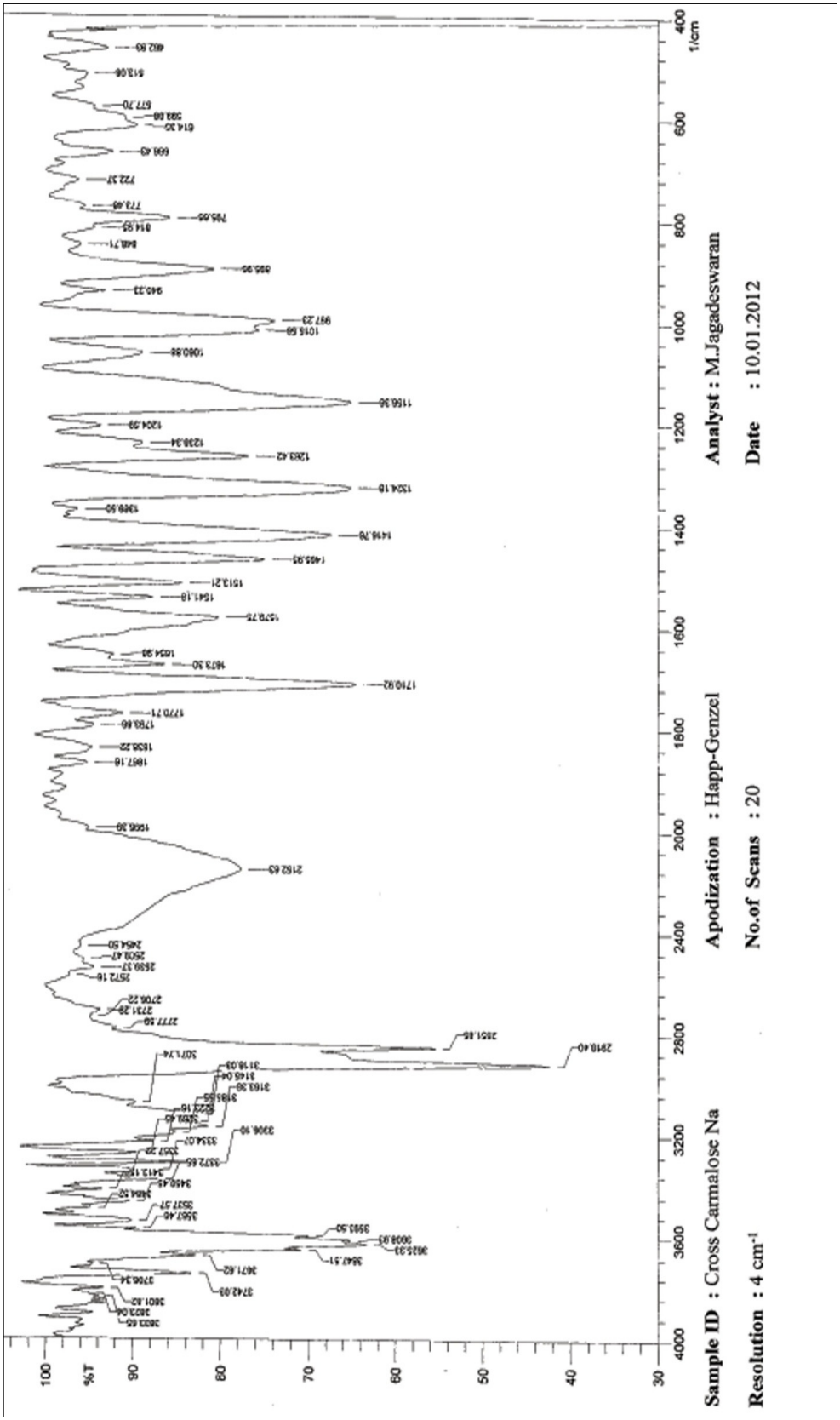


Fig 2: FT-IR Spectrum of Crosscarmellose Sodium

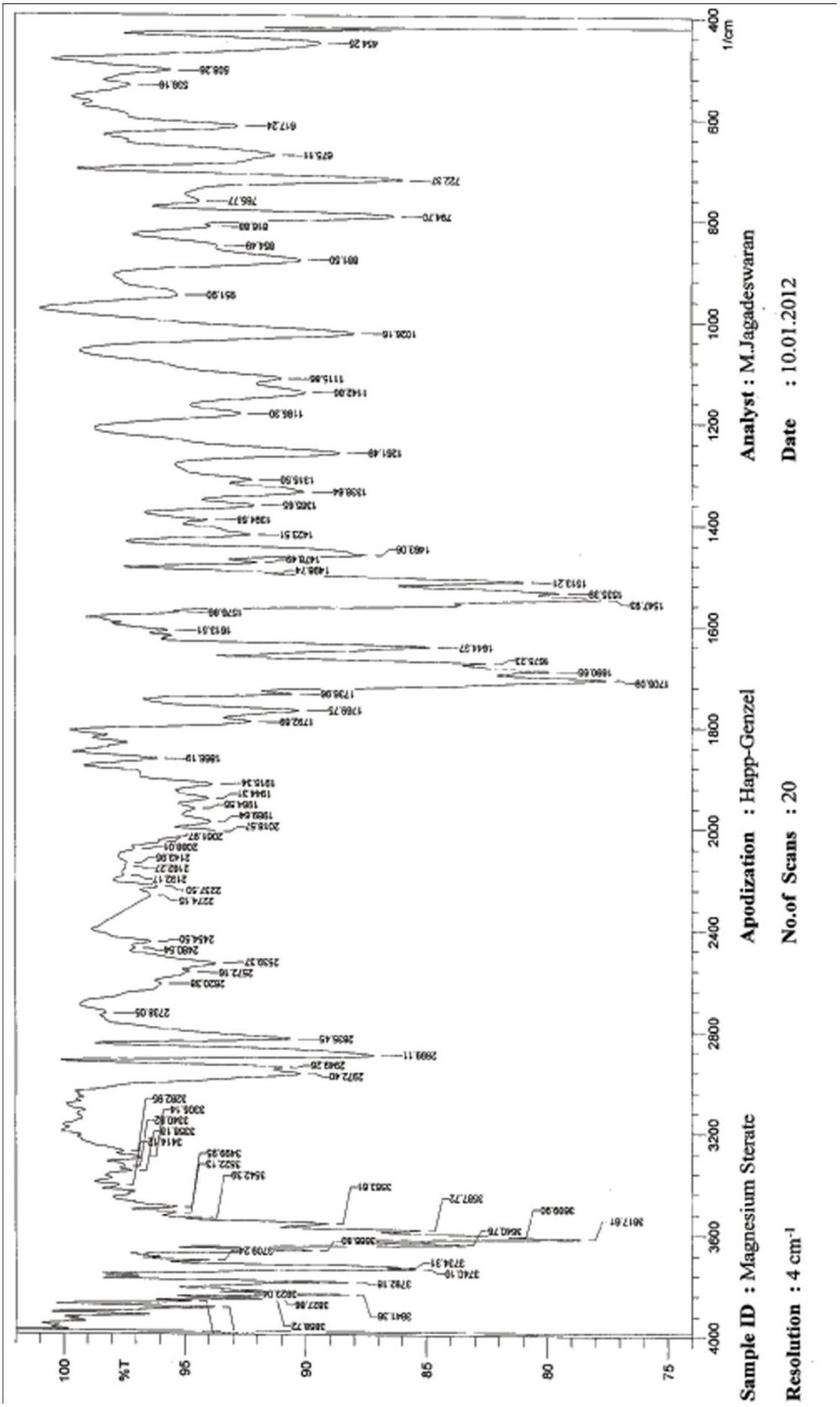


Fig 3: FT-IR Spectrum of Magnesium Sterate

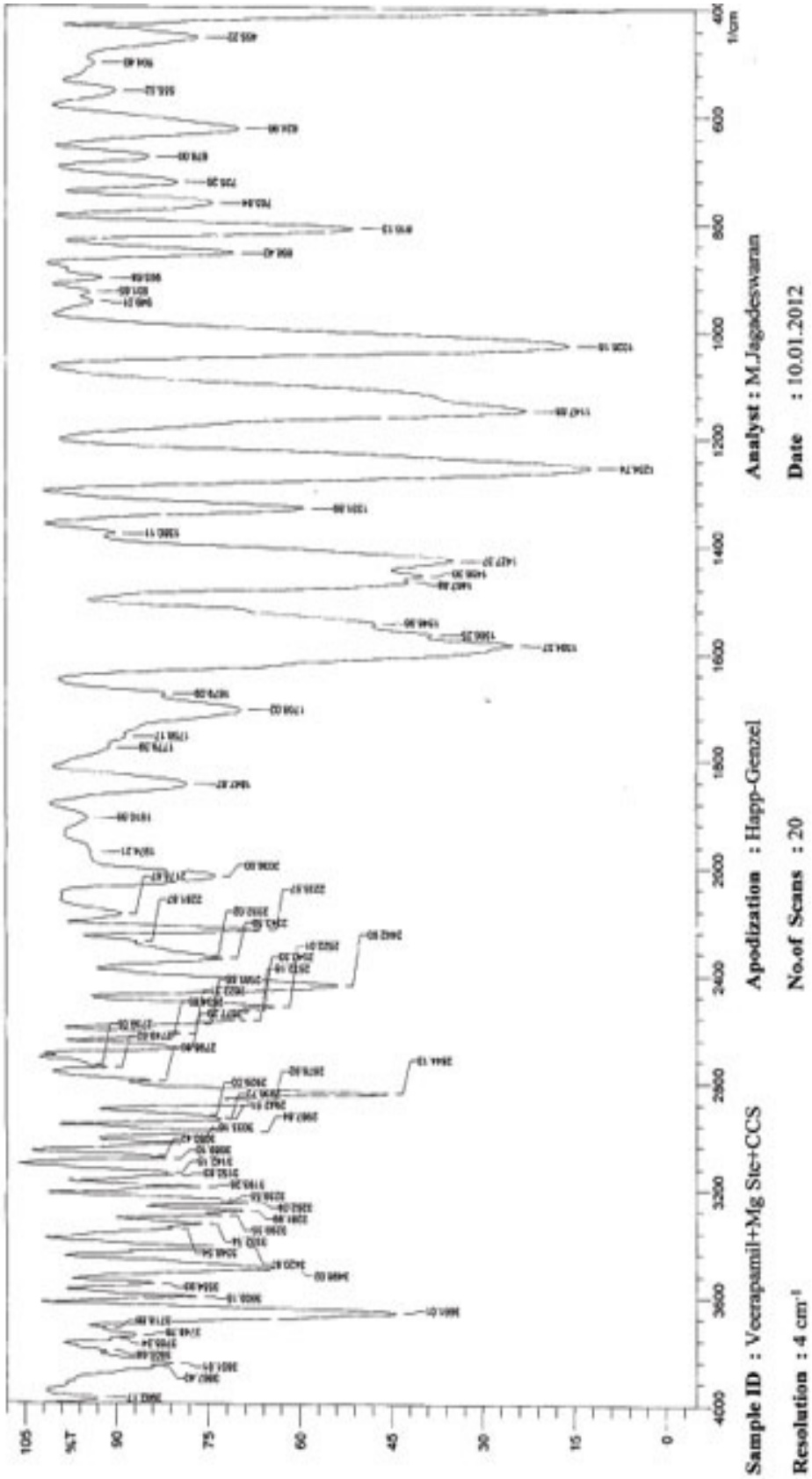


Fig 4: FT-IR Spectrum of Verapamil HCL + CCS + Mg.Sterate

8.1.2. Standard curve of Verapamil hydrochloride

The standard curve of Verapamil hydrochloride was determined in 0.1 N HCl (pH 1.2) by using UV-Visible spectrophotometer at 279 nm. Graph was plotted by taking absorbance (nm) on X-axis verses concentration (µg/ml) on Y-axis and it is follows the Beer's law. The results were shown in table 11.

Table 11: Standard curve results of Verapamil hydrochloride in 0.1N HCl

Concentration (µg/ml)	Absorbance (nm)
0	0
5	0.140
10	0.299
15	0.441
20	0.570
25	0.710
30	0.820
Slope	0.029
R^2	0.998

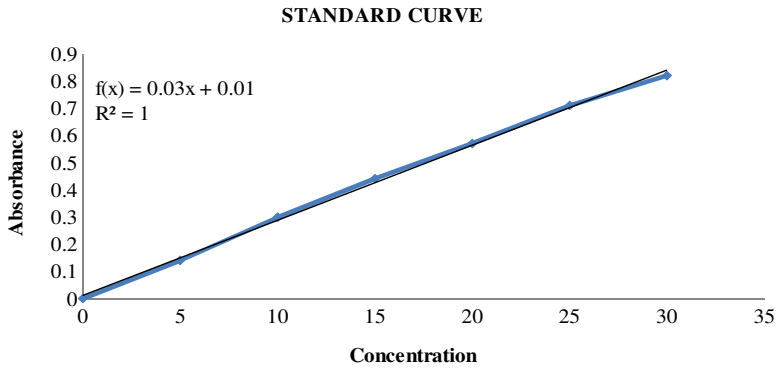


Fig 5: Standard curve results of Verapamil hydrochloride in 0.1N HCl

8.1.3. Powder Characterization

The blended powder of different formulations was evaluated for angle of repose, bulk density, tapped density, compressibility index and Hauser's ratio. The results of these evaluations are as follows.

Angle of repose (ɵ)

The angle of repose for the blended was shown in the table 12. The entire formulation blend was found to be in the range 21^0.62'±1.030 to 26^0 .05'±2.847. Thus it indicating that the angle of repose of the formulated blend is within pharmacopeial limits.

Bulk density and tapped density

Bulk and tapped densities are used for the measurements of compressibility index are shown in the table 13. The bulk density and tapped density ranged from 0.69±0.011 to 0.76±0.025 and 0.76±0.020 to 0.88±0.026.

Compressibility index (Carr's index)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. The values are shown in the table 13. The compressibility index is in the range from 5.99±0.588 to 15.22±2.473.

Hauser's ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density. The Hauser's ratio range from are shown in the table 13.The values are in the range from 1.05±0.005 to 1.18±0.037.

Table 12: Angle of repose (θ) of all formulations

Formulation code	Height* (cm)	Radius* (cm)	h/r*	θ =tan^{-1}(h/r) *
F1	1.51±0.020	3.06±0.251	0.48±0.030	25.93±1.409
F2	1.54±0.020	3.30±0.200	0.46±0.027	24.69±0.950
F3	1.50±0.015	3.76±0.152	0.39±0.062	21.62±1.030
F4	1.52±0.011	3.62±0.208	0.42±0.079	22.77±0.970
F5	1.62±0.025	3.33±0.407	0.49±0.060	26.05±2.847
F6	1.58±0.011	3.47±0.293	0.45±0.035	24.52±1.665
F7	1.51±0.026	3.73±0.152	0.40±0.015	21.96±0.752
F8	1.52±0.015	3.43±0.416	0.44±0.047	23.88±2.283
F9	1.50±0.015	3.43±0.351	0.43±0.045	23.56±2.176

*Each value represents the mean ± S.D. of three experiments.

Table 13: Preformulation evaluation of all formulations

Formulation code	Bulk Density*	Tapped Density*	Hauser's Ratio*	Carr's Index*
F1	0.73±0.025	0.79±0.035	1.08±0.010	7.41±0.275
F2	0.72±0.015	0.84±0.023	1.16±0.041	14.28±2.680
F3	0.76±0.025	0.88±0.026	1.15±0.030	13.63±1.660
F4	0.74±0.017	0.88±0.049	1.18±0.037	15.22±2.473
F5	0.70±0.025	0.76±0.020	1.08±0.021	8.44±1.071
F6	0.73±0.015	0.78±0.017	1.05±0.005	5.99±0.588
F7	0.72±0.025	0.80±0.042	1.11±0.025	10.27±1.834
F8	0.69±0.011	0.83±0.024	1.06±0.219	17.00±1.856
F9	0.74±0.020	0.82±0.043	1.10±0.064	9.75±1.869

*Each value represents the mean ±S.D. of three experiments

8.2. PHYSICAL EVALUATION PARAMETERS OF FAST DISINTEGRATING TABLETS

Verapamil hydrochloride fast disintegrating tablets were evaluated for various physical parameters namely thickness, hardness, friability, weight variation, wetting time and uniformity of drug content etc.

8.2.1. Hardness and Thickness Test

The hardness of different formulations is ranged from 3.2±0.145 Kg/cm^2 to 5.4±0.350 Kg/cm^2 as shown in the table 14.

The thicknesses of the tablets are ranged from 3.6±0.012 mm to 3.6±0.068 mm as shown in the table 14.

Table 14: Hardness and Thickness of the Tablets

Formulation code	Hardness of the tablet (kg/cm^2)*	Thickness of the tablet (mm)*
F1	5.4±0.350	3.6±0.068
F2	5.3±0.36	3.7±0.040
F3	4.9±0.510	3.6±0.015
F4	4.6±0.05	3.6±0.008
F5	3.2±0.145	3.6±0.012
F6	4.4±0.195	3.6±0.010
F7	4.5±0.095	3.5±0.018
F8	5.3±0.090	3.6±0.008
F9	4.3±0.141	3.6±0.008

*Each value represents the mean ±S.D. of three experiments

8.2.2. Friability test

Depending upon the ingredients of different formulations, the weight of tablet was fixed. In each formulation, weight variation was within limit. Mostly the variation was within ± 1%. All the formulations exhibited less than 1% friability which was within the limit.

Table 15: Friability data of the tablets

Formulation code	Weight of 10 tablets before test	Weight of 10 tablets after test	Friability F=100(1-w0/wt)
F1	1.994	1.990	0.412
F2	1.987	1.983	0.226
F3	1.992	1.989	0.313
F4	1.972	1.968	0.212
F5	1.967	1.962	0.251
F6	1.951	1.946	0.256
F7	1.996	1.992	0.413
F8	2.010	2.005	0.249
F9	1.981	1.976	0.234

8.2.3. Weight variation test

The percentage weight variations for all formulations are performed. Both the formulations passed weight variation test as per the pharmacopial limits of 5% as shown in the table 16.

Table 16: Weight variation test of the tablets

S.NO	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	199.2	200.3	198.4	199.2	198.6	200.7	198.2	200.3	198.8
2	198.4	202.2	198.5	198.5	199.4	200.5	198.5	199.7	198.7
3	198.6	199.4	201.4	198.3	199.5	201.8	198.6	198.7	199.7
4	198.9	198.9	198.4	198.5	198.6	199.6	199.6	198.5	198.5
5	197.4	200.9	198.2	199.2	199.2	199.5	201.2	198.5	202.5
6	198.3	199.4	199.5	198.5	198.4	199.9	198.4	200.4	199.8
7	199.3	200.2	199.7	198.4	198.7	202.6	199.5	198.3	202.3
8	200.2	198.9	198.6	200.4	198.5	199.8	198.3	198.6	197.6
9	197.6	199.2	197.9	199.4	200.2	201.4	199.6	201.7	202.3
10	198.9	199.4	201.0	198.6	200.6	199.2	199.4	200.3	199.8
11	198.3	199.9	200.4	198.7	198.2	202.7	200.3	201.7	198.5
12	198.6	201.4	200.3	199.2	198.5	199.6	198.5	198.6	199.4
13	201.4	199.6	198.9	199.3	198.6	201.5	202.5	198.6	199.9
14	198.8	198.4	196.4	196.9	200.3	202.4	200.4	202.3	198.7
15	198.2	196.6	199.2	198.1	200.5	201.3	200.2	202.1	201.4
16	200.4	199.5	198.9	199.5	198.4	199.7	198.4	198.6	201.7
17	201.2	198.2	198.6	201.8	198.9	199.4	198.7	199.6	199.5
18	199.6	198.7	198.7	199.3	199.3	199.6	199.4	199.4	199.3
19	198.9	198.2	199.3	198.7	199.7	198.9	199.6	199.3	198.7
20	200.4	199.7	201.5	199.7	198.9	199.7	198.9	198.7	198.8
Avg. Weight*	199.1	199.4	199.1	199.0	199.1	200.4	199.4	199.6	199.7
Mean	1.100	1.228	1.253	0.977	0.759	1.215	1.102	1.331	1.457
%Max. positive deviation	1.15	1.00	1.20	1.40	0.75	1.13	1.55	1.35	1.40
%Min. negative deviation	0.85	1.40	1.35	1.05	0.45	0.74	0.60	0.55	0.60

8.2.4. Drug content uniformity

The content uniformity test for Verapamil hydrochloride was carried out. The results were found to be 98.64±0.402 to 99.49±0.199.The results were found to be within the USP specification limits (90% - 110%). It shows that the drug was distributed uniformly throughout the tablets is shown in table 17.

Table 17: Drug content uniformity of the tablets

Formulation Code	Drug content analysis*	No. of tablets outside 90% to 110% limit
F1	98.64±0.402	NIL
F2	98.89±0.277	NIL
F3	99.33±0.42	NIL
F4	99.48±0.350	NIL
F5	98.99±0.327	NIL
F6	98.89±0.278	NIL
F7	99.49±0.199	NIL
F8	99.24±0.188	NIL
F9	99.31±0.277	NIL

*Each value represents the mean ±S.D. of three experiments

8.3. IN VITRO DRUG RELEASE CHARACTERISTICS

8.3.1. In-Vitro disintegration time data of the tablets

The *In-Vitro* disintegration time was in the range of 20.36±0.550 to 248.23±0.13.

Table 18: *In-vitro* disintegration time of tablets

Formulation Code	In-vitro disintegration time(sec)*
F1	248.23±0.13
F2	66.08±0.18
F3	44.83±0.21
F4	39.76±0.04
F5	20.36±0.550
F6	33.06±0.80
F7	38.46±0.901
F8	162.10±0.14
F9	28.08±0.22

*Each value is mean ± SD of three determinations

8.3.2. *IN VITRO* DRUG RELEASE FOR FAST DISINTEGRATING TABLETS OF VERAPAMIL HYDROCHLORIDE

The fast disintegrating tablets were prepared by using super disintegrant, lubricant and *in vitro* drug release studies were carried out in trial (n=3) basis for total nine formulations (F1-F9).

The release of Verapamil hydrochloride from the fast disintegrating tablets were studied in 900 ml of 0.1 N HCl for 20 min by using USP XXIII paddle dissolution apparatus at 50 rpm and $37^0 \pm 0.5^0$ C. Drug content was determined by UV-Visible spectrophotometer at 279 nm. Cumulative percentage of drug release was calculated by using an equation obtained from a standard curve. The dissolution studies were performed 3 times for a period of 20 min and mean values were calculated by one way ANOVA in Graph pad software package. The results of these studies were shown in table 19 to 28.

Table 19: Dissolution profile of formulation F1

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.099	3.694	33.24	41.56±0.409
2	0.113	4.200	37.80	47.26±1.244
4	0.126	4.685	42.16	52.71±2.407
6	0.142	5.293	47.64	59.55±1.141
8	0.154	5.721	51.49	64.37±1.009
10	0.181	6.709	60.38	75.48±0.924
15	0.209	7.756	69.80	87.26±1.176
20	0.229	8.488	76.39	95.49±0.402

*Each value represents the mean ±S.D. of three experiments.

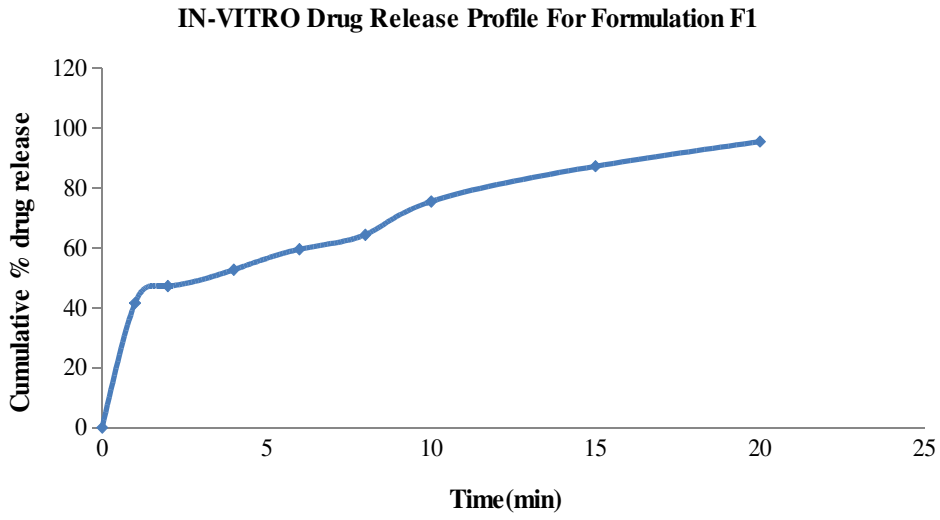


Fig: 6

Table 20: Dissolution profile of formulation F2

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.113	4.203	37.83	47.29±0.566
2	0.131	4.857	43.72	54.65±0.945
4	0.162	6.028	54.25	67.82±1.260
6	0.178	6.605	59.44	74.31±0.843
8	0.197	7.321	65.89	82.37±1.636
10	0.229	8.500	76.50	95.63±1.114

*Each value represents the mean ±S.D. of three experiments.

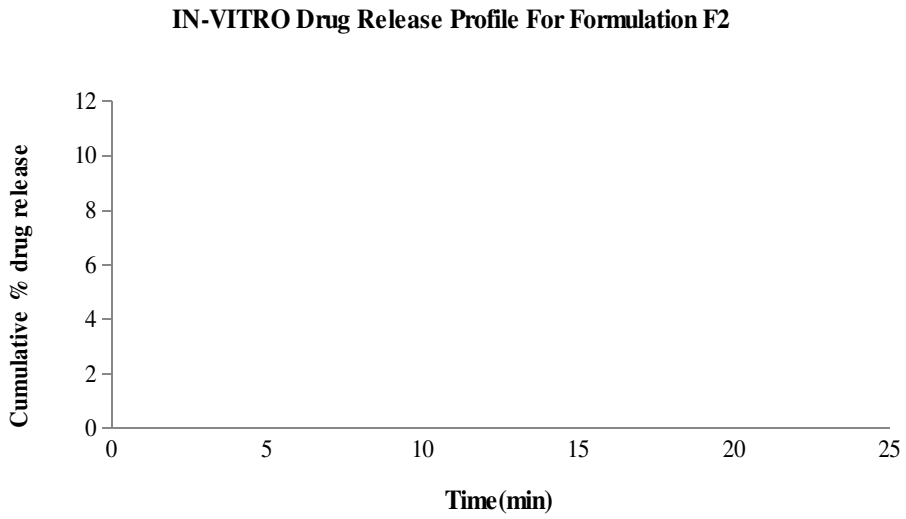


Fig: 7

Table 21: Dissolution profile of formulation F3

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.110	4.254	38.28	47.86±0.930
2	0.128	4.748	42.73	53.42±0.778
4	0.163	6.070	54.63	68.29±0.621
6	0.179	6.661	59.95	74.94±0.916
8	0.199	7.392	66.52	83.16±0.597
10	0.230	8.525	76.72	95.91±0.883

*Each value represents the mean S.D. of three experiments.

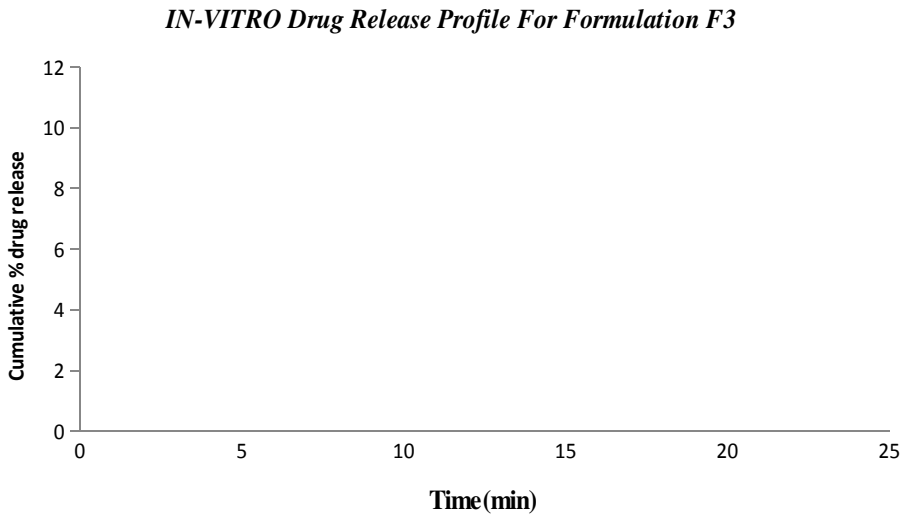


Fig: 8

Table 22: Dissolution profile of formulation F4

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.117	4.353	39.18	48.98±0.690
2	0.133	4.932	44.39	55.49±0.463
4	0.165	6.139	55.25	69.07±1.460
6	0.181	6.736	60.63	75.79±0.535
8	0.203	7.547	67.92	84.91±0.623
10	0.231	8.559	77.03	96.29±0.931

*Each value represents the mean ±S.D. of three experiments.

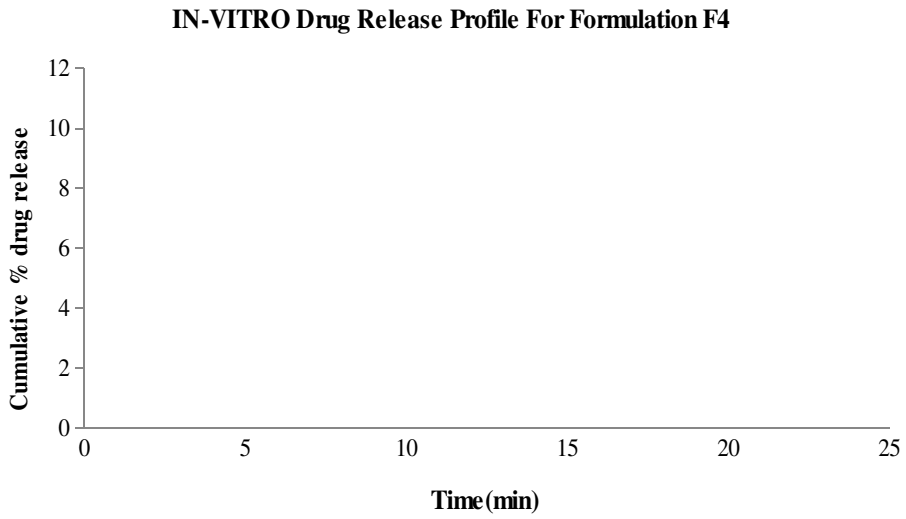


Fig: 9

Table 23: Dissolution profile of formulation F5

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.127	4.705	42.35	52.94±0.916
2	0.148	5.495	49.45	61.82±0.880
4	0.183	6.785	61.07	76.34±0.778
6	0.202	7.489	67.40	84.26±0.196
8	0.220	8.172	73.55	91.94±0.216
10	0.237	8.792	79.13	98.92±0.903

*Each value represents the mean ±S.D. of three experiments.

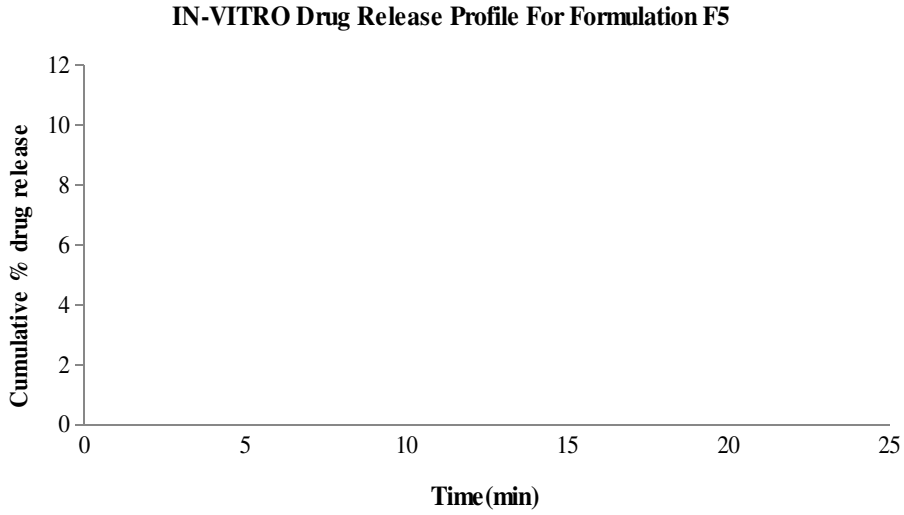


Fig: 10

Table 24: Dissolution profile of formulation F6

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.121	4.505	40.55	50.69±0.877
2	0.140	5.211	46.90	58.63±0.195
4	0.171	6.336	57.03	71.29±0.093
6	0.187	6.934	62.40	78.01±0.624
8	0.208	7.720	69.48	86.85±0.187
10	0.232	8.625	77.63	97.04±0.787

*Each value represents the mean ±S.D. of three experiments.

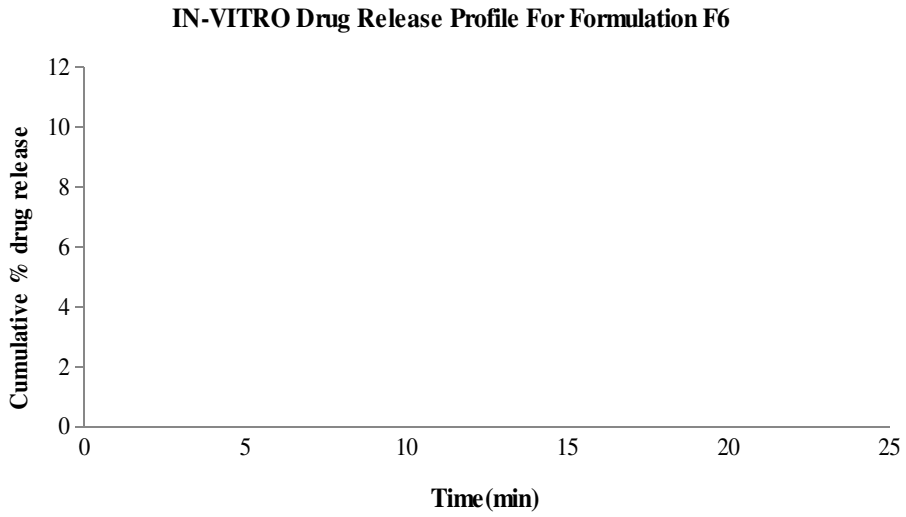


Fig: 11

Table 25: Dissolution profile of formulation F7

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.117	4.359	39.23	49.04±1.286
2	0.136	5.039	45.35	56.69±1.002
4	0.167	6.202	55.82	69.78±1.047
6	0.183	6.799	61.19	76.49±0.594
8	0.206	7.640	68.76	85.96±2.113
10	0.232	8.605	77.44	96.81±1.041

*Each value represents the mean ±S.D. of three experiments.

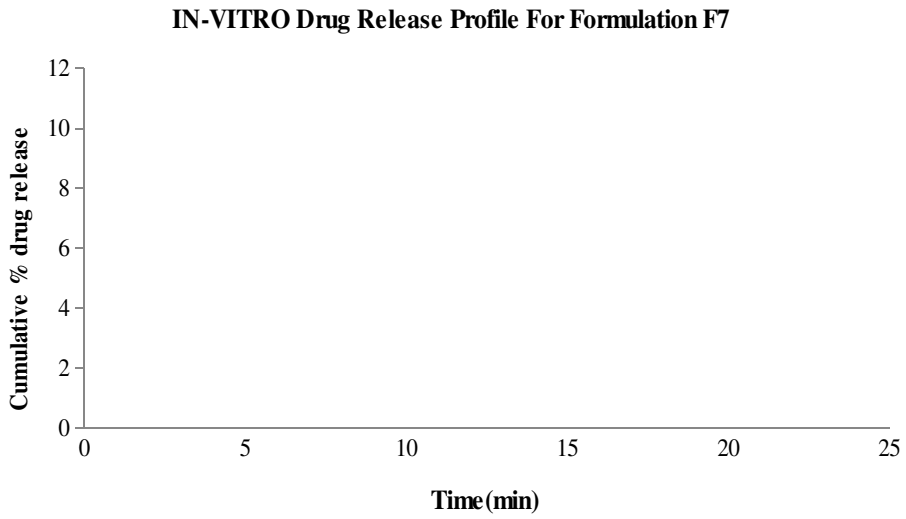


Fig: 12

Table 26: Dissolution profile of formulation F8

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.101	3.744	33.69	42.12±1.064
2	0.118	4.388	39.49	49.37±0.319
4	0.129	4.781	43.03	53.79±0.395
6	0.156	5.793	52.14	65.18±0.156
8	0.167	6.200	55.80	69.76±1.054
10	0.188	6.988	62.89	78.62±0.974
15	0.214	7.944	71.49	89.37±1.003
20	0.231	8.558	77.02	96.28±1.065

*Each value represents the mean ±S.D. of three experiments.

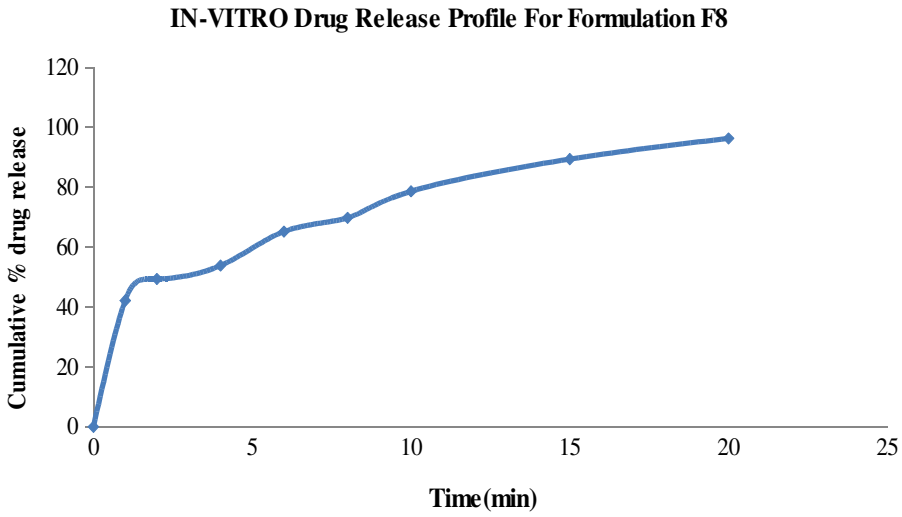


Fig: 13

Table 27: Dissolution profile of formulation F9

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.122	4.536	40.82	51.03±0.419
2	0.142	5.288	47.59	59.49±0.791
4	0.177	6.559	59.03	73.79±0.046
6	0.198	7.367	66.30	82.88±0.395
8	0.213	7.913	71.22	89.03±1.002
10	0.234	8.696	78.26	97.83±0.143

*Each value represents the mean ±S.D. of three experiments.

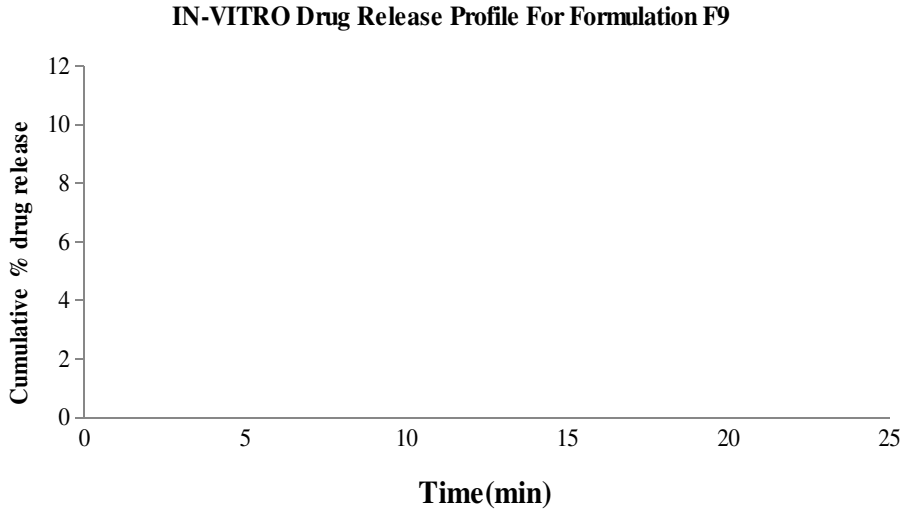


Fig: 14

Table 28: Comparative In-Vitro release data (%) for Verapamil Hydrochloride Fast Disintegrating Tablet Formulations (F1-F9)

Time (min)	Formulation code And Cumulative % of drug release*								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	41.56	47.29	47.86	48.98	52.94	50.69	49.04	42.12	51.03
2	47.26	54.65	53.42	55.49	61.82	58.63	56.69	49.37	59.49
4	52.71	67.82	68.29	69.07	76.34	71.29	69.78	53.79	73.79
6	59.55	74.31	74.94	75.79	84.26	78.01	76.49	65.18	82.88
8	64.37	82.37	83.16	84.91	91.94	86.85	85.96	69.76	89.03
10	75.48	95.63	95.91	96.29	98.92	97.04	96.81	78.62	97.83
15	87.26	-	-	-	-	-	-	89.37	-
20	95.49	-	-	-	-	-	-	96.28	-

*Each value represents the mean ±S.D. of three experiments.

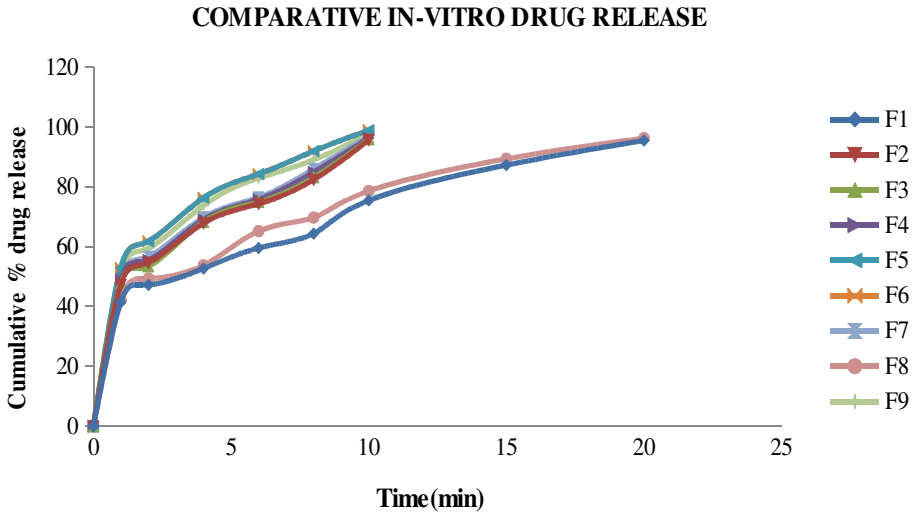


Fig: 15

8.4. STATISTICAL OPTIMIZATION TECHNIQUE BY ANOVA

The optimization was designed statistically using 3^2 factorial design. A 3-level full-factorial design consists of 9 full-factorial design points; according to the model, 9 experiments were conducted in total. This design generally involves dependent variable Y and independent or controlled variable X. The 2 independent formulation variables Y1, Y2 and 2 dependent formulation variables X1, X2 were selected.

For this study, X_1Crosscarmellose Sodium and X_2 magnesium stearate are selected. The levels of independent variables are shown in Table 29. The dependent variables are Y_1 Disintegration Time and Y2 hardness are shown in Table 29.

The results obtained from the experiment are statistically analyzed for response variables by using Design Expert 8.07 version (Stat-Ease Inc., Minneapolis, Minnesota). The statistical model incorporating interactive and polynomial terms are used to evaluate the response:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1X_1 + b_{22}X_2X_2$$

The regression coefficients for each term in the regression were shown in Table 30 to 37.

EFFECT OF FORMULATION VARIABLES DISINTEGRATION TIME

In the case of Y1 (Disintegration Time) b1, b12, b11, b22 were found to be significant with interaction of b2.The b2 is not significant since P>0.05.When the X1 (Crosscarmellose Sodium) level is increased Y1 (Disintegration Time) also increased. The X2 (Magnesium Sterate) slightly influence the Y1 (Disintegration Time).

EFFECT OF FORMULATION VARIABLES ON HARDNESS

In the case of Y2 (hardness), all the coefficients b1, b12, b11 were found to be significant with interaction of b2 and b22.The b2 and b22 were not significant since P>0.05.Whan we increase the b2 concentration it does not influence on the Y2 (Hardness).When we increase the b1 concentration it will influence slightly on Y2 (Hardness).

8.4.1. PARAMETERS OF OPTIMIZED FORMULATIONS

In-Vitro disintegration time and Hardness Data in a 3^2 Full Factorial Design

The disintegration time of different formulations are ranged from 18±0.015 to 280±0.084. And the hardness *was* in the range of 3.1±0.078 Kg/cm^2 to 5.3±0.084 Kg/cm^2 as shown in the table 29.

Table 29: *In-vitro* disintegration time and hardness data of the optimized tablets

FORMULATION CODE	CODED VALUES		DISINTEGRATION TIME (SEC)*	HARDNESS (kg/cm^2)*
	X1	X2		
Ff1	-1	-1	332±0.021	5.3±0.084
Ff2	-1	0	280±0.084	5.2±0.015
Ff3	-1	1	208±0.015	5.1±0.036
Ff4	0	-1	29±0.056	4.4±0.058
Ff5	0	0	40±0.031	4.7±0.199
Ff6	0	1	28±0.083	4.3±0.005
Ff7	1	-1	18±1.000	3.2±0.151
Ff8	1	0	30±0.036	4.5±0.161
Ff9	1	1	20±0.051	4.2±0.049

*Each value represents the mean ±S.D. of three experiments

Table 30: Factorial fit: Disintegration Time Vs X1 and X2

Estimated regression coefficients for Disintegration Time using Data In coded units			
Term	Coefficient	T	P
Constant	39.56	63.83	0.0030
X1	-125.33	235.47	0.0006
X2	-20.50	6.30	0.0869
X1*X2	31.50	0.0513	0.0000
X1*X1	115.67	0.0038	0.0000
X2*X2	-10.83	0.4995	0.0075

Table 31: Model Summary Statistics

Std. Dev.	20.01
Mean	109.44
PRESS	18.28
C.V%	14636.96
R-Squared	0.9907
Adjusted R-Squared	0.9752
Predicted R-Squared	0.8865
Adeq.Precision	19.202

Table 32

Estimated regression coefficients for Disintegration Time using un coded units	
Term	Coefficient
Constant	39.565555
X1	-125.33333
X2	-20.500000
X1*X2	31.500000
X1*X1	115.67666
X2*X2	-10.83333

Regression coefficient

$$Y1 = 39.56 - 125.33X1 - 20.50X2 + 31.50X1X1 + 115.67\ X1^2 - 10.83X2^2$$

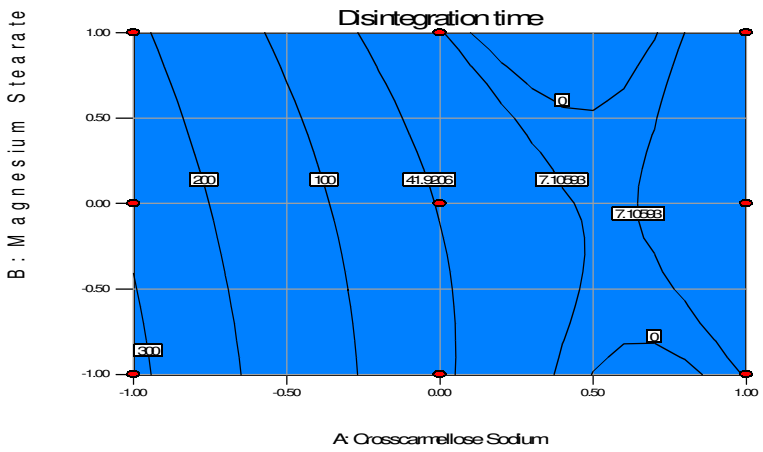


Fig.16: Contour plot of Disintegration Time Vs Crosscarmellose Sodium (X1), Mag. Stearate (X2)

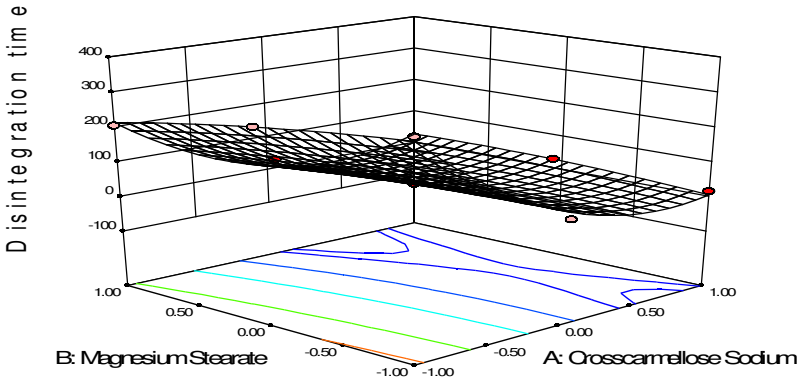


Fig.17: Surface Plot of Disintegration Time Vs Crosscarmellose Sodium (X1), Mag. Stearate(X2)

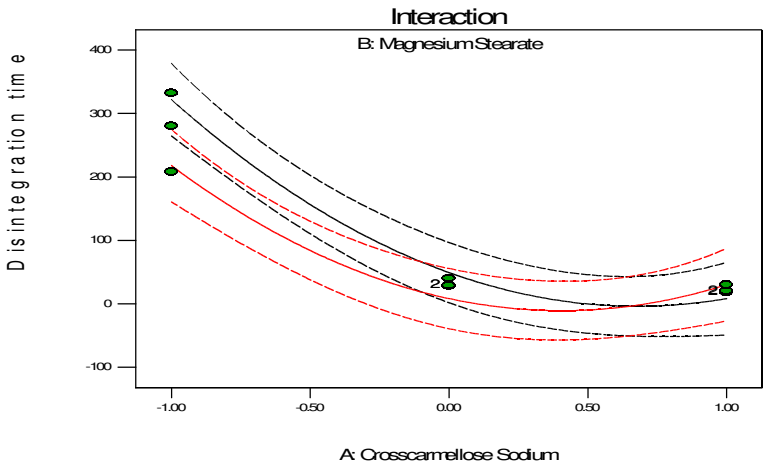


Fig.18: Interaction Plot of Disintegration Time Vs Crosscarmellose Sodium (X1), Mag. Stearate(X2)

Table 33: Factorial fit: Hardness Vs X1 and X2

Estimated regression coefficients for Hardness using Data In coded units			
Term	Coefficient	T	P
Constant	4.53	7.07	0.0264
X1	-0.63	13.39	0.0106
X2	0.15	0.75	0.4194
X1*X2	-0.0945	10.0425	0.0044
X1*X1	0.3969	179.2921	0.0001
X2*X2	0.0225	0.5625	0.1758

Table 34: Model Summary Statistics

Std. Dev.	0.42
Mean	4.53
PRESS	9.35
C.V%	2.74
R-Squared	0.7021
Adjusted R-Squared	0.6028
Predicted R-Squared	0.2419
Adeq.Precision	6.401

Table 35

Estimated regression coefficients for Hardness using un coded units	
Term	Coefficient
Constant	4.53333
X1	-0.63333
X2	0.15000
X1*X2	-0.094999
X1*X1	0.4011068
X2*X2	0.0225

Regression coefficient

$Y2 = 4.53-0.63X1+0.15X2-0.0945X1X1 +0.3969\ X1^2 +0.0225X2^2$

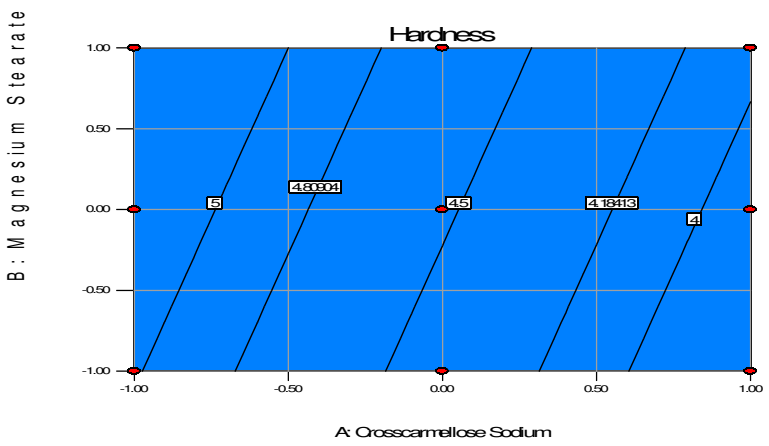


Fig. 19: Contour plot of Hardness Vs Crosscarmellose Sodium (X1), Mag. Stearate (X2)

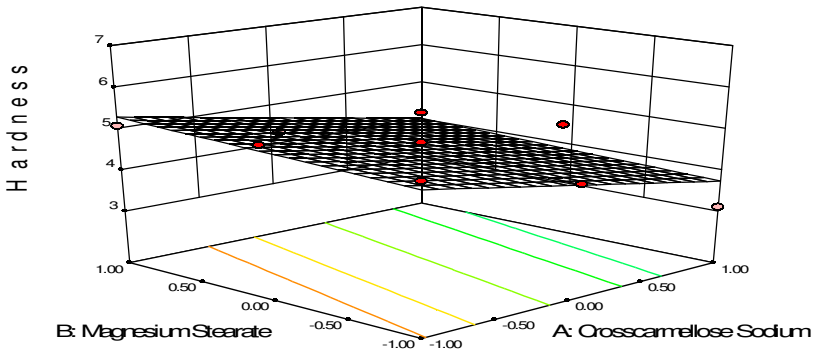


Fig. 20: Surface Plot of Hardness Vs Crosscarmellose Sodium (X1), Mag. Stearate (X2)

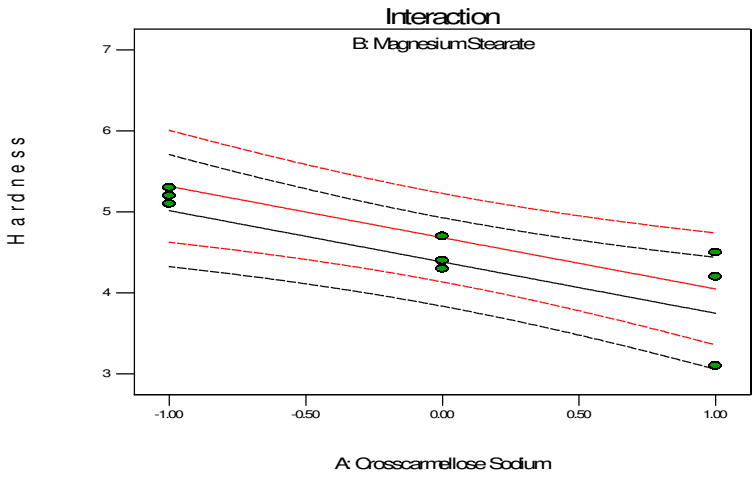


Fig.21: Interaction Plot of Hardness Vs Crosscarmellose Sodium (X1), Mag. Stearate (X2)

Table 36: The regression coefficients for each term in the regression model are summarized as follows

POLYNOMIAL EQUATIONS	R^2
Y1 = 39.56-125.33X1-20.50X2+31.50X1X1 +115.67 $X1^2$ -10.83$X2^2$	0.9907
Y2 = 4.53-0.63X1+0.15X2-0.0945X1X1 +0.3969 $X1^2$ +0.0225$X2^2$	0.7021

Table 37: Results of analysis of variance for measured response

Parameters	Degree of freedom	Sum of Square	Mean Sum of Square
For Disintegration Time			
Regression	5	1.277E+005	25546.69
Residual	3	1200.78	400.26
Total	8	1.289E+005	25946.95
For Hardness			
Regression	2	2.54	1.27
Residual	6	1.08	0.18
Total	8	3.62	1.45

OPTIMIZATION

The polynomial equations generated for the dependent variables and independent variables are shown in the Table 36. The process was optimized for the

responses Y1 and Y2. The optimized formulation was arrived at by the disintegration time and hardness to obtain the desired levels of X1 and X2. It was illustrated by the results that the hardness was not influenced. To verify the reproducibility, a new formulation was prepared (Table 38).

Table 38: Formulation of finally optimized batch Ff7

Composition	Weight in mgs
Verapamil HCl	80
Crosscarmellose sodium	30
Magnesium stearate	0
Lactose	10
Micro crystalline cellulose	20
Mannitol	60

Table 39: The dependent variables calculated for the optimized formulation are tabulated as follows

Dependent variables	**Trial 1**	**Trial 2**	**Trial 3**	**AVG ± S.D.**
Disintegration Time in sec	17	18	19	18±1.000
Hardness in kg/cm^2	3.1	3.4	3.2	3.2±0.151

IN VITRO DRUG RELEASE FOR OPTIMIZED FAST DISINTEGRATING TABLETS OF VERAPAMIL HYDROCHLORIDE

Table 40: Dissolution profile of formulation Ff1

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0

1	0.103	3.844	34.60	43.25±0.219
2	0.116	4.316	38.84	48.56±0.36
4	0.131	4.863	43.76	54.71±0.336
6	0.152	5.648	50.84	63.55±0.342
8	0.166	6.167	55.50	69.38±0.234
10	0.181	6.707	60.36	75.46±0.163
15	0.209	7.759	69.83	87.29±0.612
20	0.232	8.599	77.39	96.74±0.32

*Each value represents the mean ±S.D. of three experiments.

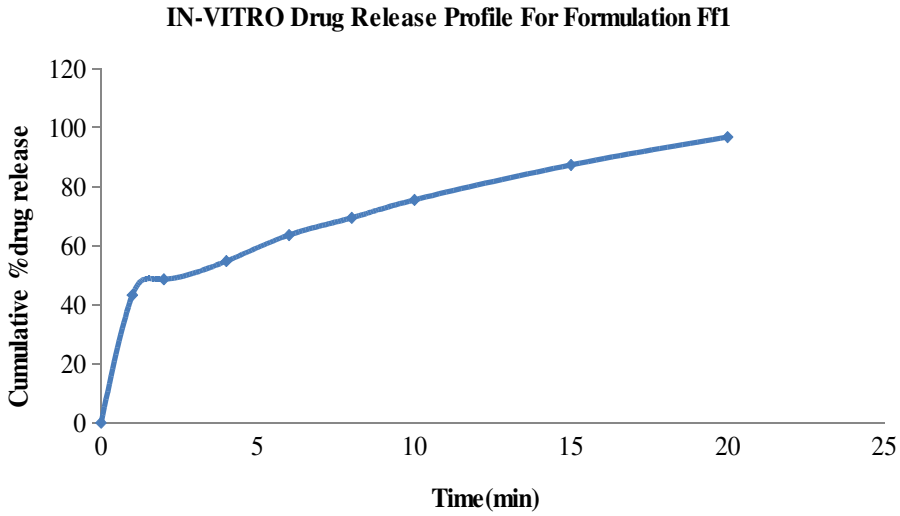


Fig: 22

Table 41: Dissolution profile of formulation Ff2

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.103	3.824	34.42	43.03±0.2013

2	0.118	4.374	39.36	49.21±0.091
4	0.125	4.656	41.90	52.38±0.474
6	0.152	5.640	50.76	63.45±0.532
8	0.162	6.020	54.18	67.73±0.274
10	0.179	6.661	59.95	74.94±0.289
15	0.204	7.581	68.23	85.29±0.346
20	0.229	8.489	76.40	95.51±0.34

*Each value represents the mean ±S.D. of three experiments.

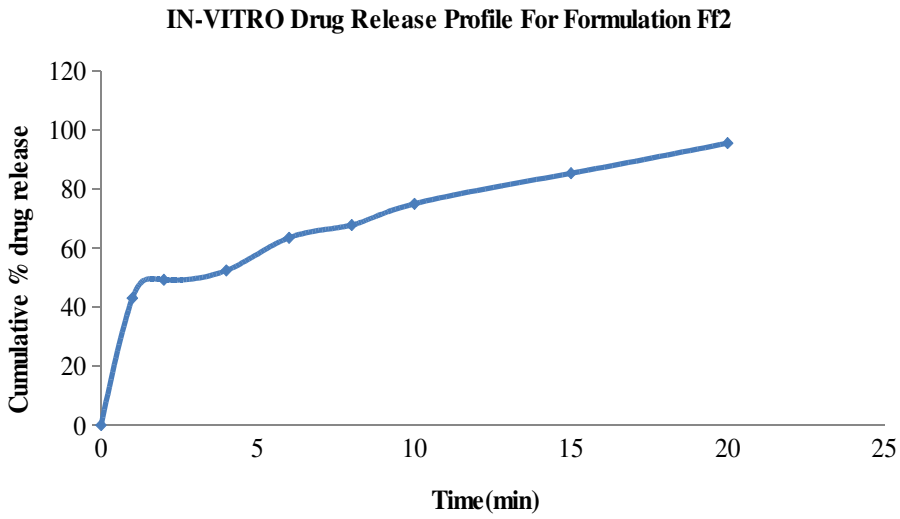


Fig: 23

Table 42: Dissolution profile of formulation Ff3

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0

1	0.104	3.886	34.97	43.72±0.392
2	0.118	4.402	39.62	49.53±0.475
4	0.134	4.984	44.86	56.08±0.364
6	0.154	5.735	51.61	64.52±0.258
8	0.166	6.178	55.60	69.51±0.249
10	0.185	6.868	61.81	77.27±0.346
15	0.211	7.848	70.64	88.30±0.623
20	0.232	8.621	77.59	96.99±0.464

*Each value represents the mean ±S.D. of three experiments.

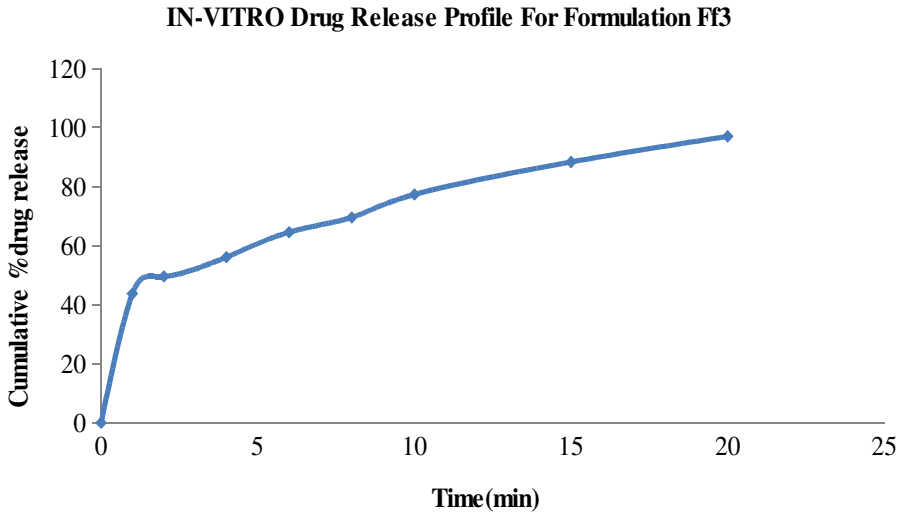


Fig: 24

Table 43: Dissolution profile of formulation Ff4

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*

0	0	0	0	0
1	0.123	4.576	41.18	51.48±0.440
2	0.141	5.249	47.24	59.06±0.395
4	0.173	6.420	57.78	72.23±0.371
6	0.190	7.070	63.63	79.54±0.606
8	0.205	7.610	68.49	85.62±0.605
10	0.233	8.643	77.79	97.24±0.44

*Each value represents the mean ±S.D. of three experiments.

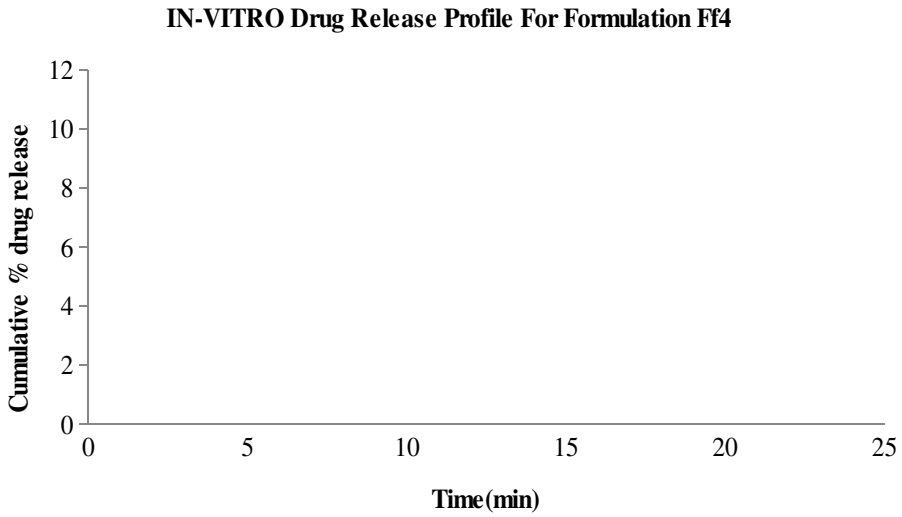


Fig: 25

Table 44: Dissolution profile of formulation Ff5

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*

0	0	0	0	0
1	0.118	4.390	39.51	49.39±0.285
2	0.137	5.095	45.85	57.32±0.622
4	0.165	6.145	55.31	69.14±0.392
6	0.180	6.685	60.16	75.21±0.285
8	0.200	7.420	66.78	83.48±0.457
10	0.230	8.539	76.85	96.07±0.392

*Each value represents the mean ±S.D. of three experiments.

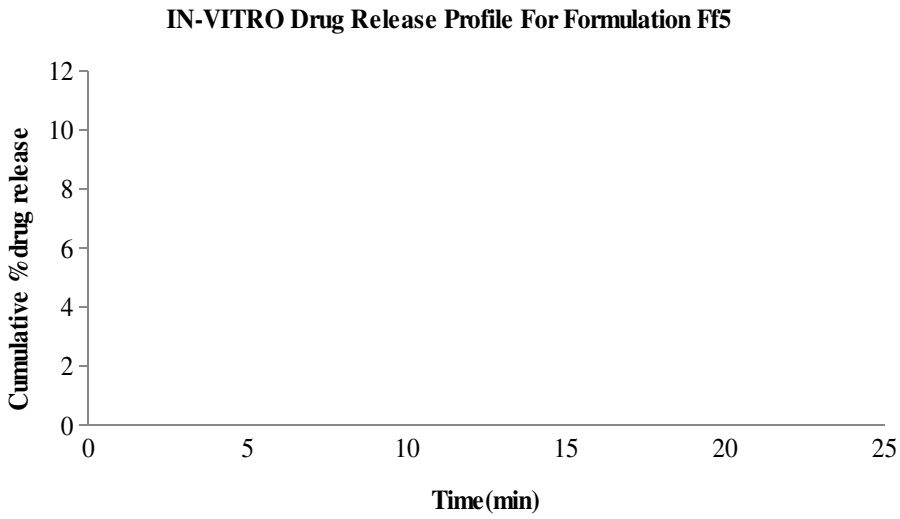


Fig: 26

Table 45: Dissolution profile of formulation Ff6

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.124	4.598	41.38	51.73±0.26
2	0.143	5.302	47.72	59.65±0.520
4	0.177	6.558	59.02	73.78±0.487
6	0.190	7.064	63.57	79.47±0.429
8	0.206	7.663	68.96	86.21±0.290
10	0.234	8.692	78.23	97.79±0.268

*Each value represents the mean ±S.D. of three experiments.

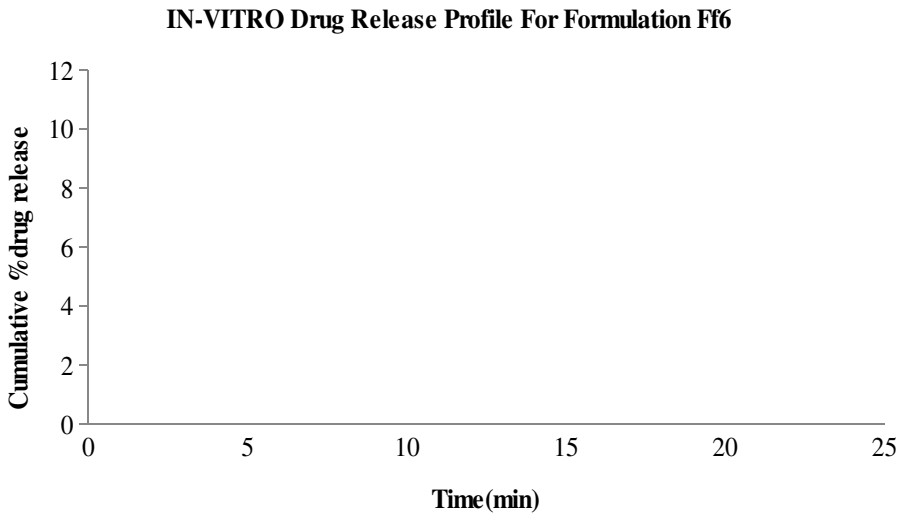


Fig: 27

Table 46: Dissolution profile of formulation Ff7

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.131	4.870	43.81	54.79±0.499
2	0.150	5.568	50.11	62.64±0.298
4	0.186	6.920	62.28	77.86±0.423
6	0.202	7.510	67.59	84.49±0.372
8	0.222	8.225	74.03	92.54±0.294
10	0.238	8.841	79.57	99.47±0.342

*Each value represents the mean ±S.D. of three experiments.

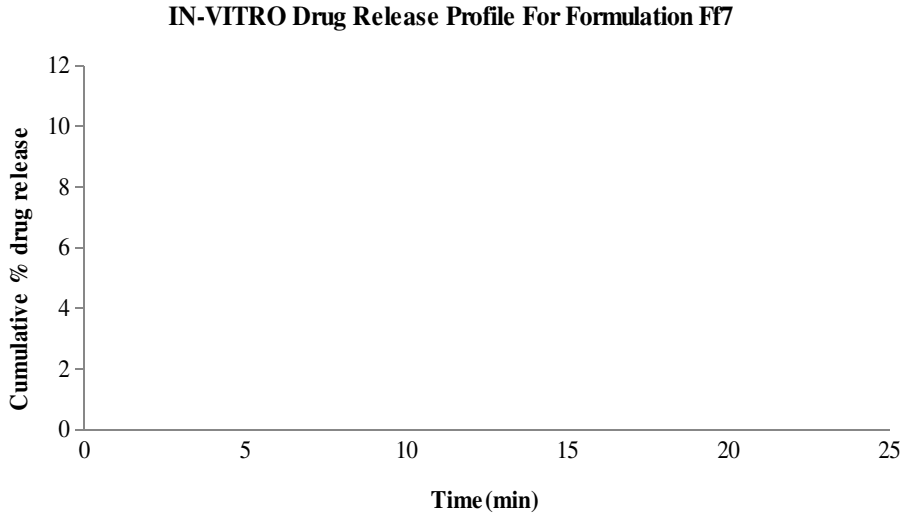


Fig: 28

Table 47: Dissolution profile of formulation Ff8

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.121	4.512	40.60	50.76±0.231
2	0.140	5.189	46.70	58.38±0.325
4	0.167	6.187	55.68	59.61±0.344
6	0.185	6.871	61.84	77.30±0.346
8	0.204	7.562	68.06	85.08±0.145
10	0.232	8.614	77.52	96.91±0.143

*Each value represents the mean ±S.D. of three experiments.

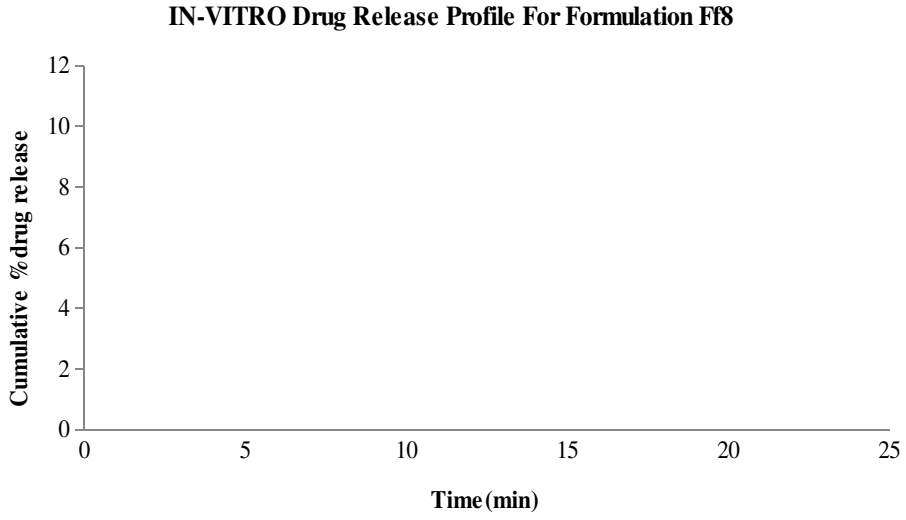


Fig: 29

Table 48: Dissolution profile of formulation Ff9

Time (min)	Absorbance (nm)	Concentration (µg/ml)	Amount of drug release	Cum % of drug release*
0	0	0	0	0
1	0.125	4.646	41.81	52.27±0.435
2	0.145	5.383	48.44	60.56±0.614
4	0.177	6.559	59.03	73.79±0.561
6	0.202	7.494	67.44	84.31±0.982
8	0.217	8.039	72.35	90.44±0.862
10	0.237	8.794	79.15	98.94±0.274

*Each value represents the mean ±S.D. of three experiments.

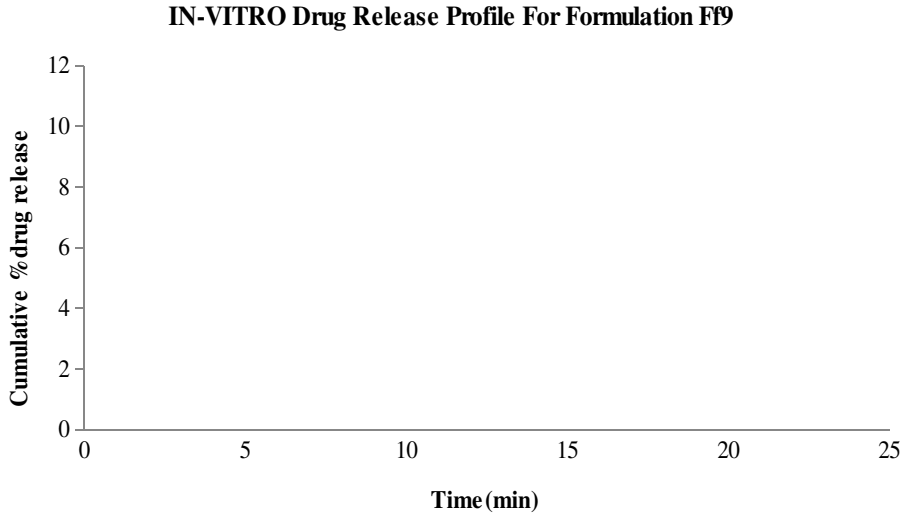


Fig: 30

Table 49: Comparative Optimized In-Vitro release data (%) for Verapamil Hydrochloride Fast Disintegrating Tablet Formulations (Ff1-Ff9)

Time (min)	Formulation code And Cumulative % of drug release*								
	Ff1	Ff2	Ff3	Ff4	Ff5	Ff6	Ff7	Ff8	Ff9
0	0	0	0	0	0	0	0	0	0
1	43.03	43.03	43.72	51.48	49.39	51.73	54.79	50.76	52.27
2	49.21	49.21	49.53	59.06	57.32	59.65	62.64	58.38	60.56
4	52.38	52.38	56.08	72.23	69.14	73.78	77.86	59.61	73.79
6	63.45	63.45	64.52	79.54	75.21	79.47	84.49	77.30	84.31
8	67.73	67.73	69.51	85.62	83.48	86.21	92.54	85.08	90.44
10	74.94	74.94	77.27	97.24	96.07	97.79	99.47	96.91	98.94
15	85.29	85.29	88.30	-	-	-	-	-	-
20	95.51	95.51	96.99	-	-	-	-	-	-

*Each value represents the mean ±S.D. of three experiments.

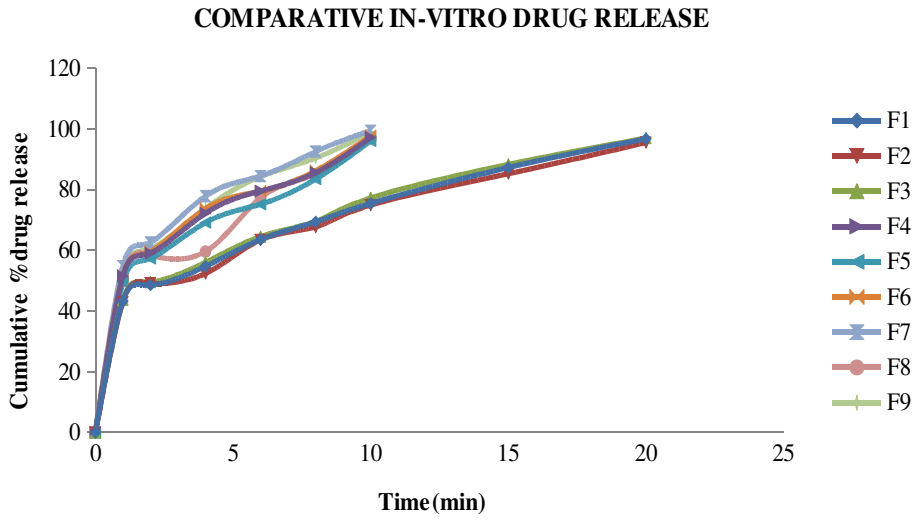


Fig: 31

DISCUSSION

9. DISCUSSION

The present investigation was undertaken to find out the effect of super disintegrating agent and lubricant on optimized fast disintegrating tablets of Verapamil hydrochloride.

The compatibility study of drug and excipients were studied by FTIR. The FT-IR spectral analysis showed that there was no appearance or disappearance of any characteristic peaks of pure drug Verapamil hydrochloride in the physical mixture of drug and with excipients, which confirmed that there is no chemical interaction between drug and excipients.

The tablets were prepared by direct compression method using Crosscarmellose sodium as a super disintegrant and Magnesium stearate as a lubricant. The mixture of all formulation before compression were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index and drug content. The angle of repose value ranged from 21^0.62'±1.030 to 26^0 .05'±2.847.The results were found to be below 30^0 and hence the blend was found to have good flow ability. Bulk and tapped densities were used for the measurement of Compressibility index. The LBD (loose bulk density) and TBD (tapped bulk density) ranged from 0.69±0.011 to 0.76±0.025 and 0.76±0.020 to 0.88±0.026 respectively. The compressibility index (%) was then calculated from the LBD and TBD and it ranged from 5.99±0.588 to 15.22±2.473. The blend was found to have free flowing property as the result was found to be below 20%. The Hauser's ratio ranged from 1.05±0.005 to 1.18±0.037. The value was found to be below 1.2 which is suitable for free flowing.

The tablets were prepared by using direct compression method and the tablets of all formulation were subjected to various evaluation parameters such as hardness, thickness, friability, weight variation, drug content, in-vitro disintegration time and in-vitro dissolution study.

The results of all these tests were found to be within the limits. The hardness of tablets in all batches ranged from 3.2±0.145 Kg/cm^2 to 5.4±0.350 kg/cm^2. The thickness of the tablets was uniform in all formulations and ranged from 3.6±0.012 mm to 3.6±0.068 mm. All the formulations (F1-F9) passed the weight variation test as

per the pharmacopeial limit of ± 5%. All the formulations exhibited less than 1% friability which was within the limit. Drug content was also found to be uniform among the all formulations and ranged from 98.64±0.402% to 99.49±0.199%. And in-vitro disintegration time was found to be in the range from 20.36±0.550 to 248.23±0.13.

The drug release studies were performed on the prepared formulations (F1-F9) using 0.1N HCL for 20min.Table 19 to 28 enlists the comparatives *In-vitro* drug release data for F1 to F9 formulations. The percentage drug release of Verapamil hydrochloride for all formulations showing 95.49%, 95.63%, 95.91%, 96.29%, 98.92%, 97.04%, 96.81%, 96.28 and 97.83% respectively. In the above results all formulations release drug within 10 minutes except F1 and F8 because of the absence of disintegrating agent. From the above results, the F5 formulation showed faster and maximum drug release than the other formulations. The comparative release of all the six formulations was plotted on the Fig 15.

Factorial design is an efficient method of finding the relative significance of number of variables and their interaction on the response. Here 3^2 full factorial design was applied to best formulation (F5) to determine the effect of disintegrating agent and lubricant on fast disintegrating tablets of Verapamil hydrochloride. Magnesium stearate decreases the wettability of the matrix and thus, may increase the disintegration time of an optimized formulation. Hence, concentration of lubricant was selected as one of the independent variables for the experimental design. Crosscarmellose Sodium, a disintegration-promoting agent was selected as another variable which may decrease the disintegration time of the optimized fast disintegrating tablets.

The values of the X1 and X2 are associated with the effect of variables Y1 and Y2 response. Coefficients with more than one factor represent an interaction effect (e.g. X1X2) while those with higher order (e.g. $X2^{2)}$ terms denote quadratic relationships. A positive sign signifies a synergistic effect while a negative sign stands for an antagonistic effect. Only statistically significant ($p < 0.05$) coefficients were retained in the equations.

Disintegration time and hardness values for all the formulations (Ff1-Ff9) are varied from 18±1.000 to 332±0.021 and 3.2±0.151 to 5.3±0.084 kg/cm^2 respectively. These results indicate that the selected variables have strong influence on disintegration time and hardness of the fast disintegrating tablets. Analysis of variance for the responses (ANOVA) indicated that the assumed regression models were significant and valid for each of the responses ($p<0.05$).

From the analysis of the fitted data we can conclude that the crosscarmellose sodium (X1) had an significant influence on the disintegration time and the hardness of the fast disintegrating tablet formulation, and the optimum concentration of lubricant have only influence on the disintegration time and the hardness of the fast disintegrating formulation because disintegration time increased with increased concentration of the lubricant, magnesium stearate (*X*2). Disintegration was delayed due to the general agreed observation that magnesium stearate forms a hydrophobic membrane on the surface of the powder particles. Hence, disintegration time will increase with the increased concentration of magnesium stearate. These results were quiet interesting and contradictory to the general notion that the tablet hardness is known to decrease with increase in the magnesium stearate concentration. Several authors have demonstrated that because of high extensibility of magnesium stearate, it spreads over the surface of the powder particles. This in turn prevents bonding among powder particles, giving low tensile strength and decrease in tablet hardness with increase in the concentration of magnesium stearate.

Based on this study, magnesium stearate was chosen as a lubricant at 1.5% concentration as it gave optimum hardness value with low disintegration time. The drug release studies were also performed on the prepared formulations (Ff1-Ff9) using 0.1N HCL for 20min.The percentage drug release of optimized fast disintegrating Verapamil hydrochloride for all formulations were within the limits. From the above results Ff7 is taken as best formulation.

CONCLUSION

10. CONCLUSION

- Fast disintegrating tablet is a promising approach with a view of obtaining faster action of the drug and would be advantageous in comparison to currently available conventional forms. Fast disintegrating tablets of Verapamil hydrochloride were prepared by direct compression method using croscarmellose sodium as a super disintegrant and magnesium stearate as a lubricant. *In vitro* drug release from the tablets shows significant improvement in drug dissolution. By the comparative statistical data F5 was taken as the best formulation.
- The application of full factorial design was useful in evaluating influence of disintegrating agent (crosscarmellose Sodium) concentration and lubricant (magnesium stearate) concentration on an optimized fast disintegrating formulation of Verapamil hydrochloride. From the statistical design, crosscarmallose Sodium concentration had an influence on the disintegration time and tablet hardness. 1.5% magnesium stearate concentration was selected as an optimum concentration where it has an influence on disintegration time and hardness of the optimized fast disintegrating tablet formulation. From the in-vitro drug release studies Ff7 was taken as the best formulation. Further it is recommended to perform in-vivo studies for the fast disintegrating tablets of Verapamil hydrochloride.

REFERENCES

11. REFERENCES

1. Sam Corveleyn, Jean Paul Remon .Formulation and production of rapidly disintegrating tablets by lyophilisation using hydrochlorothiazide as a model drug. Int J Pharm.1997; 152:215–225.
2. Kuno Y, Kojima M, Ando S, Nakagami H. Evaluation of rapidly disintegrating tablets manufactured by phase transition of sugar alcohols. J Control Release. 2005; 105:16-22.
3. Siraj Shaikh ,R.V.Khirsagar , Aamer Quazi .Fast Disintegrating Tablets: An Overview OF Formulation And Technology. Int J Pharm Pharm Sci. 2010; 2:0975-1491.
4. Suhas M. Kakade1, Vinod S. Mannur, Ravindra V. Kardi, Ketan B. Ramani1 , Ayaz A. Dhada Formulation And Evaluation Of Orally Disintegrating Tablets Of Sertraline IJPRD.2010;1:12.
5. Shinde S.K , S. K. Banerjee, N. D. Grampurohit, D.D. Gaikwad, M.V. Gadhave, K.S. Sabale. Mouth dissolving tablets: an overview of formulation technology. Dec J Pharm & Cosmet 2011; 2(2).
6. Late SG, Yu YY, Banga AK. Effects of disintegration-promoting agent, lubricants and moisture treatment on optimized fast disintegrating tablets. Int J Pharm. 2009; 365:4-11.
7. Aoshima H, Miyagisnima A, Nozawa Y, Sadzuka Y, Sonobe T. Glycerin fatty acid esters as a new lubricant of tablets. Int J Pharm. 2005; 293:25-34.
8. Wang J, Wen H, Desai D. Lubrication in tablet formulations. Eur J Pharm Biopharm. 2010; 75:1-15.
9. Uchimoto T, Iwao Y, Takahashi K, Tanaka S, Agata Y, Iwamura T, Miyagishima A, Itai S. A comparative study of glycerin fatty acid ester and magnesium stearate on the dissolution of acetaminophen tablets using the analysis of available surface area. Eur J Pharm Biopharm. 2011; 78:492-498.
10. López-Solís J, Villafuerte-Robles L. Effect of disintegrants with different hygroscopicity on dissolution of Norfloxacin/Pharmatose DCL 11 tablets. Int J Pharm. 2001; 216:127-35.
11. Ferrero C , N. Mufioz, M.V. Velasco, A. Mufioz-Ruiz, R. Jim6nez-Castellanos. Disintegrating efficiency of croscarmellose sodium in a direct compression formulation. Int J of Pharm. 1997; 147:11- 21.

12. Patil C and S. Das. Effect of various super disintegrants on the drug release profile and disintegration time of Lamotrigine orally disintegrating tablets. African Journal of Pharmacy and Pharmacology. 2011; 5: 76-82.

13. Biljana Govedarica1, Rade Injac, Rok Dreu and Stane Srcic. Formulation and evaluation of immediate release tablets with different types of paracetamol powder prepared by direct compression. African Journal of Pharmacy and Pharmacology 2011; 5: 31-41.

14. Chowdary K.P.R, sunil kumar. Formulation Development of Selected Drugs by Direct Compression Method. IJPRD, 2011; 3: 273 – 279.

15. Bodea A, Leucuta SE. Optimization of propranolol hydrochloride sustained-release pellets using box-behnken design and desirability function. Drug Dev Ind Pharm. 1998; 24:145-55.

16. Coyne KS, Davis D, Frech F, Hill MN. Health-related quality of life in patients treated for hypertension: a review of the literature from 1990 to 2000. Clin Ther. 2002; 24:142-69.

17. Gary J. Okano, PhD, Karen L. Rascati, PhD, z James P. Wilson, PhD, Daniel D. Remund, MS, MHA, John D. Grabenstein, EdM, MS, and Diana I. Brixner, PhD. Patterns of Antihypertensive Use Among Patients in the US Department of Defense Database Initially Prescribed an Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker. Clin Ther 1997; 19:6.

18. Bertram Pitt, MD. Diversity of Calcium Antagonists. Clin Ther, 1997; 19.

19. Cheng JW, Behar L. Calcium channel blockers: association with myocardial infarction, mortality, and cancer. Clin Ther. 1997; 19:1255-68.

20. Valvo L, Alimenti R, Alimonti S, Raimondi S, Foglietta F, Campana F. Development and validation of a liquid chromatographic method for the determination of related substances in verapamil hydrochloride. J Pharm Biomed Anal. 1997; 15:989-96.

21. Rahman N, Hejaz Azmi SN. Spectrophotometric method for the determination of verapamil hydrochloride in pharmaceutical formulations using N-bromosuccinimide as oxidant. Farmaco. 2004; 59:529-36.

22. Syed azeem, Shaweta sharma . Immediate Release Drug Delivery Systems: A Review. International Journal of Biopharmaceutics & Toxicological. 2011; 1:1.

23. Schiermeier S, Schmidt PC. Fast dispersible ibuprofen tablets. Eur J Pharm Sci. 2002; 15:295-305.

24. passerini n, perissutti b, albertini b, voinovich d, moneghini m, rodriguez. Controlled release of verapamil hydrochloride from waxy microparticles prepared by spray congealing. J control release. 2003; 88:263-75.

25. Gonçalves-Araújo T, Rajabi-Siahboomi AR, Caraballo I. Application of percolation theory in the study of an extended release Verapamil hydrochloride formulation. Int J Pharm. 2008; 361:112-7.

26. L. Maggi, G. Massolini, E. De Lorenzi, U. Conte, G. Caccialanza. Evaluation of stereoselective dissolution of verapamil hydrochloride from matrix tablets press-coated with chiral excipients. Int J Pharm.1996; 136:43-52.

27. Kiliçarslan M, Baykara T. The effect of the drug/polymer ratio on the properties of the verapamil HCl loaded microspheres. Int J Pharm. 2003; 252:99-109.

28. Kuno Y,Kojima M, Nakagami H,Yonemochi E, Terada K. Effect of the type of lubricant on the characteristics of orally disintegrating tablets manufactured using the phase transition of sugar alcohol.Eur J Pharm Biopharm.2008;69:986-92.

29. Chandrasekhar R, Hassan Z, Alhusban F, Smith AM, Mohammed AR. The role of formulation excipients in the development of lyophilised fast-disintegrating tablets. Eur J Pharm Biopharm. 2009; 72:119-29.

30. Rai V.K , Pathak N, Bhaskar R , Nandi B.C, Dey S, Tyagi L.K.Optimization Of Immediate Release Tablet Of Raloxifene Hydrochloride by Wet Granulation Method.IJPSDR.2009;1:51-54.

31. Bansal T, Mishra G, Jaggi M, Khar RK, Talegaonkar S. Effect of P-glycoprotein inhibitor, verapamil, on oral bioavailability and pharmacokinetics of irinotecan in rats. Eur J Pharm Sci. 2009; 36:580-90.

32. Good man & Gillman. The pharmacological basis of therapeutics. Hardman JG, Limbird LE, Alfred GG,editors 8thed.New york : MC.Graw-Hill;2001.P.774-778.

33. Passerini N, Perissutti B, Albertini B, Voinovich D, Moneghini M, Rodriguez L. Controlled release of verapamil hydrochloride from waxy microparticles prepared by spray congealing. J Cont Rel. 2003; 8:263-75.

34. Richer C, Giroux B, Plouin PF, Maarek B, Giudicelli JF. Captopril: pharmacokinetics, antihypertensive and biological effects in hypertensive patients. Br J Clin Pharmacol. 1984; 17:243-50.

35. Emami J, Varshosaz J, Saljoughian N. Development and evaluation of controlled-release buccoadhesive verapamil hydrochloride tablets. DARU 2008; 16: 2.

36. Stockelyes drug interactions.9thed.In: Karen Bartex editor. United Kingdom: Pharmaceutical press; 2010; 1025-46.

37. Martindale. The complete drug reference.33rd Ed. In: Sweet man SL editor. United Kingdom: Pharmaceutical press; 2002; 1278-81.

38. Robert M. Silverstein., Francis X. Webster., ”Infrared Spectrometry. In: Robert M. Silverstein”. Editors. Spectrometric Identification of Organic Compounds. 6th Ed. John Wiley and Sons. Inc. New York. Pg. 71 – 143.

39. Banker G S., Anderson N R., and Tablets In: Lachman L. Lieberman HA, Kanig JL, And Editor. The Theory and Practice of Industrial Pharmacy.3rd Edition 1986, 293-335.

40. Bushra R, Shoaib MH, Aslam N, Hashmat D, Ur Rehman M. Formulation development and optimization of Ibuprofen tablets by direct compression method. Pak J Pharm Sci.2008; 21:113-20.

41. Abdelbary G, Eouani C, Prinderre P, Joachim J, Reynier J, Piccerelle P. Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. Int J Pharm. 2005; 292:29-41.

42. Ozkan Y, Yilmaz N, Ozkan SA, Biryol I. High-performance liquid chromatographic analysis of verapamil and its application to determination in tablet dosage forms and to drug dissolution studies. Farmaco. 2000; 55:376-82.

43. Adrian Bodea , Sorin E. Leucuta .Optimization of hydrophilic matrix tablets using a D-optimal design. Int J Pharm. 1997; 153: 247–255.

44. Martinello T, Kaneko TM, Velasco MV, Taqueda ME, Consiglieri VO. Optimization of poorly compactable drug tablets manufactured by direct compression using the mixture experimental design. Int J Pharm.2006; 322:87-95.

45. J.A. Westerhuis , P. de Haan b, J. Zwinkels b, W.T. Jansen c, P.J.M. Coenegracht , C.F. Lerk d .Optimisation of the composition and production of mannitol/microcrystalline cellulose tablets . Int J Pharm. 1996; 143: 151-162.