FORMULATION AND EVALUATION OF REPAGLINIDE IMMEDIATE RELEASE TABLETS WITH IMPROVED DISSOLUTION USING SOLID DISPERSION TECHNIQUE

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1. INTRODUCTION

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. The drug may be administered by variety of routes in a variety of dosage forms. Drugs are more frequently taken by oral administration. The solid dosage forms available mostly in unit dosage forms such as tablets, capsules, lozenges etc[1]. When drugs are administered orally in dry state, tablets and capsules are most convenient dosage form[2].All practical purposes only compression tablets are almost universally used while molded tablets being rate commodity. Drugs are more frequently taken by oral administration[3].

Although a few drugs taken orally are intended to be dissolved within the mouth, vast majority of drugs taken oral are swallowed[4]. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for the conventional delivery of drug[5].

It is considered most natural, uncomplicated, convenient, safe means of administering drugs[6]. Some of its advantages are greater flexibility in dosage design, ease of production and low cost[7].

Many patients find it difficult to swallow tablets and hard gelatin capsules and thus do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. Recent advances in novel drug delivery systems (NDDS) aim to enhance the safety and efficacy of drug molecule by formulating a convent dosage form for administration and to achieve better patient compliance[8].

Nearly 35 - 50% of the general population, especially the elderly and children suffer from dysphasia or difficulty in swallowing, which results in high incidence of non-compliance and ineffective therapy[9]. Swallowing problems also are very common in young individuals because of their poorly developed muscular and nervous systems. Other groups who may experience problems in swallowing conventional oral dosage forms are the patients with tremors of extremities, mentally ill, develop mentally disabled, non-cooperative and patients with reduced liquid intake or patients suffering from nausea, as well as patients travelling or who do not have easy access

to water. The swallowing problems are also common in some cases such as patients with motion sickness, sudden episodes of allergic attack or coughing and due to lack of water.

To overcome this problem, scientists have developed innovative drug delivery system known as a "Immediate release tablets[10]".

Immediate release tablets are designed to disintegrate and release their medication in absence of any special rate-controlling features as special coating and others techniques[11].

1.1Advantages of Immediate Release Tablets[12,13,14];

1. Large scale manufacturing is feasible in comparison to other dosage forms, therefore economy can be achieved.
2. Accuracy of dosage is maintained since tablet is a solid unit dosage form.
3. Longer expiry period and microbial spillage owing to lower moisture content.
4. Easy of packaging (blister or strip)and easy handling over liquid a form.
5. Easy to transport in bulk. Emergency supplies can be carried by patients.
6. Easy to transport in bulk. Emergency supplies can be carried by patients[15].
7. Product identification is easy and marking done with the help of grooved punched and printing with edible ink,

Disadvantages of Immediate Release Tablets[16,17];

1. It is difficult to convert a high dose poorly compressible API into tablet of multiple size for human use[18].
2. Difficult to formulate a drug with poor wet ability, slow dissolution in to tablet.
3. Slow onsets of action as compared to parenterals, liquid orals are capsules.
4. Difficult to swallow for kids, terminally ill and geriatric patients.
5. Patients undergoing radiotherapy cannot swallow tablet.

1.2. Desired Criteria For Immediate Release Drug Delivery System (IRDS):

Immediate release dissolving tablet should address the following:

- Requires no water for oral administration, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be compatible with taste masking agent.
- Be portable.
- Have a pleasing mouth feel.
- Leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental condition as humidity and temperature.
- Allow high drug loading.
- Allow the manufacturing of tablets using conventional processing and packaging equipments at low cost.

1.2.1. Salient Features of Immediate Release Drug Delivery System:

Ease of administration to patient who refuses to swallow a tablet, such as pediatric, geriatric and psychiatric patients.

- Require no water to swallow the dosage form, which is highly convenient feature for patients who are travelling and do not have immediate access to water.
- Rapid dissolution and absorption of drug, which will produce quick onset of action.
- Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach; in such cases bioavailability of drug is increased.
- Pregastric absorption can result in improved bioavailability and as a result of reduced dosage; improve clinical performance through a reduction of unwanted effects.

Direct compression is the easiest method to manufacture immediate release tablets (IRTs) and immediate melting tablets (IMTs). The great advantages of direct

compression are its low manufacturing cost. It uses conventional equipment, commonly available excipients and a limited number of processing steps.

Direct compression is the method of choice in tablet manufacture to produce high quality finished product and applied to prepare dispersible tablets[18].

In direct compression method, previously only crystalline compounds or materials were considered to be directly compressed, but now the scenarios changing and this technique is being applied for many non -crystalline materials too. Formulations constituted by <-25% w/w of drug material are easy to be directly compressed by simply using diluents, which are easy to be compressed and which acts as a carrier for the drug[19].

1.2.2. FACTORS AFFECTING THE DRUG RELEASE[20]:

1. Physiochemical properties of drug and
2. Dosage form factors

The various physiochemical properties of drug that effect drug dissolution and its rate are - solubility, partical size, polymorphism, salt form, pseudo-polymorphism, complexation, wetability etc.

Dosage form factors include manufacturing process and excipients incorporated in them[21].

Several manufacturing process influence drug dissolution form. Processes of such importance in manufacturing of tablets are;

1. Method of granulation
2. Compression force.

The excipients such as binders, lubricants, disintegrants, etc influence the drug dissolution[26].

The techniques used in the preparation of immediate release tablets:

1.3.Conventional Techniques[22,23,24];

1. Tablet moulding:

In this method, the delivery system is prepared in the form of tablets using

water soluble additives to allow the tablet to dissolve rapidly and completely in mouth. All the ingredients of the formulation are passed through fine mesh dry bended, wetted with a hydro - alcoholic solvent and then compressed into tablets using low compression forces. The solvent is then removed by air drying.

2. Freezing drying:

Lyophilisation is a pharmaceutical manufacturing technology, which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. Lyophilization results in preparations which are highly porous, with a very high specific surface area, which dissolve rapidly a show improved absorption and bioavailability.

3. Spray drying:

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

4. Sublimation:

This method includes the addition of a sublime of a sublime salt to the table ting components, compressing the blend and removing the salt by the process of sublimation. The active ingredient, diluents, a sublime salt (camphor / ammonium bicarbonate) a binder and other excipient are blended and tablets are prepared.

5. Addition of disingredients:

Addition of disingredients in immediate release tablets, leads to quick disintegration of tablets and hence improves dissolution. Microcyrstalline cellulose, cross-linked carboxy methyl cellulose sodium, cross-linked polyvinyl pyrolidine and partially substituted hydroxy propel cellulose, absorb water and swell due to capillary action and are considered as effective disintegrates in the preparation of immediate releasing tablets.

6. Sugar based excipient:

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

7. Mass Extrusion:

This technology involves softening the active blend using the solvent, mixture of water soluble polyethylene glycol using methanol and explusion of softened mass through the extruder or syringe to get a cylinder of the product and cutting into even segments upon heated blade to form tablets.

Patented Technologies:

8. Zydis:

In zydistechnology, drug is added to a solution carrier material (preferably gelatin) to obtain dispersion, and the dispersion is filled into performed pockets of blister pack by automatic means and freeze dried to produce the final dosage form.

9. Orasolv:

The system essentially make tablets that contain the taste masked active ingredients an effervescent disintegrating agent, which on contact with saliva, rapidly disintegrates and releases the active ingredient. The tablets are made by direct compression at very low compression forces in order to minimize oral dissolution time. The tablets produced are soft and friable.

10.Durasolv:

The tablet made by this technology consists of a drug, filler and a lubricant. Dura Solve tablets are prepared by using conventional tableting equipment and have good rigidity.

11. Flash dose:

Flash dose tablets consist of self-binding shear form matrix termed as "floss". Shear form materials are prepared by flash heat processing and are of two types.

- Single floss
- Dual floss

1.4. SUPER DISINTEGRANTS

Disintegrates have a major in the disintegration and dissolution process of or dispersible tablets made by direct compression [25]. The choice of a suitable type and optimal amount of disintegrant is important for ensuring high disintegration rate. The addition of other formulation components such as water soluble excipient or effervescent agents further enhance dissolution or disintegration properties[26]**.** The understanding of disintegrant properties and their effect on formulation has advanced significantly during last few years practically regarding superdisintegrants[27].

Addition of super disintegrates in ODTs leads to quick disintegration of tablets and hence improves dissolution. Microcrystalline cellulose, crosslinked carboxy methyl cellulose sodium, crosslinked Polyvinyl pyrrolidone and partially substituted hydroxy propyl cellulose etc absorb water and swell due to capillary action and are considered as effective disintegrants in the preparation immediate release of tablets[28].

1.4.1. MECHANISM OF SUPERDISINTEGRANTS

The tablet breaks to primary particles by one or more of the mechanism listed below.

1. Because of heat of wetting (air expansion):

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

2. Swelling:

The most widely used mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. swelling force is exerted in the tablet with low porosity.

3. Porosity and capillary action (Wicking):

The first step for this is disintegration by capillary action. The tablet will be put into the suitable aqueous medium; the medium penetrates into the tablet and replaces the air adsorbed on the particles. Which uptake by tablet depends upon hydrophilicity of the drug/ excipient and on tableting conditions.

4. Due to disintegrating particle/particle repulsive forces:

Another mechanism of disintegration attempts to explain the swelling of tablet made with "non-swellable" disintegrates. Guyot – Hermann has proposed a particle repulsion theory based on the observation that non-swelling particle also cause disintegration of tablets.

5. Due to deformation:

During tablet compression, disintegrated particles get deformed and those deformed particles get into their normal structure when they come in contact with aqueous media or water. The swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produce produces a breakup of the tablet. This type of mechanism of starch has been recently to be studied.

6. Due to release of gases:

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet.

Table No 1: List of Superdisintegrants

Super disintegrants	**Examples**	**Mechanism of action**
Croscarmellose®	Cross Linked Cellulose	Sweling and Wickling
Crospovidone	Cross linked PVP	Very little swelling, act by capillary action.
Sodium starch glycolate	Cross linked starch	Swelling

Alginic acid NF	Cross linked Alginic acid	Rapid swelling and wicking action
Natural super disintegrants		
Calcium silicate(20 – 40%)		Wicking action

1.5.Techniques for Solubility Enhancement

There are various techniques available to improve the solubility of poorly soluble drugs, some of the approaches to improve the solubility are:

1. Physical Modification:

A.Particle size reduction

a. Micronization

b. Nanosuspension

B.Modification of the crystal habit

a. polymorphs

b. Pseudopolymorphs

C. Drug dispersion in carriers

a. Eutectic mixtures

b. Solid dispersions

c. Solid solutions

D. Complexation

a. Use of complexing agents

E. Solubilization by surfactants:

a. Microemulsions

b. Self microemulsifying drug delivery systems

2. Chemical Modifications

1.6. Solid dispersion Technique[29]:

40 - 60% of drugs used in pharmaceutical industry are poorly water soluble or lipophilic compounds. Poorly water soluble drugs show unpredictable absorption, since their bioavailability depends upon dissolution in the GIT. The dissolution characters of poorly water soluble drugs can be enhanced by several methods like pH adjustment, salt formation, co-crystallization, co-grinding, cosolvency, hydrotrophy, solubilization, size reduction like micronization, nano technology, complexation, and drug dispersion in carriers[30]. The solid dispersion can be prepared by fusion method,melting method, solvent method, Hot meltbextrusion method and Supercritical fluid method.

a. Fusion Method:

The fusion method is sometime otherwise called as melting method, if the starting material is crystalline. In this method, the carrier is heated to a temperature just above its melting point and the drug is incorporated in to the matrix. The first dispersion of sulfathiazole and urea was prepared by fusion method, by melting at the eutectic composition followed by cooling step. Polymers like Polyethylene glycols and Poly (vinyl pyrolidone) PVP are mostly used in this method.

Limitations:

- This method is suitable if the drug and polymer are compatiable and can be mixed homogeneously at the heating temperature in order to prevent formation of two incompatible liquids phases or a suspension in heated mixture. This problem can be overcome by using surfactants.
- Sometimes this problem during cooling stage when the drug – matrix miscibility changes which may produce phase separation. This problem is observed when cooling is done at slow rate, resulting in formation of crystalline drug.
- This method is not suitable if the carrier is high – melting solid and the drug is heat sensitive.

b. Hot melt extrusion method:

This method is same as fusion method except that the intensive mixing is included by the extruder. In this method twin – screw extruder or single extruder is used. This method offers the potential to shape the heated mixture in to implants, implants inserts, oral dosage forms. To detect the solid – state solubility and to select matrix suitable for melt extrusion, the solubility parameters are investigated. Higher shear forces resulting in high temperature in extruder may create a problem for heat sensitive materials.

The main advantage is the handling of product is easier because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.The polymers like Hydroxylpropyl cellulose, Hydroxypropyl cellulose phthalate, Eudragit, Celulose acetate phthalate (CAP), Poly vinyl alcohol (PVA), and Hydroxypropyl cellulose (HPC) can be used. Leing Wang, et al., have prepared solid dispersion of Nitredipine with silica particles using the melt mixing method[31].

c. Solvent method:

In this method, the carrier and the active ingredients are dissolved in suitable organic solvent. The second step involves the removal of solvent(S) under vacuum. When the solvent evaporates, super saturation may occur followed by simultaneous precipitation of the constituents resulting in a solid residue. In this formulation the scientist has to face two challenges.

- It is difficult to mix drug and polymer in one solution having different polarity.
- It is difficult to prevent phase separation during removal of solvent(s).
- The recovery of solvent from co precipitate takes longer time.

Example:

Ethanol:-5 C and reduced pressure followed by drying for 12h in vaccum Methanol / chloroform: 115 C for 1hr 125 C for 25min from Griseofulvin – PEG 6000 dispersion.

Drying at high temperature speeds up the drying process and reduces the time available for phase separation. On the other hand, high temperature speeds up the

phase separation (example: crystallization) because of the increase in the mobility of drug and polymer.

For example: Dimethyl sulfoxide (DMSO) has high melting point (190 C)but it has very low vapour pressure (0.08 kPa) hence not suitable solvent, but 2-methyl-2-propanol or tertiary butanol(TBA) is suitable solvent because it has high melting point (125 C) and vapor pressure (5.49 kPa).

Advantages:

Minimal thermal stress during preparation.

Reduction in chances of phase separation.

d. Supercritical fluid method:

In this method carbon dioxide is used either as solvent for drug and polymer or as an anti-solvent. When carbon dioxide is used as a solvent, the solution mixture of carbon dioxide with drug and polymer is sprayed through nozzle into an expansion vessel with lower pressure and resulting in formation of particles. As this techniques does not involve use of any organic solvent termed as "Solvent free technique" and also known as Rapid Expansion of Supercritical Solution (RES).

1.6.1. Advantages of Solid Dispersion Technology:

- Single formulation can be used to multiple dose formulation
- Improves bioavailability of drug.
- Improves dissolution of poorly water soluble drugs.
- Controlled release formulations can be formulated.

1.6.2. Breakthrough in Solid Dispersion Technology:

Recently, the primary goal of pharmaceutical industry is to discover a new chemical entity that would be safe and effective. Initially, because of the limited bulk drug supply and accelerated time line would not allow formulator to formulate solid dispersion formulations. Even though, the below two recent breakthroughs in the formulation of solid dispersion technology have renewed the interest for use in commercial development of drug product[32],[33].

The development of technology to fill solid dispersion directly into hard gelatin capsules. For example: Chatham prepared PEG-based solid dispersion by filling drug-PEG melts in hard gelatin capsules followed by solidification at room temperature. The availability of surface-active and self-emulsifying carriers For example: Gelucire 44/14, Polysorbate 80.

The availability of surface-active and self-emulsifying agent may help to increase bioavailability of the drug.

- For example: The bioavailability of ritronavir (solubility<lmcg/ml at pH.2) [Norvir®, Abbot Lab] was enhanced by incorporating dispersion into mixture of surfaceactive carriers as Gelucire 50/13, Polysorbate 80, and Polyoxyl 35 castoroil.

Table No 2: Commercially immediate release Tablets

Technologies	Trade Name	Active Ingredient	Manufacturer
Freeze Drying	Feldene Fast Melt	Piroxicam	Pfizer, USA
	Claritin Red i Tab	Loratidine	Schering plough, USA
	Maxalt MLT	Rizatriptan	Merck, USA
	Z Yprexia	Olanzepine	Eli Lilly, USA
	Pepcid RPD	Famotidine	Merck, USA
	Zofran ODT	Ondansetron	Glaxo, UK
	Zooming ZMT	Zolmitriptan	AstraZeneca, USA
	Zelapar TM	Selegilline	Amarin,UK
Disintegrant Addition	Tempra Quicklets	Acetaminophen	Bristol Myers, USA
	Febrectol	Paracetamol	Prographarma, France
	Nimulid MDT	Nimesulide	Panacea Biotech, India
	Torrox MT	Rofecoxib	Torrent pharma, India
	Olanex Instab	Olanzapine	Ranbaxy, India
	Romilast	Montelukast	Ranbaxy, India
Sugar Based Excipient	Benadryl Fastmelt	Diphenhydramine & Pseudoephedrine	WarnerLambert, USA

1.7. ANTI-DIABETIC [34]

Repaginate is a meglinide analogue used in the treatment of type II Diabetes mellitus.

It controls high blood sugar levels and helps in preventing kidney damage, blindness, nerve problems, loss of limbs, sexual problems & heart complications. This should not be used in type I Diabetes mellitus. It is a poorly water soluble drug belongs to BCS class II drug with short biological half - life 1hr. Repaglinide was enhanced by solid dispersion techniques like 1) drop melt techniques. Repaglinide dispersion was selected based on dissolution and formulated as tablet dosage form using various diluents and super disintegrates. The final; formulation was selected based on the dissolution profile that is formulation with MCC as a diluents and cross povidone as a super disintegrants.

1.7.1. Diabetes mellitus type 2 [35,36,37]:

Diabetes mellitus type 2 (formelycalle non - insulin dependent diabetes mellitus(NIDDM), or adult- onset diabetes) is a disorder that is high blood glucose in the context of insulin resistance and relative insulin deficiency. It is often initially managed by increasing exercise and dietary modification; medications are typically needed as the disease progresses.

1.7.2. Signs and symptoms[38]

- Early symptoms may be nothing more than chronic fatigue, generalized weakness and malaise
- Excessive urine production.
- Excessive thirst and increased fluid intake.
- Blurred vision
- Unexplained weight loss.
- Lethargy.

1.7.3.Classification of Antidiabetic agent

1. Insulin

2. Oralantidiabetic drugs

    a) Sulfonylureas

I. First - generation agents

    a. Tolbutamide

    b. ACetohexamide

    c.Tolazamide

    d. Chlorpropamide

II. Second - generation agents

    a. Glipizide

    b. Glyburide

    c. Glimepride

    d. Gliclazide

b) Meglitinides

    I. Repaglinide

ii. Nateglinide

c) Biguanides

I. Metformin

II. Phenformin

III. BUformin

2. LITERATURE REVIEW

D. Karthikeyan et al[39]., investigated the feasibility of formulating a biphasic delivery system using mini-tablets in hard gelatin capsules delivering drug with a variety of release profiles. Aceclofenac (NSAID analgesic) were chosen as model drug.

Noorana Tehseen et al[40]., worked on design and characterization of twice daily mini-tablets formulation of pregabalin in order to improve the half life and bioavailability.

Carla M. Lopes et al[41]., developed compressed mini tablets as a biphasic delivery system designed for zero-order sustained drug release. The outer layer that fills the void spaces between the mini-tablets was formulated to release the drug in a very short time (immediate release), while the mini-tablets provided a prolonged release. Different composition (HPMC or EC) and number (10 or 21) of mini-tablets were used to obtain different drug release rates. Based on the release kinetic parameters calculated, it can be concluded that mini-tablets containing HPMC were particularly suitable approaching to zero-order (constant) release over 8 h time periods.

Intender Joshi et al[42]., developed a once-daily sustained release matrix tablet of repaglinide using sodium alginate as release controlling factor. In order to achieve required sustained release profile tablets were compressed using sodium CMC, sodium alginate, Magnesium stearate, and PVP. Six different formulation of repaglinide were prepared by using different ratio of drug: polymer. The tablet was characterized by hardness, wetting time, weight variation and In Vitro Drug Release which shows the satisfactory result. All batches of solid matrix tablets were satisfactory in terms of dissolution profile. The batches of all formulations, MT5 batch [Sodium CMC With drug (1:3)] showed more release than the other concentration and better results.

Bhatti et al[43] prepared fast dissolving tablets of diazepam and provided it`s advantages and evaluation methods.

C.MalligarjunaShetty et al[44] described the formulation of fast dispersible aceclofenac tablets and described the Effect of functionality of super disintegrants.

Caramella et al[45] described the role of swelling property in the disintegration process also described how it influences the disintegration process.

Cirri M et al[46] formulated fast dissolving tablets of Glyburide based on ternary solid dispersion with PEG6000 and surfactants.

Sarasija Suresh et al [47]prepared mouth dissolving tablets of salbutamol sulphate by using sublimable ingredients. Selection of the filter also had an important role in deciding of the disintegration time. Evaluation of the tablets showed that all the tablets were found to be within official limits and the disintegration time for the formulations ranged from 5s to 4s .Amongest all, the formulation contraining micro crystalline cellulose and ammonium bicarbonate showed the least disintegrating time of 5s.

USPTO Patent 20601657821[48] described about orally disintegrating tablets for per oral administration which disintegrate quickly in the cavity of mouth, in particular less than 30 seconds and the process of obtaining them.

Kaushik D et al[49]., studied mouth dissolving tablets emerged at an alternative to conventional oral dosage forms. Freeze drying, sublimation, spray drying, disintegrant addition, tablet moulding and use of sugar-based excipients are the techniques available for the formulation of mouth dissolving tablets. Despite the different mechanisms involved in these techniques, the aim is, to provide the tablet that quickly disintegrates or dissolves upon contact with saliva and also provides a god mouth feel.

Zhao et al[50] described the development of disintegrating functionality test for super disintegrants, also provides methods to test the efficiency of superdisintegrants.

Koizumi et al [51], described about rapidly saliva tablets using sublimation technique. Compressed tablets of mannitol did not dissolve in water due to the low porosity. To increase the porosity of tablets sublimation was done. Tablets were prepared by direct compression containing mannitol and camphor. A high porosity was achieved due to formation of many pores due to camphor sublimation. The

compressed tablets have high porosity (approximately 30%) rapidly dissolved within 15 seconds in saliva.

Combo P et al[52] described about disintegration force, showed disintegration force is a new formulation parameter.

D.P.Venkadesh et al [53]formulated taste masked orodispersible tablets of ambroxxol hydrochloride.

Ferrari F et al[54] provided the information about influences of porosity and solubility of disintegrant in tablets.

Caramella et al [55] described the role of swelling property in the disintegration process also described how it influences the disintegration process.

Jeevana Jyothi et al[56] developed immediate release tablets of glibenclamide using crosspovidone and its Kneading Mixture.

M M Patel et al [57] prepared rapid disintegrating tablets of valdecoxib by using various superdisintegrants following direct compression technique.

Martin et al[58]., reviewed the cyclodextrin and their uses. It provides information regarding the history preparation, complex formation of cyclodetrins and industrial applications.

Pisal et al [59] formulated and evaluated tasteless complexes of ciprofloxacin with Iodine 234. Studies showed that complication affected by pH, but temperature not affected. Volunteers rated the complex as tasteless.

3. AIM AND OBJECTIVE

The aim of the present work is to investigate the possibility of obtaining immediate release tablet of repaglinide with improved dissolution using Solid dispersion technique.

Basic goals in the immediate release tablets are to increase patient compliance, ease of administration, safety and appropriate dosing. Orally disintegrating formulations are provide benefits for pharmaceutical companies like lifecycle management , line extension, market expansion, cost effective drug development programs.

Immediate release tablet has perceived faster onset of action. repaglinide is a white or half white powder, relatively insoluble in water. It is a class 2 drug according to BCS Classification Solubility and dissolution was improved by formulating solid dispersion. The advantage of this delivery system, in the present study were made to formulate immediate release tablet repaglinide, which is useful to reduce sudden increased glucose level in the treatment of non- insulin dependent diabetes mellitus (NIDDM).

The direct compression was used to compress the tablets as it is easy way to manufacture tablets. Conventional equipments, commonly available excipients and limited number of processing steps are involved in direct compression and so manufacturing cost is low. Tablets produced by direct compression are relatively strong and hardness and have less friability.

4. PLAN OF WORK

Stage – 1

- Literature Survey
- Selection of Drug and Excipients

Stage - 2

Preformulation Studies

- Evaluation of Physical Parameters of repaglinide
- Drug Excipients Compatibility study
- Construction of standard curve

Stage – 3

- Preparation of Solid Dispersion and Physical Mixture
- Characterization of Solid Dispersion and Physical Mixture

Stage – 4

- Preparation And Evaluation of Natural Superdisintegarants

Stage – 5

Precompression Parameters

- Formulation of Immediate Release Tablets With Different super Disintegrants

Stage – 6

Evaluation of Immediate Tablets.

- Weight variation
- Friability
- Thickness
- Hardness

- disintegration
- Wetting time
- Uniformity of dispersion
- Water absorption ratio
- Assay
- *In-vitro* dissolution study

Stage – 7

- Stability Study of optimised formulaiton as per ICH Guidelines

5. PROFILES

5.1. DRUG PROFILE:

REPAGLINIDE:

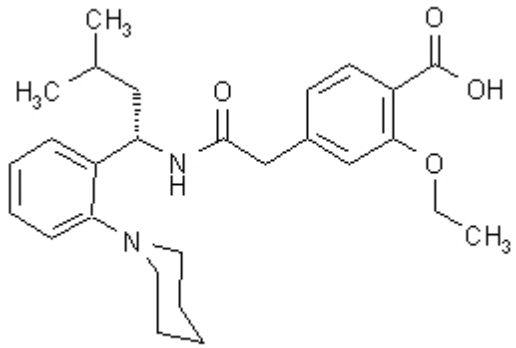
PRANDIN® (repaglinide) is an oral blood glucose-lowering drug of the meglitinide class used in the management of type 2 diabetes mellitus (also known as non-insulin dependent diabetes mellitus or NIDDM).

CHEMICAL NAME:

Repaglinide, S (+) 2-ethoxy-4(2((3-methyl-1-(2-(1-piperidinyl) phenyl)-butyl) amino)-2-oxoethyl) benzoic acid, is chemically unrelated to the oral sulfonylurea insulin secretagogues.

Chemical Structure:

The structural formula is as shown below:



Molecular Weight: 452.6

Category: (ß) cells in the pancreatic islets.

Description: white to off – white.

Storage: Do not store above 25° C (77° F). Protect from moisture. Keep bottles tightly closed. Dispense in tight containers with safety closures.

Mechanism of Action

Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta (ß) cells in the

pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations.

Repaglinide closes ATP-dependent potassium channels in the ß-cell membrane by binding at characterizable sites. This potassium channel blockade depolarizes the ß-cell, which leads to an opening of calcium channels. The resulting increased calcium influx induces insulin secretion. The ion channel mechanism is highly tissue selective with low affinity for heart and skeletal muscle.

Pharmacokinetics

Absorption:

After oral administration, repaglinide is rapidly and completely absorbed from the gastrointestinal tract. After single and multiple oral doses in healthy subjects or in patients, peak plasma drug levels (Cmax) occur within 1 hour (Tmax). Repaglinide is rapidly eliminated from the blood stream with a half-life of approximately 1 hour. The mean absolute bioavailability is 56%. When repaglinide was given with food, the mean Tmax was not changed, but the mean Cmax and AUC (area under the time/plasma concentration curve) were decreased 20% and 12.4%, respectively.

Distribution:

After intravenous (IV) dosing in healthy subjects, the volume of distribution at steady state (Vss) was 31 L, and the total body clearance (CL) was 38 L/h. Protein binding and binding to human serum albumin was greater than 98%.

Metabolism:

Repaglinide is completely metabolized by oxidative biotransformation and direct conjugation with glucuronic acid after either an IV or oral dose. The major metabolites are an oxidized dicarboxylic acid (M2), the aromatic amine (M1), and the acyl glucuronide (M7). The cytochrome P-450 enzyme system, specifically 2C8 and 3A4, have been shown to be involved in the N-dealkylation of repaglinide to M2 and the further oxidation to M1. Metabolites do not contribute to the glucose-lowering effect of repaglinide.

Excretion:

Within 96 hours after dosing with 14C-repaglinide as a single, oral dose, approximately 90% of the radiolabel was recovered in the feces and approximately 8% in the urine. Only 0.1% of the dose is cleared in the urine as parent compound. The major metabolite (M2) accounted for 60% of the administered dose. Less than 2% of parent drug was recovered in feces.

It indicate that repaglinide did not accumulate in serum. Clearance of oral repaglinide did not change over the 0.5 - 4 mg dose range, indicating a linear relationship between dose and plasma drug levels.

Variability of Exposure:

Repaglinide AUC after multiple doses of 0.25 to 4 mg with each meal varies over a wide range. The intra-individual and inter-individual coefficients of variation were 36% and 69%, respectively. AUC over the therapeutic dose range included 69 to 1005 ng/mL*hr, but AUC exposure up to 5417 ng/mL*hr was reached in dose escalation studies without apparent adverse consequent

5.2.EXCIPIENT PROFILE:

CROSS POVIDONE[60]

Synonyms	:	Crosslinkedpovidone ; EI 202 ; Kollidon CL ; Kollidon CL-M;polyplasdon XL 10 ; Polyvinyl poly pyrrolidone ; PVPP ; 1-vinyl -2- pyrrolidone homopolymeress or nearly odourless hygroscopic powder.
Description	:	Crospovidone is a white to creamy white finely devided, free Flowing practically tasteless, odorless
Chemical name	:	1-ethenyl -2 – pyrrolidone homopolymer.
Molecular weight	:	>1000000
Functional category	:	Tablet disintegrant

Applications in Pharmaceutical Formulation

Cross povidone is a water –insoluble tablet disintegrant and dissolution agent used at 2-5% concentration in tablet prepared by direct compression method (1-6). It rapidly exibit high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets

SODIUM STARCH GLYCOLATE[60]

Synonyms	:	Primojel; Starch carboxy Methyl ether, sodium salt, Tablo;
Description	:	Tasteless, free flowing powder. The PhEur 2005 states that it consist of oval or spherical granules, 30-100 um in diameter, with some less spherical granules ranging from 10-35um in diameter.
Chemical name	:	Sodium carboxy methyl starch.
Molecular weight	:	5 X 10 5 -1
Functional category	:	Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation

Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablets prepared by either direct compression or wet granulation process. The usual concentration employed in a formulation is between 2% and 8% with the optimum concentration about 4% although in many cases 2% is sufficient. Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.

Although the effectiveness of many disintegrant is affected both presence of hydrophobic excipients such as lubricant the disintegrant efficiency of sodium starch glycolate is unimpaired increasing the tablet compression pressure also appears to have no effect on disintegration time. Sodium starch glycolate has also been investigated for use as a suspending vehicle.

CARBOXY METHYL CELLULOSE CALCIUM[60]

Synonyms	:	Calcium CMC ; ECG 505 ; Nymcel ZSC ; Calcium Carboxy methyl cellulose
Description	:	It occurs as a white to yellowish- white hygroscopic fine powder
Chemical name	:	Cellulose, carboxy methyl ether, calcium salt
Functional category	:	Stabilizing agent, suspending agent, tablet and capsule disintegrant; tablet binder; viscosity increasing agent Water Abosrbing agent.

Application in Pharmaceutical Formulation

It used as binder, diluents and disintegrant. It is an effective disintegrant as it swells to several times it's original bulk on conduct with water. Concentration up to 15 % w/w may be used in tablet formulations; above this concentration, tablet hardness is reduced.

It is also used as suspending or viscosity increasing agent in oral and topical formulations. And also used in modern wound dressings for it's water absorption, retension and hemostatic properties.

SODIUM STEARYL FUMERATE[60]

Synonyms	:	Fumeric acid, Otadecyl ester sodium salt; Pruv ; Sodium monosrearylfumerate.
Description	:	Sodium stearylfumerate is a fine white powder with agglomerates of flat, circular shaped particles.
Chemical name	:	2-butenedioic acid, monooctadecyl ester, sodium salt.
Molecular weight	:	390.5
Functional category	:	Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation

Sodium stearylfumerate is used as lubricant, in capsule and tablet formulations at 0.5 – 2.0 % w/w concentration. It is also used in certain food applications conditioning or stabilizing agent in various backery Products, flour-thickened foods, dehydrated potatos and processed cereal up to 0.2-1.0 % by weight of the food.

TALC [61]

Synonyms : talc ; E 55 3 b; hydrous magnesium calcium silicate ; hydrous magnesium Silicate; magnesium hydrogen metasilicate; Magsilosmanthus; magsil star; powdered talc; purified French chalk; Purtalc ; soapstone; steatite; superior

Description : Talc is very fine to grayish –white, odorless, impalatable, unctuous, crystalline powder. It adheres readily to the skin and is soft to touch and free from grittiness.

Chemical name : Talc

Functional category : Anticaking agent; glidant; tablet and capsule diluents;

Applications in pharmaceutical formulation

Talc was once widely used in oral solid dosage formulations as a lubricant and diluent although today It is less commonly used. It is widely used as dissolution retardant in the development of controlled release product. Talc is used as a lubricant in tablet formulations; in novel powder coating for extended-release pellets; and as an adsorbent**.**

In topical preparations, talc is used as a dusting powder, although it should not be used to dust. Surgical gloves. As it is a natural material it may contain microorganisms and should be sterilized when used as dusting powder. Talc used to clarify liquids and is also used in cosmetics and food products, mainly for it's lubricant properties

POLYETHYLENE GLYCOL 6000[60]

Synonyms : Breox peg; carbowax; hodag peg; lutrol E; PEG: polyethylene glycol.

Description : Polyethylene glycols grades 6000 and above are available as free-flowing milled powders, colorless or slightly yellow colured. They have a slight, but characteristic odour and a bitter, slightly burning taste.

Chemical name : ά-hydro-ω- hydro- poly (oxy-1, 2- ethane diyl) and [25322-68-3]

Molecular weight: : 5000 – 7000 (average molecular weight)

Typical properties:

1. Density; 1.15–1.21 g/cm^3 at 25°C.
2. Melting Point: 55–63°C
3. pH (5% w/v solution): 4.0-7.0.
4. Hydroxyl value: 16–22.

Incompatibilities:

All grades can exhibit some oxidizing activity due to the presence of peroxide impurities and some secondary product formed by auto- oxidation. Solid polyethylene glycols grades may be incompatible with some colour.

Safety:

Nontoxic and non-irritant material, when administered topically may cause stringing.

Application in pharmaceutical formulation:

Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble compounds by making solid dispersions with an appropriate polyethylene glycol. Animal studies have also been performed using polyethylene glycols as solvents for steroids in osmotic pumps.

MICROCRYSTALLINE CELLULOSE[60]

Nonproprietary Names:

- BP: Microcrystalline cellulose
- JP: Microcrystalline cellulose
- PhEur: Cellulosummicrocristallinum
- USPNF: Microcrystalline cellulose

Synonyms:

Cellulose gel;; crystalline cellulose; E460;; Fibrocel;; Tabulose.

Chemical Name and CAS Registry Number:

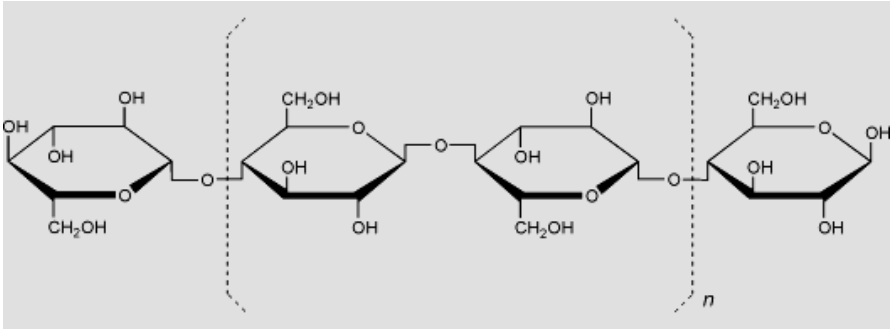
Cellulose [9004-34-6]

Empirical Formula and Molecular Weight:

$(C_6H_{10}O_5)_n$ ≈36 000

where n ≈ 220.

Structural Formula:



Functional Category:

Adsorbent; suspending agent; tablet and capsule diluents; tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a 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 a binder/diluents (20–90%), microcrystalline cellulose also has some lubricant and disintegrant (5–15%) properties that make it useful in tableting.

Description:

Microcrystalline 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 sizes and moisture grades that have different properties and applications.

Density (bulk)

- 0.337 g/cm^3;
- 0.32 g/cm^3 for Avicel PH-101; 0.29 g/cm^3 for Emcocel 90M; 0.29 g/cm^3 for VivaPur 101.

Density (tapped) :

- 0.478 g/cm^3;
- 0.45 g/cm^3 for Avicel PH-101;
- 0.35 g/cm^3 for Emcocel 90M.

Density (true):

- 1.512–1.668 g/cm^3

Melting point:

Chars at 260–270°C.

Solubility:

Slightly soluble in 5 % w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Stability and Storage Conditions:

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

6. MATERIALS AND METHODS

MATERIALS USED

List of Materials used for the research work was given in table by:

TABLE NO. 3

INGREDIENTS	SUPPLIERS
Repaglinide	Microlabs Ltd,Hosur
PEG6000	MicrolabsLtd,Hosur
Micro crystalline cellulose	Lobachemi,Mumbai
Sodium Starch Glycolate	Research lab fine chem, Mumbai
Cross Povidone	Research lab fine chem, Mumbai
Sodium alginate	Lobachemi,Mumbai
Talc	Lobachemi,Mumbai
Aspartame	Bangalore antibiotics &Biological, Salem
Methanol	Himmedialab,Mumbai
Aerosil	Lobachem. Mumbai
Hcl	Microlab,Mumbai

TABLE NO.4

List of Instrument Used

Name of Instrument	Manufacturing Company
Digital Balance	Shimadzu Corporation Japan
Magnetic stirrer	Remiequipments
Hot air oven	In lab equipments, chenai
Orbit Shaker	Lab India
Proton Pump Mini Single Punch	Proton
Hardness tester	Tab machines
Friability tester	Roche Friabilator
Vernier caliper	Mituyoko Japan
Dissolution Apparatus	Lab India Disso 2000
UV Visible spectrophotometer	Lab India
FT IR Spectrometer	Bruker Germany
Disintegration	Rolex

6.1 PRE-FORMULATION STUDIES[62]:

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms.

6.1.1 Organoleptic properties:

Appearance

Transferred approximately 2gm of the sample on a white paper spreaded uniformly and examined visually.

Colour: a small quantity of pure repaglinide powder was taken in a butter paper and viewed in well illuminated place.

Taste and odour: very less quantity of repaglinide was used to get taste with the help of tongue as well as smelled to get the odour.

6.1.2 Angle of repose:

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The prepared granules were allowed to flow out of the funnel orifice fixed at a height of 2 cm from the surface on a plane paper kept on the horizontal platform. The gradual addition of the granules from the funnel mouth forms a pile of granules at the surface this is continued until the pile touches the stem tip of the funnel. A rough circle is drawn around the pile base and the radius of the granule cone was measured.

Angle of repose was then calculated with the use of the following formula:

$$\tan\theta = h / r$$

Where, θ = angle of repose, h= height of the pile, r = average radius of the powder cone.

Limits:

TABLE NO. 5

Angle of repose	Flow property
<25°	Excellent
25-30°	Good
30-40°	Passable
>40°	Very poor

6.1.3: DETERMINATION OF DENSITIES

Bulk Density: Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle become more spherical in shape, bulk density was increased. In addition as the granule size increases bulk density decreases.

METHODS:

Bulk density of the sample was determined by pouring gently 10g of sample through a glass funnel into a 50ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density will be calculated as follows:

Bulk Density (g/ml) = Weight of sample in grams Volume occupied by the sample.

TAPPED DENSITY:

10 grams of sample was being poured gently through a glass funnel into a 50ml graduated cylinder. The cylinder will be tapped from height of 2 inches until a constant volume will be obtained. Volume occupied by the sample after tapping will be recorded and tapped density will be calculated as follows:

Tapped Density (grams/ml) = Weight of sample in grams Volume occupied by the sample.

6.1.4.Measurement of Powder Compressibility:

Based on the apparent bulk and the tapped density, the percentage compressibility of bulk was determined by the following formula

Compressibility index*:* $100\frac{(V_0 - Vf)}{V_0}$

Where, Vf = final tapped volume, Vo = initial un tapped volume

Limits:

TABLE NO.6

S. No.	Compressibility index	Flow
1	5-12	Free flow
2	12-16	Good flow
3	18-21	Fair
4	23-25	Poor
5	33-38	Verypoor
6	>40	Extremely poor

HausnerRatio*:* = $\frac{V_0}{Vf}$

Where, Vf = final tapped volume, Vo = initial un tapped volume

6.1.5 LOSS ON DRYING:

Determine on 1 g by drying in an oven at 100°C to 105°C for 3 hours. Mixed and accurately weighed the substance to be tested. Tare a glass stopper, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Weighed the empty bottle (W_1). Put the sample in bottle, replace the cover, and accurately weighed the empty bottle with contents (W_2). By gentle, sidewise shaking, distributed the sample as evenly as practicable to a depth of about 5 mm. placed the loaded bottle in the drying chamber. Dried the sample at the specified temperature in desicator before weighing. Weighed the bottle (W_3).The difference between successive weights should not less than 0.3%.

The loss on drying is calculated by the formula:

$$\% LOD = \frac{(W_2 - W_3)}{(W_2 - W_1)} x\ 100$$

Where, W_1 = Weight of empty weighing bottle

W_2 = Weight of weighing bottle + sample

W_3 = Weight of weighing bottle + dried sample

6.1.6 SOLUBILITY ANALYSIS :

Solubility is important pre-formulation parameter because it affects the dissolution of drug, bio availability of drug, less soluble in water, solubility of repaglinide was determined in methanol, ethanol, dimethyl fluoride methylchloride, 0.1NHCl. Solubility studies were performed by taking excess amount of repaglinide in different beakers containing the solvent.

6.1.7. P^H

Weighed and transferred accurately about 1.0 g of sample in 20 ml clean and dried volumetric flask dissolved in methanol free water and made up the volume to 20 ml with the same solvent, mixed. Determined the p^H of freshly prepared solution by using recalibrated p^H meter.

6.1.8.ASSAY

Weighed accurately 10mg of repaglinide sample and added to 100 ml volumetric flask. Added 1ml of methanol mixed for 10 minutes added 60ml of 0.1 N Hydrochloric acid and dissolved it. Made up the volume to 100ml with 0.1 N Hydrochloric acid. Took 10ml and diluted to 100ml with 0.1 N HCL. Took 1ml and diluted to 10 ml with 0.1 N HCL, absorbance measured at 283nm.

6.2 DRUG-EXCIPIENT COMPATIBILITY STUDY BY FTIR

Infra red spectroscopy is one of the most widely used tools for purity analysis of drugs in pharmaceutical Industry. Fourier Transform IR spectra were recorded using bruker Germany. IR spectrophotometer. KBr powder was used to prepare pellet for sampling. The scanning range was 4000- 40cm

6.3 PREPARATION OF STANDARD CURVE

The calibration curve is based on the spectrophotometry. The maximum absorption was observed at 283nm.

The Standard solution in repaglinide in pH acetate buffer 10mg of repagilinde is accurately weighed and dissolved in 10ml containing methanol in a volumetricflask. The various concentrations of repaglinide prepared are 10, 20, 30, 40, 50, 60, ug/ml. The absorbance of various solutions of repaglinide are determined spectrophotometricaly at 283nm employing UV double beam spectrophotometer using acetate buffer of pH.

6.4 PREPARATION OF SOLID DISPERSION AND PHYSICAL MIXTURE[63] :

6.4.1. Solid dispersions prepared by melting the carrier

Solid dispersions (SDs) preparations containing different weight ratios of repaglinide in PEG6000 (1:1, 1:3, 1:5) were prepared by the melting method. repaglinide was added to the melted PEG 6000 at 75^{o}C and the resulting homogenous preparation was rapidly cooled in a freezing mixture of ice and sodium chloride, and stored in desiccators for 24h.Subsequently, the dispersion was ground in a mortar and sieved through 100#

6.4.2.Physical Mixture

Physical mixture (PMs) having the same weight ratios were prepared by thoroughly mixing appropriate amounts of repaglinide and PEG 6000 in a mortar until a homogenous mixture was obtained. The resulting mixture were sieved through a 100# sieve and denoted as PM.

6.5 Characterization of solid dispersions of repaglinide with PEG 6000[64]

6.5.1 Drug content

About 10mg of drug equivalent of physical mixture and solid dispersion (theoretical) were weighed accurately and transferred to 50ml volumetric flask to which 10ml methanol was added and sonicated for 15min and volume was made up with methanol. From this stock solution further dilution were done and assayed using ultraviolet spectrophotometer measured at 283nm.

6.5.2 Phase-Solubility Study

Phase-solubility studies were carried out to evaluate the possible solubilizing effect of the carrier by adding an excess amount of drug to flask containing 10ml of aquous solutions containing increasing concentrations of PEG6000.The flask were placed in a mechanical shaker at 75rpm and room temperature for 24hour.After 24 Hours the solutions were filtered and analysed by UV-Spectrophotometer at 283nm..

6.5.3 Dissolution Studies:

Dissolution studies of repaglinide in powder form, SDs, and PMs were performed by using the USP type II paddle apparatus at the paddle rotation speed of 75 rpm in 900ml of pH 5 acetate buffers as a dissolution medium at 37±0.5 °C. The SDs or PMs Equivalent to 2mg of repaglinide was weighed using a digital balance and added into the dissolution medium. At the specified times (every 10 min for 2 hours), 10ml samples were withdrawn by using syringe filter (0.45 μm) and then assayed for repaglinide content by measuring the absorbance at 283 nm using a UV-Visible spectrophotometer. Fresh medium (10ml), which was prewarmed at 37 °C, was added to the dissolution medium after each sampling to maintain its constant volume throughout the test.

6.5.4. Fourier transforms IR spectroscopy:

Fourier-transform infrared (FT-IR) spectra were obtained by using Bruker Germany FTIR. The samples (repaglinide or SDs or PMs) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample/KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press.

6.6. Preparation of natural superdisintegrants (plantago ovata seed powder, mucilage and husk powder)[65]:

The powder of seeds and husk were prepared by an automatic grinder and sieved (#80). Then it stored in a dedicator until use .For isolation of seed mucilage, the cleaned seeds of Plantagoovata were soaked in distilled water 48 hrs and then boiled few minutes so that mucilage was completely released in to water. This material squeezed through muslin cloth for filtering and separating out the marc. Then an equal

volume of acetone was added to the filtrate so as to precipitate the mucilage .The mucilage was dried in oven (less than 60^{o}C), powdered, sieved (# 80) and stored in desiccators until use.

The natural super disintegrants were evaluated for their physicochemical properties. The swelling index is calculated, it is the volume in milliliters that is occupied by 1g of drug or any substance after it has swollen in an aqueous liquid for4 hr. The physical mixture of drug complex with this super disintegrants was allowed to stand for 7 days and the assay of drug was performed for compatability studies.

Preparation of the prepared natural super disintegrants were evaluated for swelling factor, bulk density, tapped density, angle of repose. Angle of reposewere calculated according to the formula procedure in 6.1.4 bulk density and tapped density were found out using the procedure given compressibility and hausner's ratio were found out according to the formula 6.1.4.

6.7. FORMULATION OF IMMEDIATE RELEASE TABLETS OF REPAGLINIDE.[66]

Different repaglinide Immediate Release Tablets were prepared according to the proportions given in the table no 9. The raw materials passed through a screen (# 60). Prior to mixing powdered separately the repaglinide Solid dispersion, and weighed the amount equivalent to 10 mg repaglinide, was mixed with other excipients and compressed proton mini press tablet punching machine. All formulation prepared according to the following formulation table.

FORMULATION OF IMMEDIATE RELEASE TABLET

Table No - 7

S. No.	Ingredient Name	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	1:5 Solid Dispersion equivalent to 2mg Repaglinide	10	10	10	10	10	10	10	10	10	10	10	10
2	Micro crystalline Cellulose	92	92	92	92	92	92	92	92	92	92	92	92
3	Mannitol	80.0	78.0	80.0	78.0	80.0	78.0	80.0	78.0	80.0	78.0	80.0	78.0
4	Isphagol Mucilage	10	12.0	-	-	-	-	-	-	-	-	-	-
5	IsphagolPowder	-	-	10.0	12.0	-	-	-	-	-	-	-	-
6	Iphagol husk powder	-	-	-	-	10.0	120	-	-	-	-	-	-
7	Cross Povidone	-	-	-	-	-	-	10.0	12.0	-	-	-	-
8	CMC		-	-	-	-	-	-	-	-	-	10.0	12.0
9	SSG	-	-	-	-	-	-	-	-	10.0	12.0	-	-
10	Talc	2	2	2	2	2	2	2	2	2	2	2	2
11	Aspartame	1	1	1	1	1	1	1	1	1	1	1	1
12	Aerosil	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
13	Orange Flavour	1	1	1	1	1	1	1	1	1	1	1	1
	Total weight	200	200	200	200	200	200	200	200	200	200	200	200

6.8. Evaluation of Immediate Release Tablet[67]:

6.8.1 PHYSICALAPPEARANCE

Prepared immediate release Tablets were evaluated for the smoothness and absence of cracks, chips and other undesirable characteristics

6.8.2 WEIGHT VARIATION

Twenty tablets were randomly selected and weighed to determine the average weight and were compared with individual tablet weight. The percentage weight variation was calculated. As per Indian Pharmacopoeia specification, tablet with an average weight between 80 – 250 mg, percentage deviation should not more than ±o.5 % and the tablet with an average weight more than 250 mg should not be more than ± 10 %.

$$\% \text{ Deviation} = \frac{\text{Tablet weight} - \text{Average weight}}{\text{Tablet weight}} \times 100$$

6.8.3 FRIABILITY[68]

Friability of the tablets was checked by Roche friabilator. In this device, tablets subjected to combined effects of abration and shock by utilizing a plastic chamber that revolves at 75 rpm, dropping the tablets at a distance of6 inches in each revolution. Pre weighed tablets were placed in friabilator, which was then operated for 100revolutions. The tablets were dusted and reweighed.

$$F = \frac{W_0 - W_1}{W_0} \times 100$$

W0 = initial weight,W_1 =final weight

6.8.4 THICKNESS

The thicknesses were measured using vernier caliper and values were tabulated. Three tablets of each batch were measured. Average and standard deviation was calculated.

6.8.5 HARDNESS

Monsanto hardness tester was used for the determination of hardness. For each formulation 3 tablets were determined.

6.8.6 DISINTEGRATION TIME[69]

A disintegration time of6 tablet from each formulation was determined by using USP disintegration apparatus. Disintegration test was carried out in 900ml buffer pH 6.8at 37 ± 2 ^{0}Cand apparatus operated for 3 minutes, six tablets were taken and one tablet was introduced in each tube, disc was placed and basket and the disintegration time in seconds was noted.

6.8.7 WETTING TIME

This is carried out as a measure of hydrophilicity of tablets. Wetting time is a length of time required to wet the tablet. A piece of tissue paper (12 x 10.75) was

folded twice was placed in the small Petri dish (I.D 6.5cm) containing 6 ml of buffer pH 6.8 simulated to salivary pH, tablet was placed on the paper and time for complete wetting was measured. Three trials of each batch were performed and standard deviation was determined.

6.8.8 UNIFORMITY OF DISPERSION TEST

Two tablets from each batch were separately kept in 100 ml water and gently stirred for 2 minutes. The dispersion was passed through 22 mesh. The tablets were considered to pass the test if no residue remained on the screen.

6.8.9 WATER ABSORPTION RATIO

Water absorption ratio, which is important criteria for understanding the capacity of disintegrants to swell in the presence of little amount of water. Weight of the tablet after and before the test was taken. Water absorption ratio (R) is calculated using following formula.

$$R = \frac{W_a - W_b}{W_b} X\ 100$$

Where,

W_a = weights of the tablets after water absorption test

W_b = weight of the tablets before water absorption test

6.8.10 ASSAY[70]

STANDARD PREPARATION

Weigh accurately 100 ml volumetric flask, dissolved in minimum quantity of methanol. The volume made up to 100 ml with 0.1 N hydrochloric acid. Took 10 ml of that solution and diluted to 100 ml with 0.1 N hydrochloric acid. Took 1 mlfrom that solution and diluted to 10 ml with 0.1 N hydrochloric acid.

SAMPLE PREPARATION

Mixed well and volume made up to 100ml. Filtered the solution and 10 ml of this solution diluted to 100 ml. From that took 1ml and diluted to 10 ml. Absorbance measured at 283 nm by UV/Visible spectrophotometer.

$$\frac{\text{Average sample absorbance}}{\text{Average sample absorbance}} \times \frac{\text{standard dilution}}{\text{sample dilution}} \times \frac{\text{avg wt.}}{\text{std.purity}} \times 100$$

6.8.11 DISSOLUTION STUDIES[71]

Dissolution studies were carried out using USP type II (paddle apparatus) at 75rpm pH 5 acetate buffer was used as dissolution medium. Temperature was maintained at 37 ±0.5 ^{0}C. Aliquots of dissolution media was withdrawn at specific time intervals and it was filtered. Same quantity of fresh media was replaced. The filtered solution was used to determine the estimation of drug content. The absorbances were measured at 283 nm by UV/Visible spectophtometer. The test was carried out for 30 minutes

6.8.12 KINETIC STUDY

The release data obtained from optimized formulation was studied further for the fitness of data in different kinetic models like, zero order, first order, Higuchi's and korsmeyer – Peppa's.

6.9 ACCELERATED STABILITY STUDIES

Selected formulation were subjected to stability studies as per I.C.H guidelines. Following conditions were used for stability testing. 40^0 C / 75 % RH analyzed every month for a period of two months as per I.C.H guidelines. By keeping 40 ± 2^{0}C /RH the formula analyzed every month for a period of 3 months.

7. RESULTS AND DISCUSSION

7.1 Preformulation Studies

7.1.1 Organlopetic Properties

These tests were performed as per procedure given in 6.1.1. The results were illustrated in table no.8.

Table No. 8: Organoleptic Properties

Test	Specification/Limits	Observations
Color	White to half-white powder	White powder
Odour	Odourless	Odourless

7.1.2 Loss on Drying

This test was done as per procedure stated in 6.1.2. The results were illustrated in table no.9.

Table No.9 : Loss on Drying

Test	Specification/Limits	Observations
Loss on drying	Not more than 0.5%	0.085%

7.1.3 Flow Properties (Angle of repose)

It was determined as per procedure given in 6.1.3. The results were illustrated in tables No. 10.

Table No.10: Flow properties

Material	Angle of repose
Repaglinide	27.85``

*Average of three determinations

7.1.4 Determination of Density

It was determined as per procedure given in 6.1.4. The results were illustrated in table no. 11.

Table No.11: Density

Material	Bulk Density (gm/ml)	Tapped density (gm/ml)
Repaglinide	0.24	0.35

*Average of three determinations

7.1.5. Powder compressibility

It was determined as per procedure given in 6.1.5. The results were illustrated in table no. 12.

Table No.12: Powder Compressibility

Materials	Compressibility index	Hausner ratio
Repaglinide	14.23%	1.84%

*Average of three determinations

7.1.6. Solubility

It was determined as per procedure given in 6.1.6. The results were illustrated in table no. 13.

Table No.13: Solubility

Test	Specification	Result
Solubility in water, Methanol, Methylene chloride.	Practically insoluble in water, freely soluble in methylene chloride, soluble in methanol	Complies

7.1.7 pH of the solutions

pH of the solution was determined as per procedure given in 6.1.7. The results were illustrated in table no. 14.

Table No.14: pH

Test	Specification	Observation
pH	5.5	5

7.1.8. Assay

It was determined as per procedure given in 6.1.8. The results were illustrated in table no. 15.

Table No.15: Assay

Assay

Test	Specification	Observation
Assay	90.8-101.75 %	101.18%

7.2 DRUG EXCIPIENTS COMPATABILITY STUDY BY FTIR;

Compatibility study was perfomed using FT-IR spectrophotometer .The IR spectrum of pure drug, physical mixture of drug and excipients were studied by making a KBr pellet.

7.2.1 FTIR Studies

The spectral details for the drug and physical mixtures are shown as follows

FT-IR Peak Of Various Components**.**

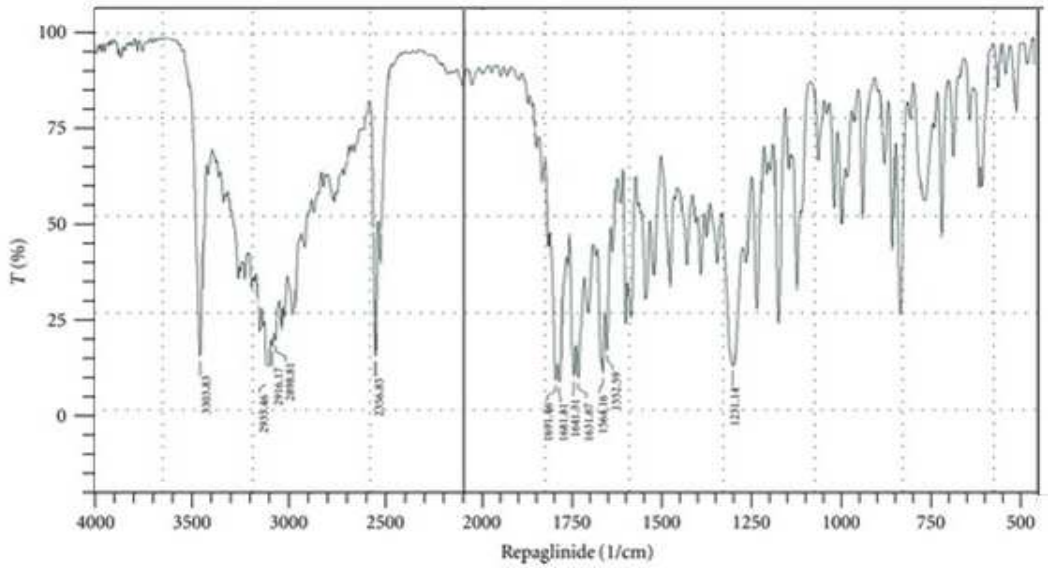


Fig.No. 1: IR spectrum of Repaglinide

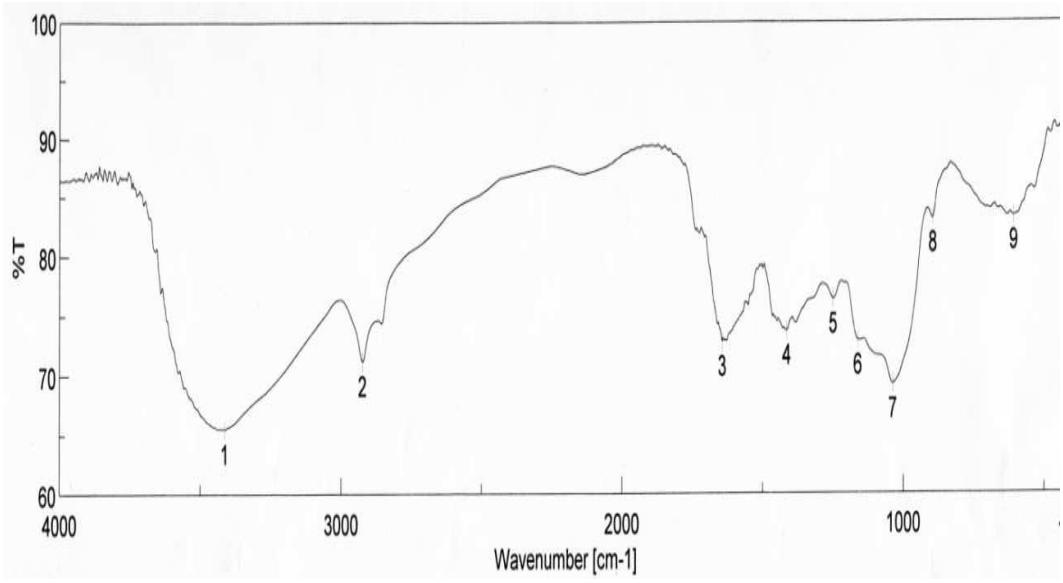


Fig. No. 2: Ispagol Mucilage

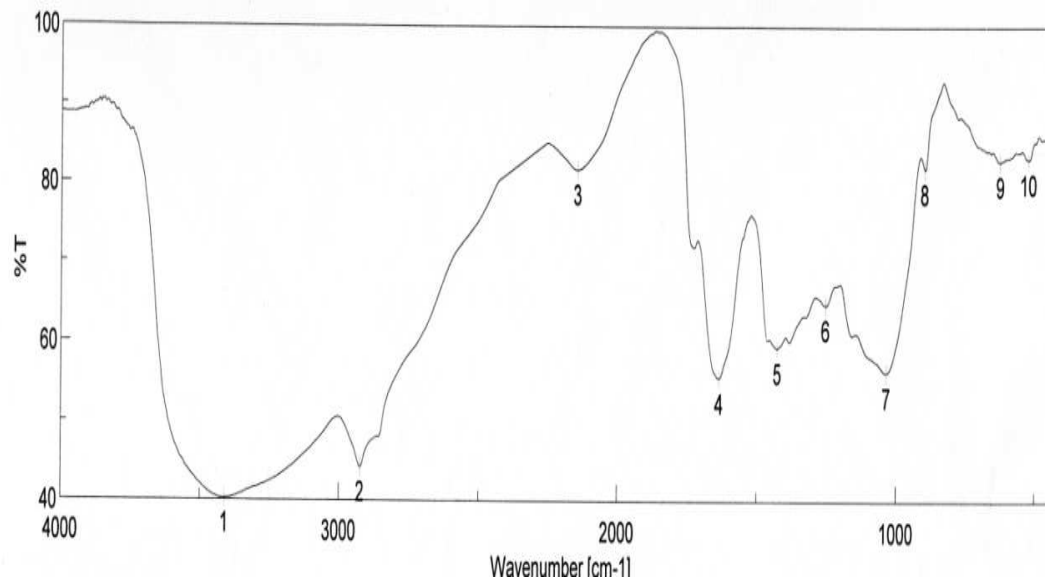


Fig. No. 3: Ispagol Seed Powder

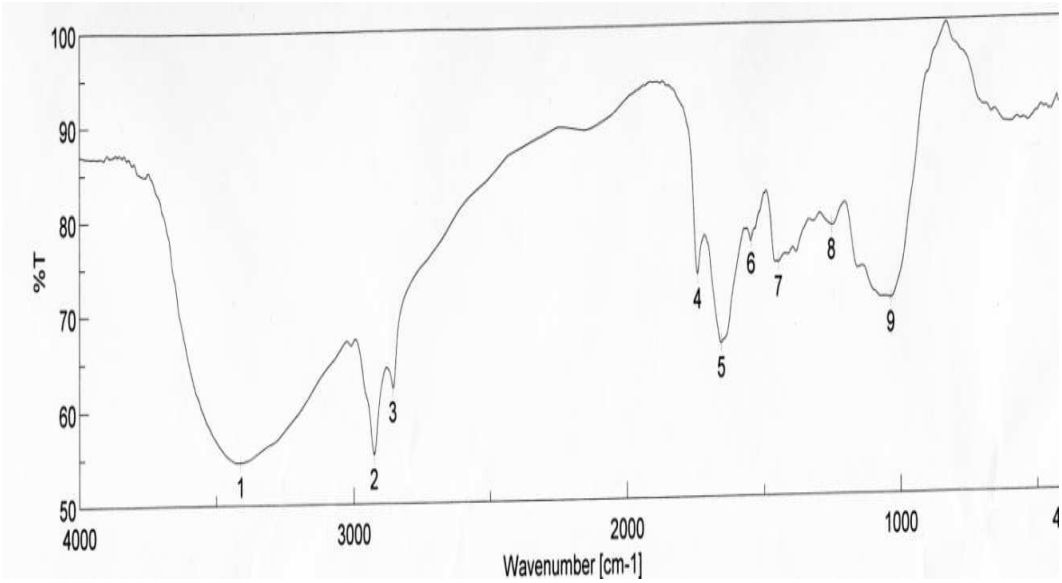


Fig. No. 4: Ispagol Husk Powder

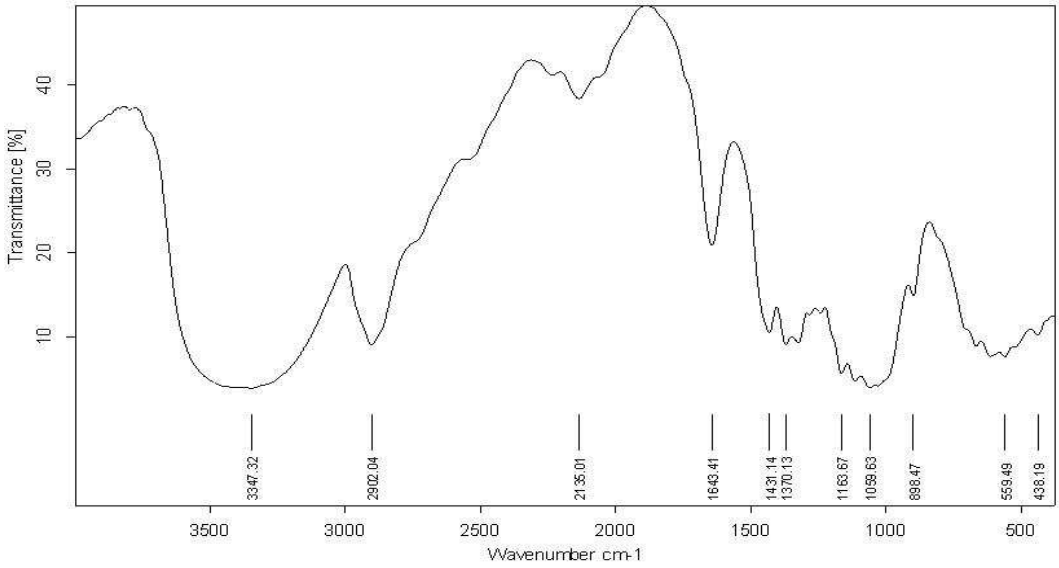


Fig. No. 5: IR Spectra of Microcrystalline Cellulose

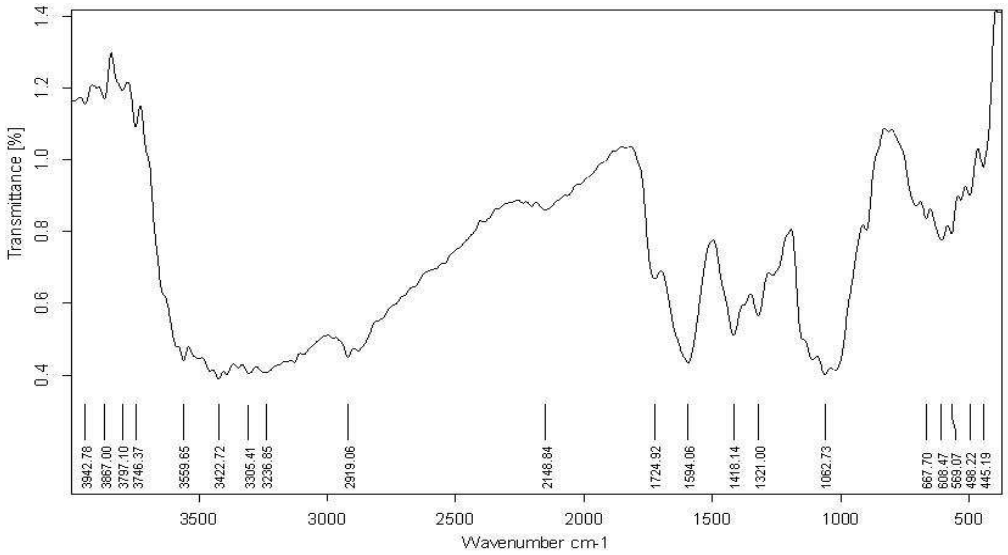


Fig. No. 6: IR Spectra of Crospovidone

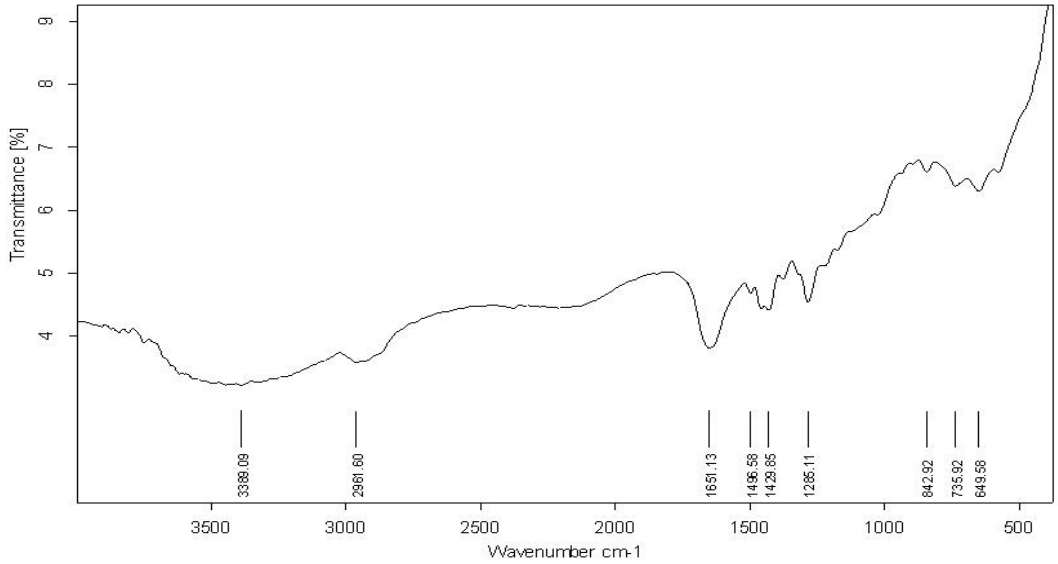


Fig. No. 7: IR Spectra of Croscarmellose Sodium

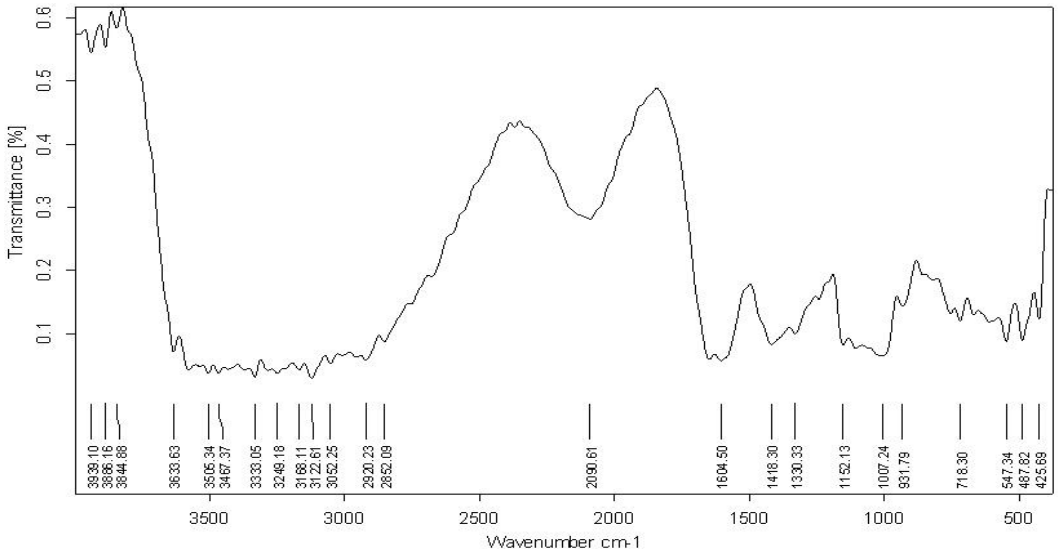


Fig. No. 8: IR Spectra of Sodium Starch Glycolate

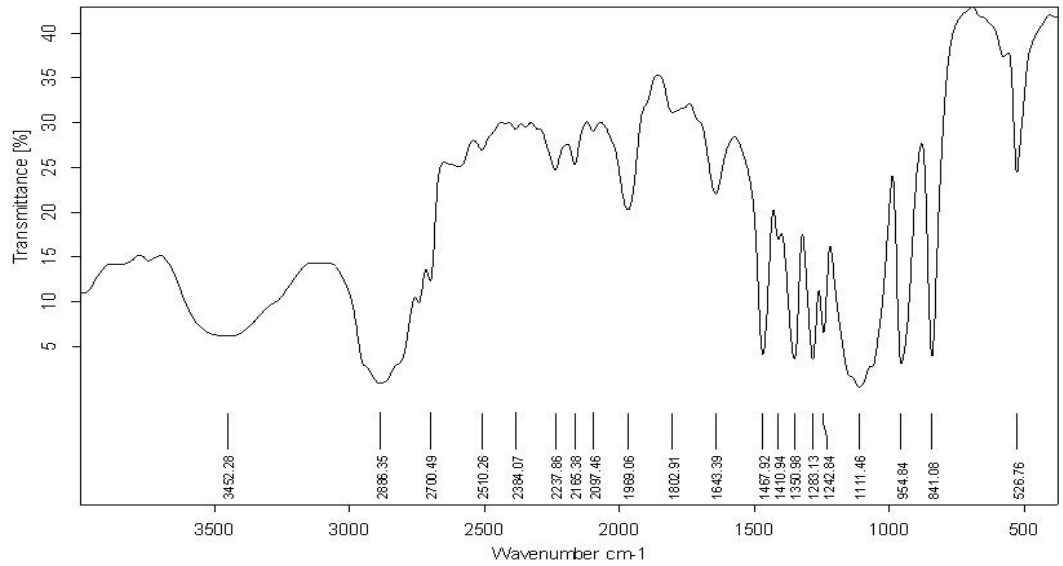


Fig. No. 9: IR Spectra of PEG 6000

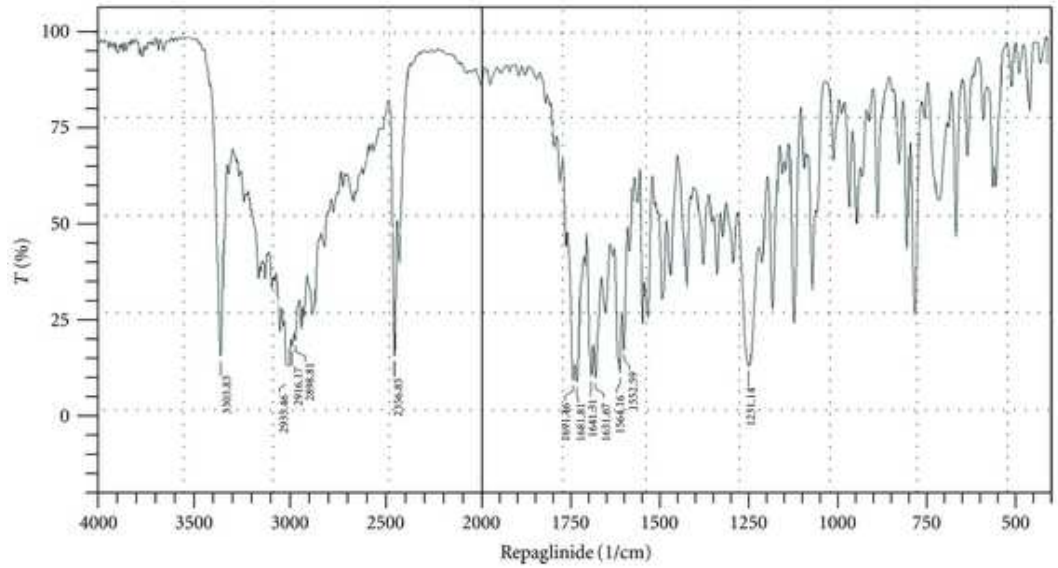


Fig. No. 10: IR Spectra of Repaglinide & Excipient Mixture

Table No. 16:

Characteristic bands	Pure drug	Physical mixture
O-H	3103.54cm-¹	3005.14cm-¹
N-H	1599.09cm-¹	1739.03cm-¹
C-O	1108.83cm-¹	1365.64cm-¹
C=C	3005.90 cm-¹	1477.26cm^{-1}
C-N	2825.87 cm-¹	1579.39cm^{-1}

The FT-IR Spectra analysis showed that there is change in percent transmittance which may be due to change in crystallinity and there is no appearance or disappearance of any characteristics peak of pure drug repaglinide and in the physical mixture of drug to polymer, which confirms the absence of chemical interaction between drug and polymer.

7.3. PREPARATION OF STANDARD CURVE

A UV spectrophometric method given in IP is used for dissolution samples of repaglinide tablet. Absorbance scans of drug is pH5 acetate buffer, showed maximum at 283nm, which is selected as the analytical wavelength. Standard curve of repaglinide in Calibration curve of repaglinide was determined by plotting absorbance versus concentration (µg/ml) at 283nm. The results obtained were as follows.

repaglinide standard calibration curve in pH 5 Acetate buffer at 283 nm

Table No – 17 :

Concentration (µg/ml)	Absorbance at 283nm
10	**0.121**
20	**0.283**
30	**0.455**
40	**0.651**
50	**0.810**
60	**0.913**

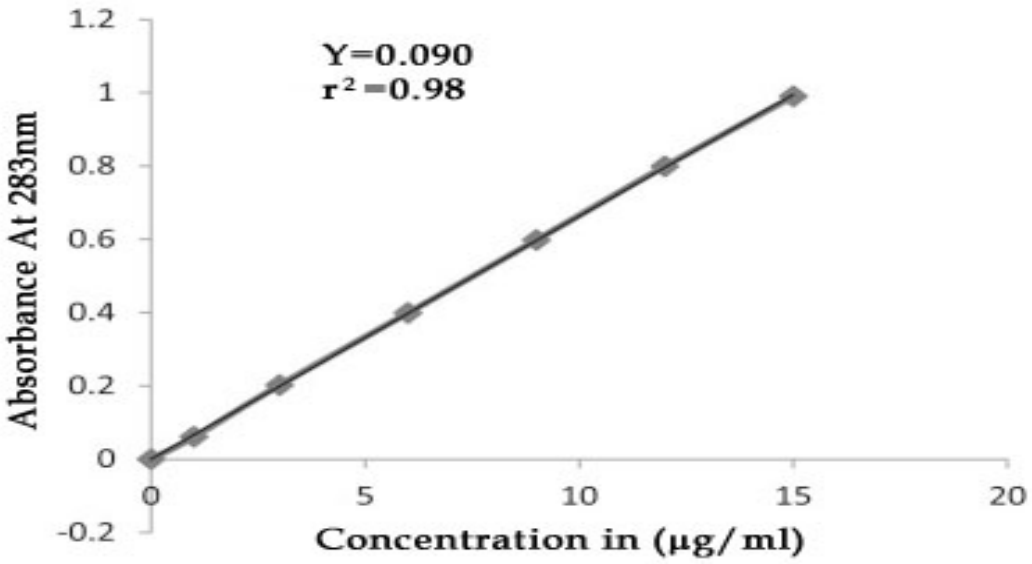


Fig. 11 : Calibration curve in pH 5 Acetate buffer at 283 nm

7.4 PREPARATION OF SOLID DISPERSION AND PHYSICAL MIXTURE

As per the method given in 6.4.1 and 6.4.2 solid dispersion and physical mixture were prepared.

7.5 Characterization of solid dispersions of repaglinide with PEG 6000

7.5.1. Drug content

It was determined as per procedure given in 6.5.1. The results were illustrated in table no. 18.

Table No. 18: Drug content in physical mixtures and solid dispersions

Solid dispersion (drug to PEG mass ratio)	Drug content (%)	Physical mixture (drug to PEG mass ratio)	Drug content (%)
SD 1:1	97.54	PM 1:1	98.05
SD 1:3	96.25	PM 1:3	97.96
SD 1:5	98.42	PM 1:5	98.18

7.5.2. Phase solubility Study

It was determined as per procedure given in 6.5.2. The results were illustrated below.

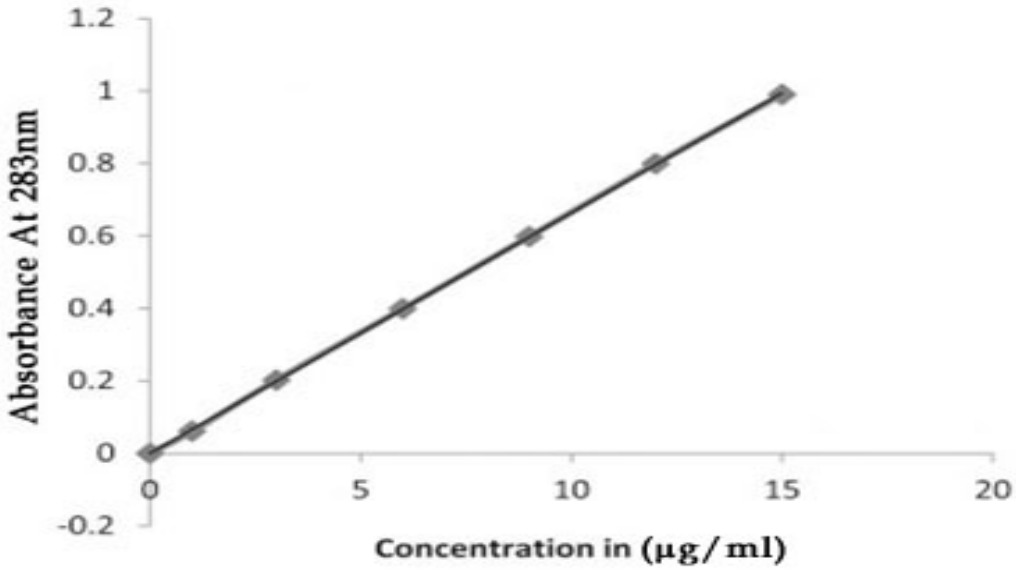


Fig. 12 : Solubility diagram of repaglinide in presence of PEG 6000

Fig no.11 represented the effect of different polymers concentration at different temperature on the solubility of repaglinide. The plots of drug solubility against the polymer concentration at the investigated temperatures indicated a linear relationship between drug solution and polymer concentration. The result shown that in both cases, the solubility of repaglinide increased with increasing temperature and carrier concentration.

Solubility of repaglinide in pure water at 25^{o}C was 0.01 (µg/ml). At the highest polymer concentration (10% w/w), the solubility increased approximately 4 fold for PEG 6000 at 25^{o}. The same tendency was observed for other temperatures.

7.5.3. Dissolution studies

It was determined as per procedure given in 6.5.3. The results were illustrated in table no. 20.

Table No. 20 : *In-vitro* Dissolution Profile of repaglinide Physical Mixture of repaglinide and Solid Dispersion of repaglinide in pH 1.2 Buffers.

Sr. No.	Formulation	Percentage drug released after 30 minutes (DR)
A1	Drug	31.23 ± 2.25 %
A2	PM 1:1	41.54 ± 2.58 %
A3	PM 1:2	44.86 ± 2.69%
A4	PM 1:5	51.12 ± 2.50%
A5	SD 1;1	87.89 ± 2.25 %
A6	SD 1:2	93.46 ± 2.35 %
A7	SD 1:5	98.35 ± 2.76 %

Fig. 12: Comparison of *in-vitro* dissolution profile of formulation A1-A7

The percentage release of repaglinide at various time intervals from the physical mixtures and solid dispersions made by using various concentration.

The percentage release of repaglinide at various time intervals from the physical mixtures and solid dispersions made by using various concentrations of PEG 6000 are shown in Fig.no.11. From table no.20 it is evident that onset of dissolution of pure repaglinide is very low, about 31.23% of drug being dissolved within 30 min. In the 30 minutes, physical mixtures of PEG 6000 (1:1, 1:2 and 1:5) showed 41.54, 44.86 and 51.12% drug release, and 87.89, 93.46, and 98.35 % drug release from solid dispersions (1:1, 1:2 and 1:5).SDs of repaglinide with PEG 6000 considerably enhanced dissolution rates within 30 min compared to pure repaglinide and PMs.

7.5.4 Fourier transforms IR spectroscopy

It was determined as per procedure given in 6.5.4. The following figures were illustrated results.

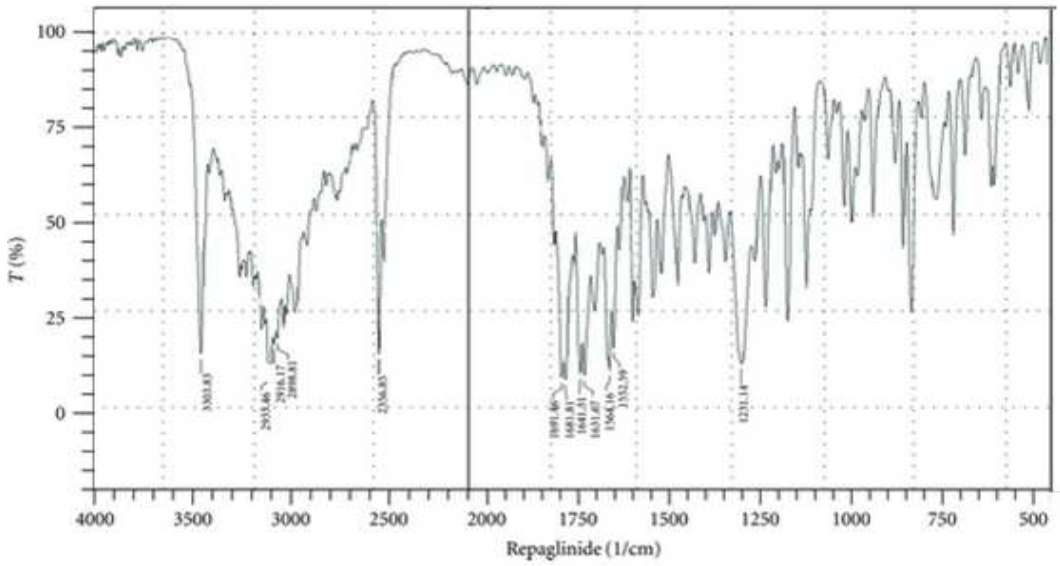


Fig. No. 13: IR Spectra of Repaglinide

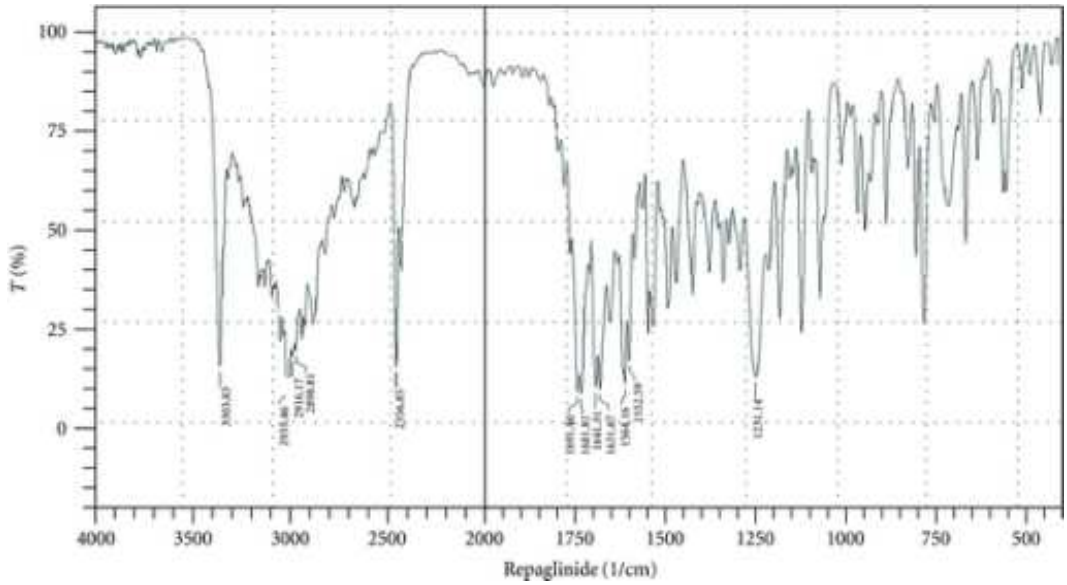


Fig. No. 14: IR Spectra of Solid dispersion 1:1

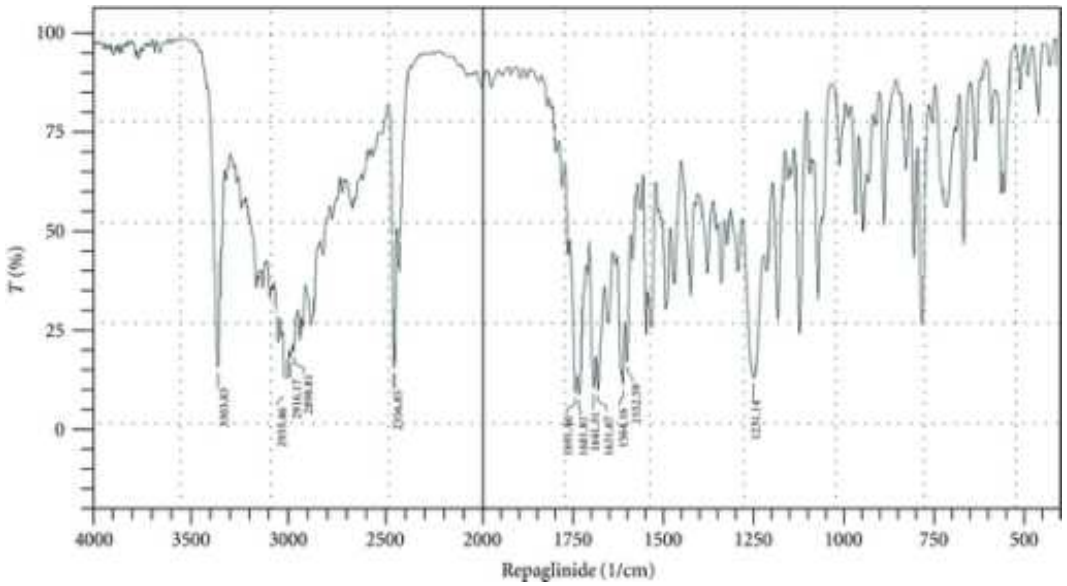


Fig. No. 15: IR Spectra of Physical mixture 1:1

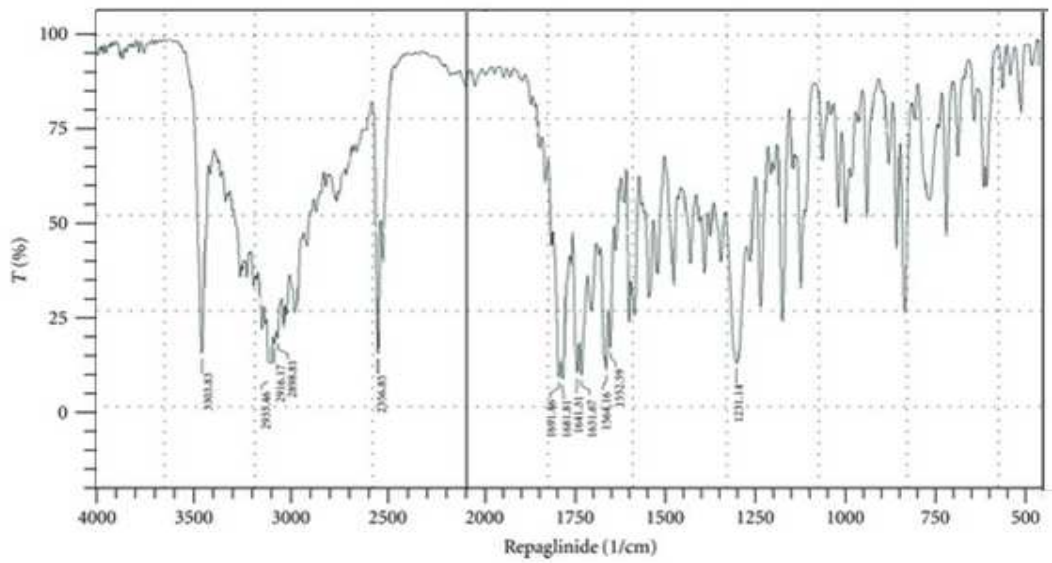


Fig. No. 16: IR Spectra of Solid dispersion 1:3

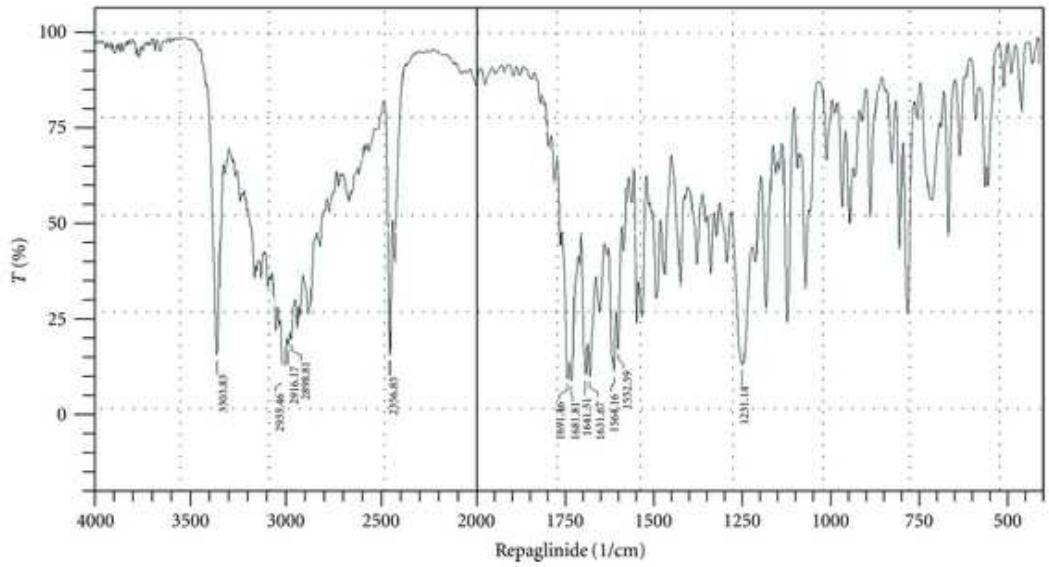


Fig. No. 17: IR Spectra of Physical mixture 1:3

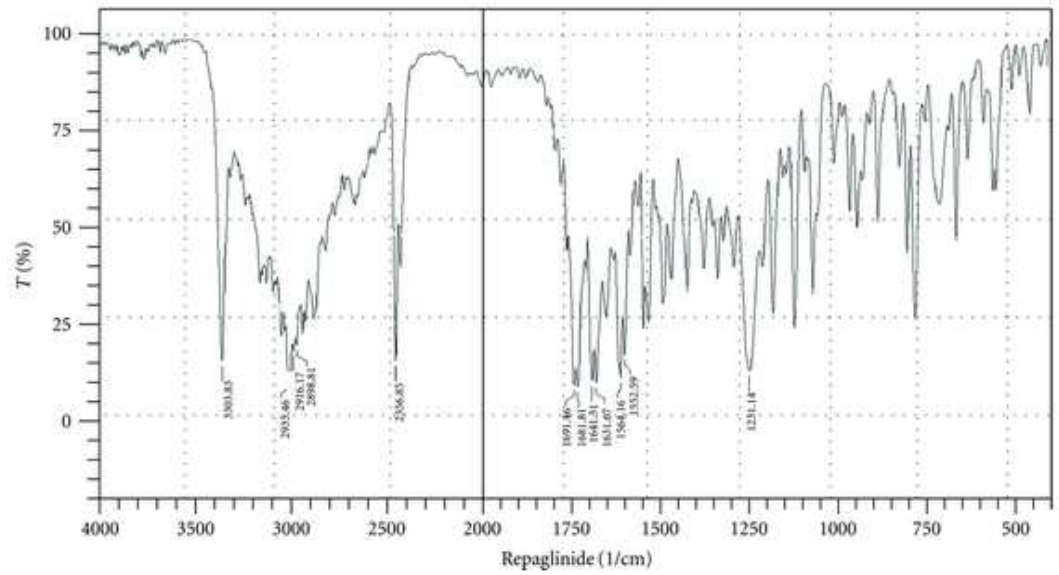


Fig. No. 18: IR Spectra of Solid dispersion 1:5

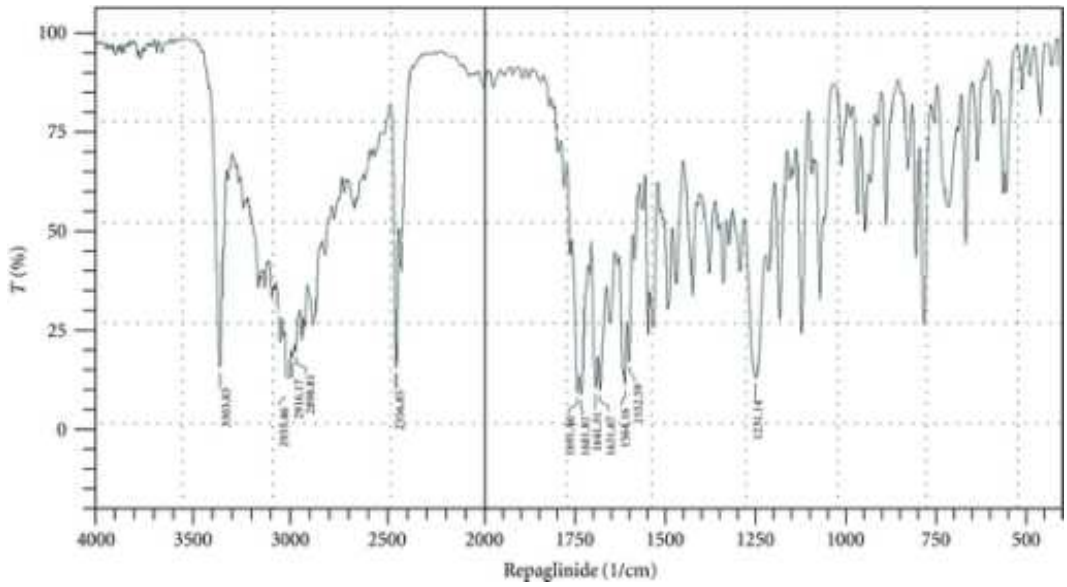


Fig. No. 19: IR Spectra of physical mixture 1:5

The IR spectra of SDs and PMs were compared with the standard spectrum of repaglinide. IR spectrum of repaglinide was characterized by the absorption of carbonyl (C-O) group at 1108.83cm^{-1}. In spectra of SDs and PMs, this band was shifted towards higher frequencies at 3005.14 and 2,825.87cm−1 respectively. Also the O-H group which is located at 3,103.54 cm−1 from the IR spectrum of repaglinide, N-H group at1599.09, C=C group at 3005.90, C-N group at 2825.87 It was concluded that there was no well defined chemical interaction between repaglinide and PEG 6000 in SDs and in PMs, as no important new peaks could be observed.

7.6. Preparation And Evaluation Of Natural Superdisintegrants

Natural super disintegrates were prepared and evaluated according to the procedure given in 6.6.

Table No. 21 : Preliminary evaluation of natural superdisintegrants

Parameters	Mucilage	Seed Powder	Husk Powder
Bulk Density (gm/cm^3)	0.96	0.50	1.17
Tapped Density (gm/Cm^3)	1.08	0.91	1.35
Hausners Ratio	1.083	1.14	1.11
Compressibility index (%)	6.58	15.37	14.66
Angle of Repose (^{o})	25.20	40.36	33.15

7.7. FORMULATION OF REPAGLINIDE IMMEDIATE RELEASE TABLET

According to the formula given in table No. 8, repaglinide immediate release tablet were formulated and before formulation precompression parameters were evaluated and given in table no. 22.

Table No : 22 Precompression parameters

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Bulk density	0.360	0.370	0.310	0.310	0.32	0.330	0.320	0.350	0.370	0.350	0.330	0.320
Tapped Density	0.450	0.440	0.430	0.420	0.43	0.440	0.410	0.440	0.44	0.45	0.43	0.41
% Compressibility	15.36	15.07	21.64	20.15	20.85	20.47	16.64	16.56	17.35	18.13	18.81	I7.65
Hausners Ratio	1.185	1.11	1.25	1.23	1.24	1.21	1.20	1.43	1.17	1.26	1.36	1.26
Angle of Repose	21.26	20.14	24.38	24.45	23.27	23.17	20.37	20.09	21.15	21.29	25.36	24.19

7.8. EVALUATION OF IMMEDIATE RELEASE TABLETS

7.8.1. TABLET PHYSICAL APPEARANCE

The tablets were evaluated for their physical properties like color uniformity, presence of cracks, chipping, etc. No undesirable properties were found out.

7.8.2. WEIGHT VARIATION TEST

It was determined as per procedure given in 6.8.2. The results were illustrated in table No. 23.

7.8.3. FRIABILITY

The friability test were carried out according to the procedure given in 6.8.3. The result was tabulated in the Table No. 24.

7.8.4. THICKNESS

The thickness was carried out according to the procedure given in 6.8.4. The result was tabulated in the table No.23.

7.8.5. HARDNESS (KG/CM^2)

The Hardness tests were carried out according to the procedure given in 6.8.5. The result was tabulated in the table No.23.

7.8.6. DISINTEGRATION TEST (IN SEC.)

It was determined as per procedure given in 6.8.6 the results were illustrated in table No.23. The results indicated that the disintegration time of tablets was within 35seconds.

7.8.7. WETTING TIME

It was determined as per procedure given in 6.8.7 .The results were illustrated in table 23.

7.8.8. TEST FOR UNIFORMITY OF DISPERSION

It was determined as per procedure given in 6.8.8. The results were illustrated in table No.23.

7.8.9. WATER ABSORPTION RATIO

The test is conducted according to the procedure given in 6.8.9. To measure the hydrophilicity of tablets, the results were illustrated in the table No.23.

7.8.10 ASSAY

It was determined according to the procedure given in 6.8.10. The percent purity was detrmined by UV method, the results were illustrated in the table No.23.

Table No.23: EVALUATION CHART OF TABLET

S.No	Para meter	Formulation Code											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Weight Variation Test	198.66 ±0.23	199.66 ±0.25	197.66 ±0.39	200.66 ±0.43	198.66 ±0.23	196.66 ±0.49	198.66 ±0.39	197.66 ±0.35	199.66 ±0.23	198.66 ±0.23	199.66 ±0.27	199.66 ±0.23
2	% Friability	0.26	0.20	0.21	0.30	0.28	0.20	0.23	0.21	0.24	0.32	0.25	0.23
3	Thickness (mm)	2.58± 0.01	2.59± 0.03	2.35± 0.05	2.30± 0.02	2.41± 0.05	2.42± 0.06	2.42± 0.02	2.48± 0.06	2.44± 0.04	2.43± 0.05	2.41± 0.04	2.35± 0.06
4	Hardness (Kg / cm^2)	2.06 ±0.10	2.06 ±0.09	2.84 ±0.41	3.17 ±0.15	2.91 ±0.18	2.95 ±0.14	2.74 ±0.14	2.79 ±0.31	2.84 ±0.36	2.90 ±0.37	2.91 ±0.39	2.96 ±0.40
5	Disintegration Time(sec)	23.36 ±2.6	21.05 ±1.5	27.39 ±2.5	23.69 ±2.8	25.63 ±2.4	26.05 ±3.5	22.00 ±2.8	22.05 ±2.5	28.05 ±2.6	26.63 ±3.7	34.68 ±2.9	34.69 ±2.5
6	Wetting time (sec)	50.69 ±1.6	47.69 ±1.9	63.04 ±2.9	66.339 ±2.9	63.36 ±2.6	57.63 ±2.6	54.36 ±1.6	52.69 ±2.7	52.05 ±2.6	53.36 ±2.9	65.39 ±2.5	63.06 ±2.6
7	Uniformity of Dispersion	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
8	W.A.Ratio (%)	65.46	65.36	73.85	74.07	66.07	67.35	65.34	65.39	66.15	66.93	74.19	73.69
9	Assay (%)	99.48	100.5	98.34	99.82	99.10	101.41	100.06	100.15	101.21	101.02	100.9	100.4

7.5.11 IN-VITRO DISSOLUTION STUDIES

Dissolution study carried out according to procedure given in 6.8.11.The study or 30 minutes, the results were illustrated in the table below.

Table No.24: Dissolution profile of formulation F1

Time In Minute	Cummulative Percent Drug Release(%)
0	**0**
5	78.45
10	80.92
15	84.76
20	89.15
25	93.82
30	97.92

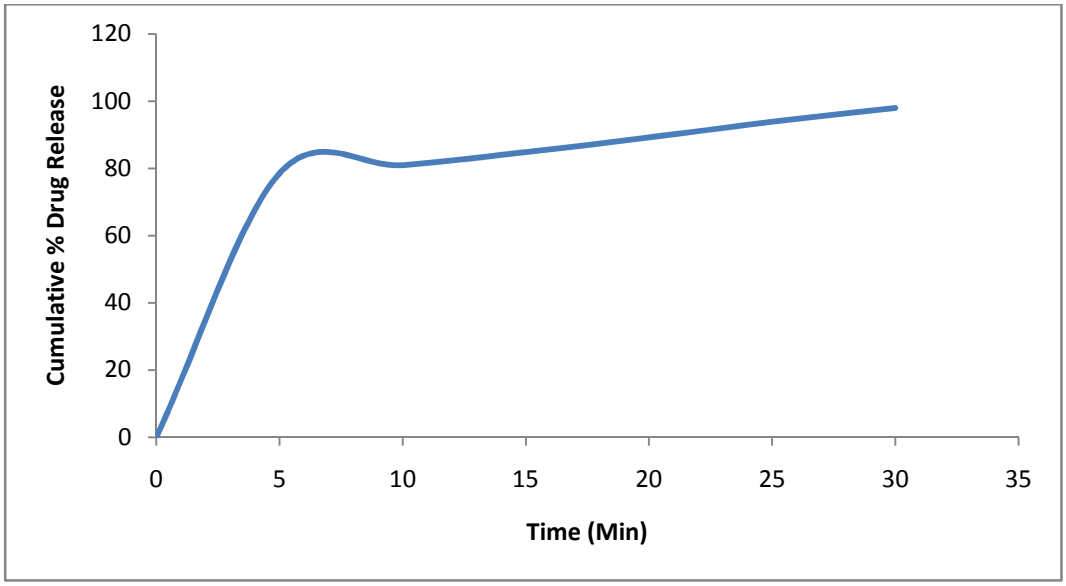


Fig.No. 20. *In-vitro* dissolution study F1

Table No.25: Dissolution profile of formulation F2

Time in Minute	Cummulative Percent Drug Release (%)
0	0
5	78.72
10	81.45
15	84.50
20	90.00
25	94.37
30	99.50

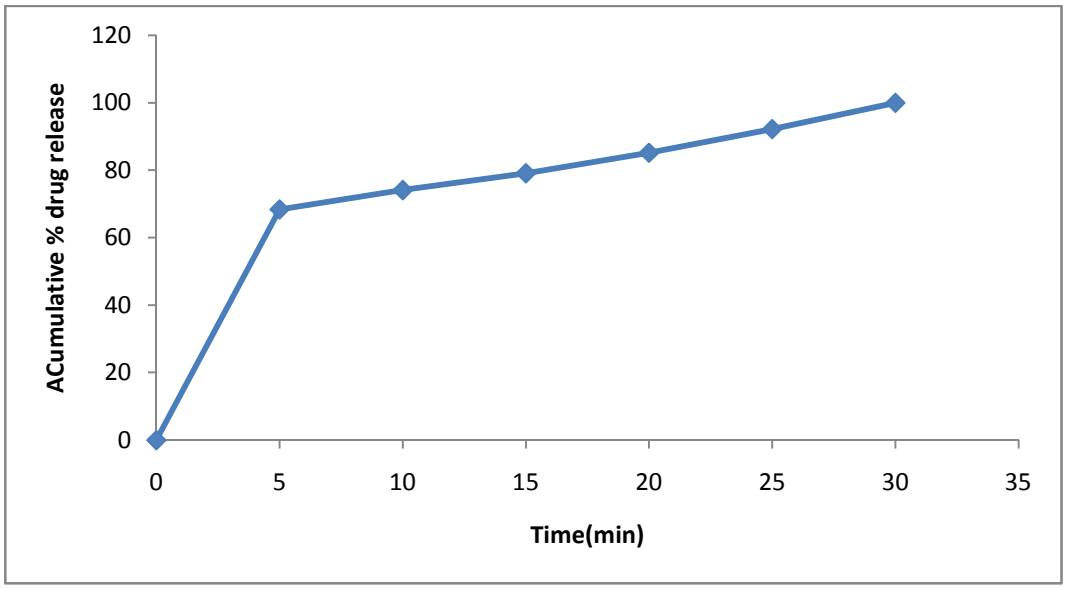


Fig.No. 21. *In-vitro* dissolution study F2

Table No.26: Dissolution profile of formulation F3

Time in minute	Percent Drug Release (%)
0	0
5	79.82
10	82.02
15	85.03
20	90.52
25	94.91
30	98.75

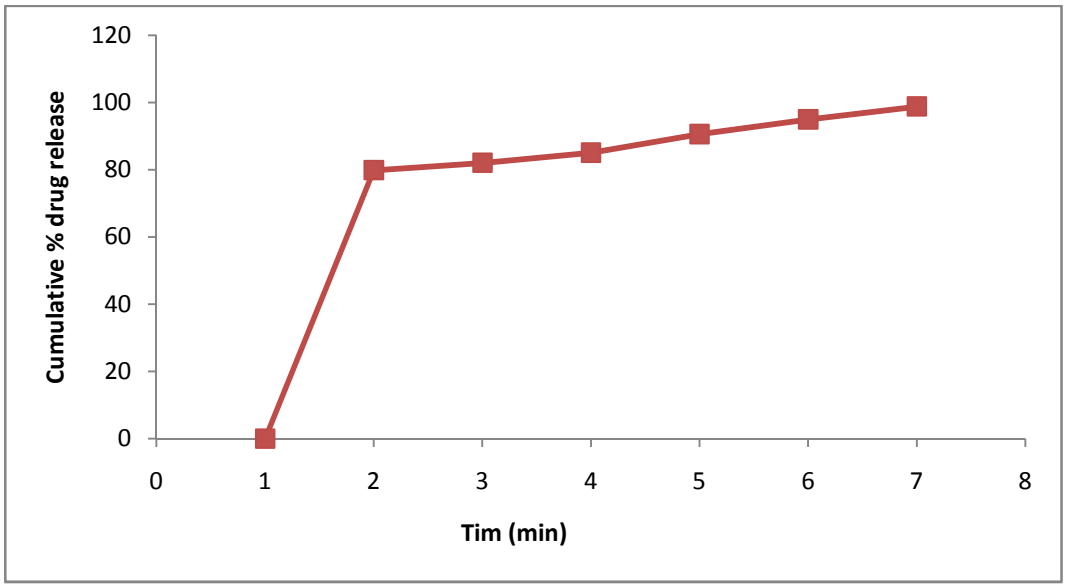


Fig.No. 22. *In-vitro* dissolution study F3

Table No.27: Dissolution profile of formulation F4

Time in Minute	Cumulative Percent Drug Release (%)
0	0
5	80.37
10	82.30
15	85.85
20	91.90
25	94.95
30	98.23

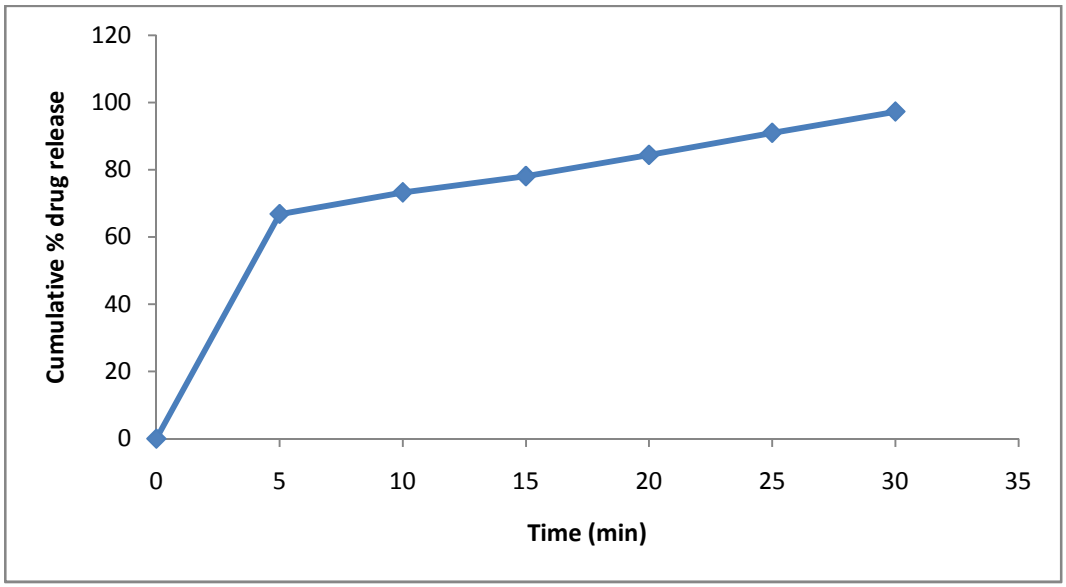


Fig.No. 23. *In-vitro* dissolution study F4

Table No.28: Dissolution profile of formulation F5

Time in minute	Cumulative Percent Drug Release (%)
0	0
5	81.47
10	84.50
15	86.14
20	90.10
25	94.15
30	98.05

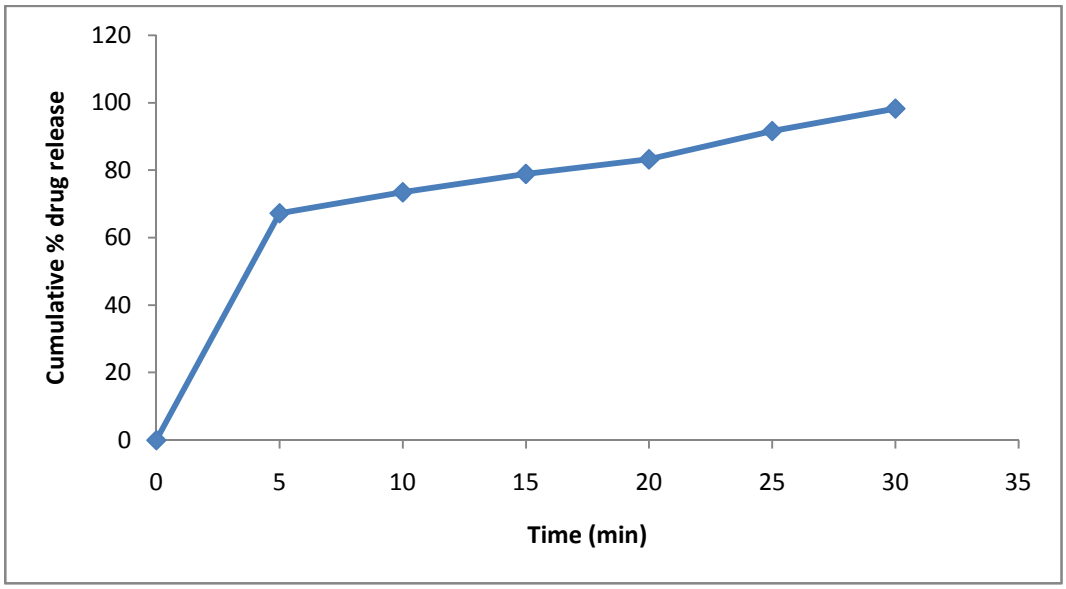


Fig.No. 24. *In-vitro* dissolution study F5

Table No.29: Dissolution profile of formulation F6

Time in minute	Cumulative Percent Drug Release (%)
0	0
5.0	84.75
10	86.69
15	89.15
20	93.25
25	97.39
30	98.87

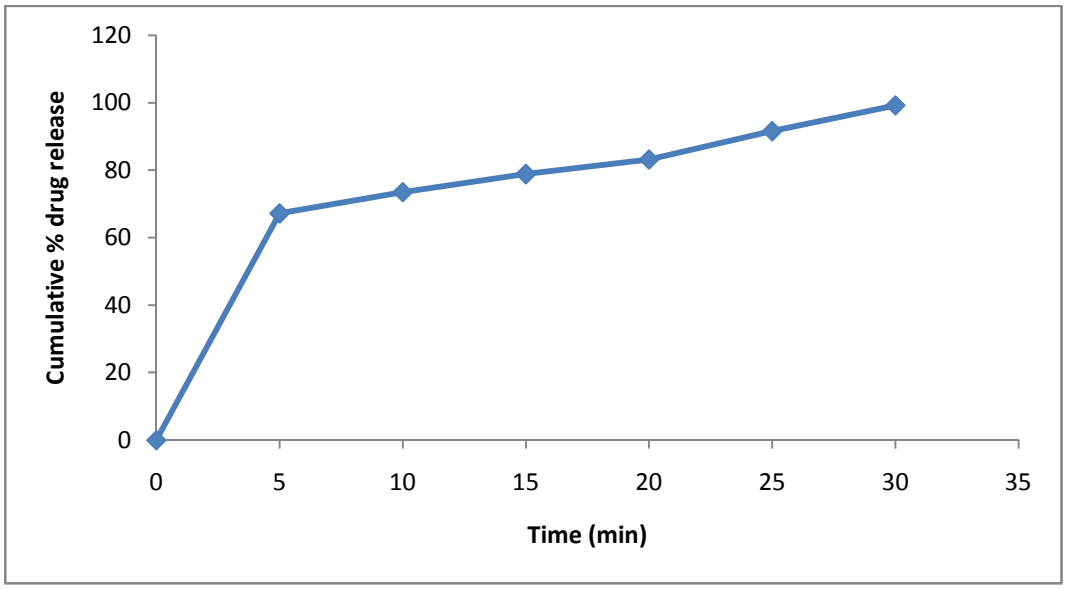


Fig.No. 25. *In-vitro* dissolution study F6

Table No.30: Dissolution profile of formulation F7

Time in minute	Cumulative Percent Drug Release (%)
0	0
5.0	82.58
10	85.05
15	57.24
20	90.53
25	95.73
30	99.35

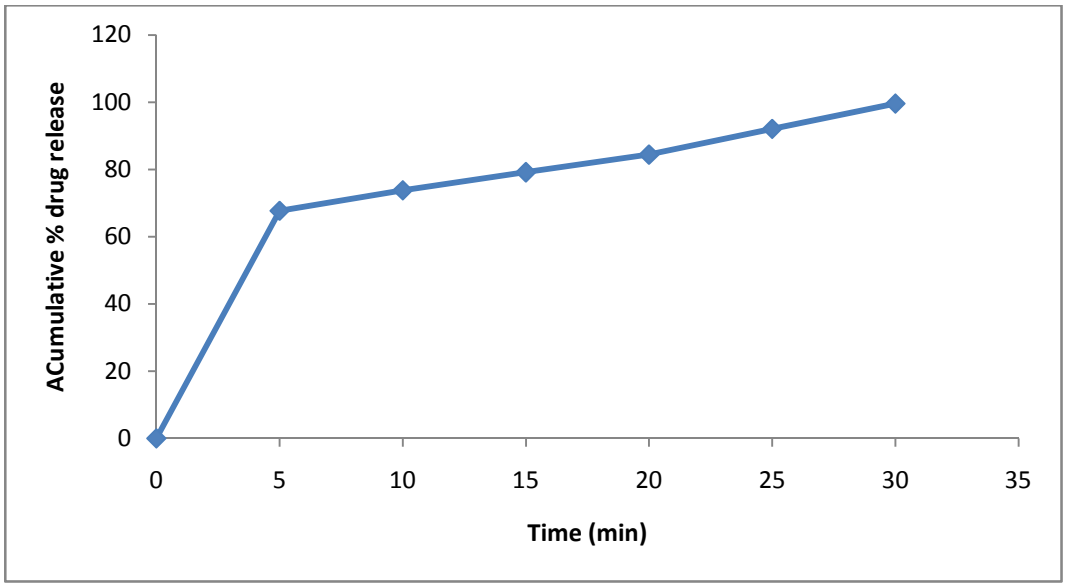


Fig.No. 26. *In-vitro* dissolution study F7

Table No.31: Dissolution profile of formulation F8

Time in minute	Cumulative Percent Drug Release (%)
0	0
5.0	80.37
10	82.15
15	85.46
20	89.11
25	94.15
30	99.65

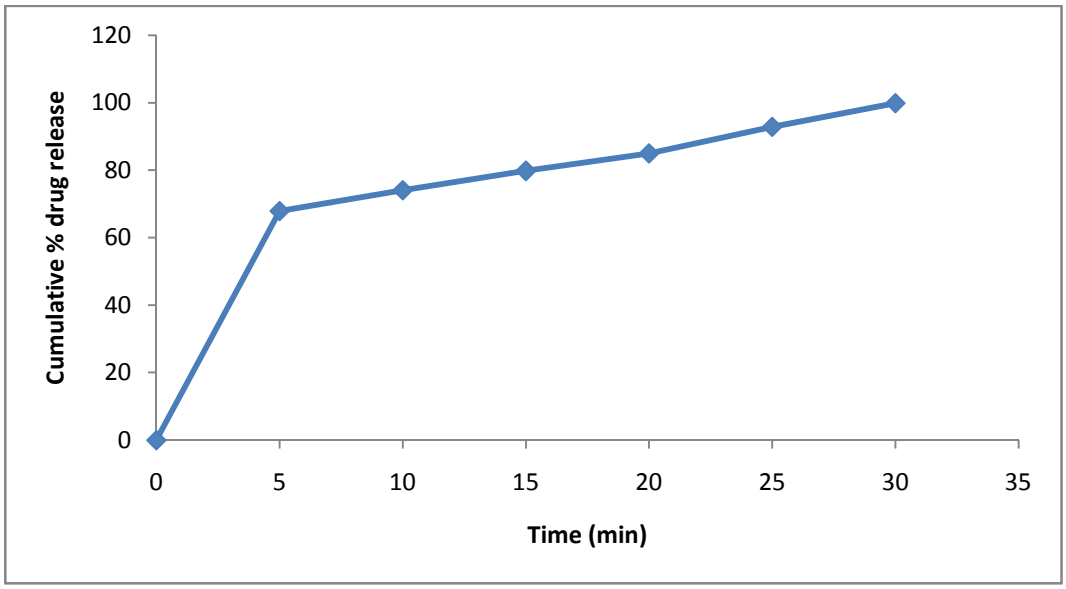


Fig.No. 27. *In-vitro* dissolution study F8

Table No.32: Dissolution profile of formulation F9

Time in minute	Percent Drug Release (%)
0	0
5.0	83.23
10	86.17
15	88.55
20	92.70
25	96.05
30	98.41

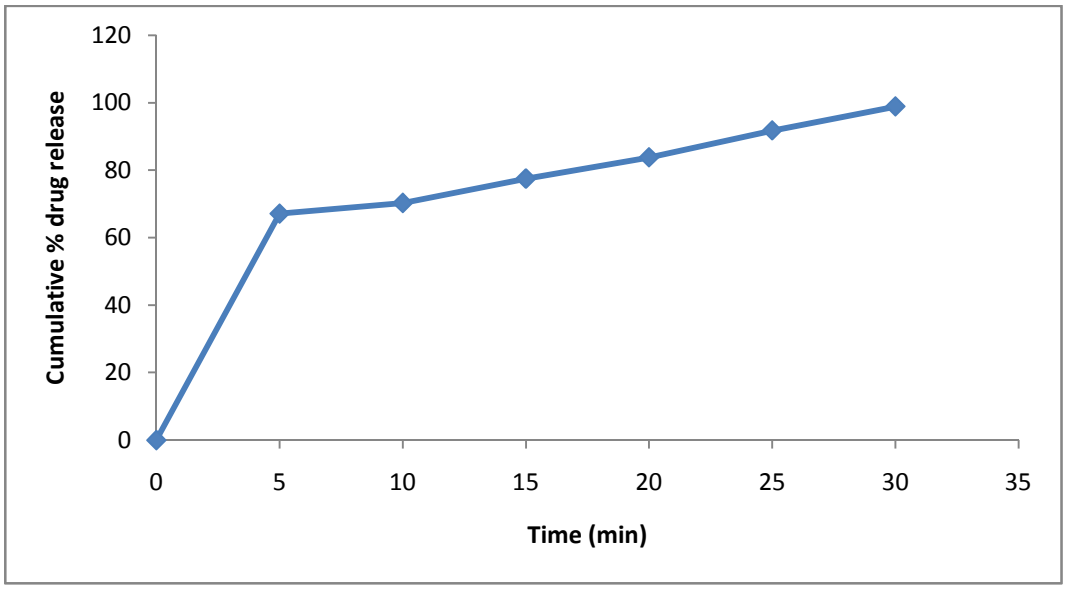


Fig.No. 28. *In-vitro* dissolution study F9

Table No.33: Dissolution profile of formulation F10

Time in minute	Cumulative Percent Drug Release (%)
0	0
5.0	84.76
10	86.70
15	89.19
20	93.29
25	96.40
30	97.50

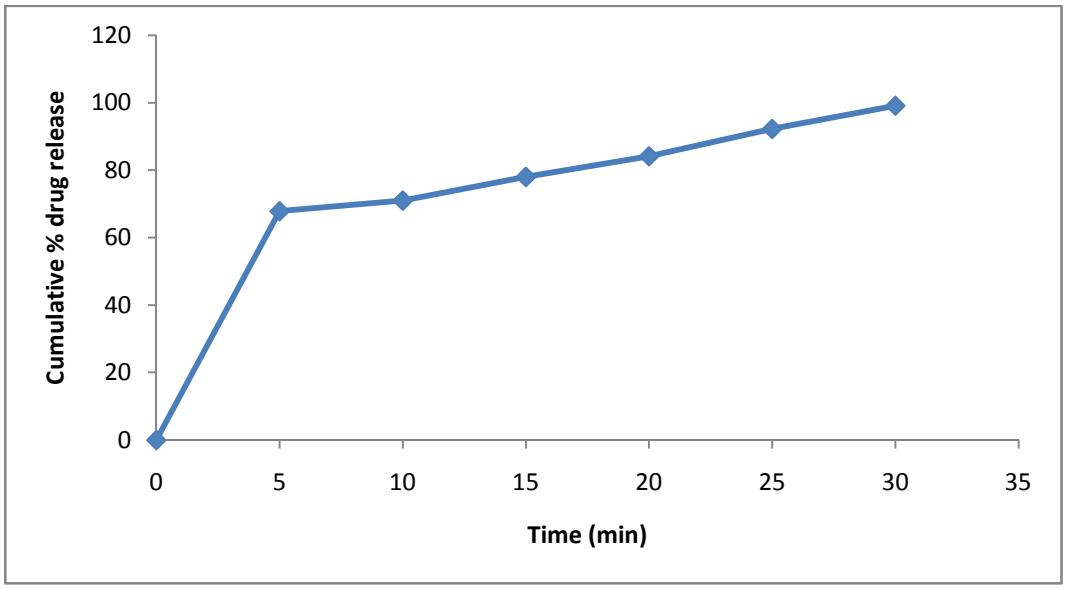


Fig.No. 29. *In-vitro* dissolution study F10

Table No.34: Dissolution profile of formulation F11

Time in minute	Cumulative Percent Drug Release (%)
0	0
5.0	83.85
10	86.05
15	89.24
20	91.55
25	95.75
30	98.35

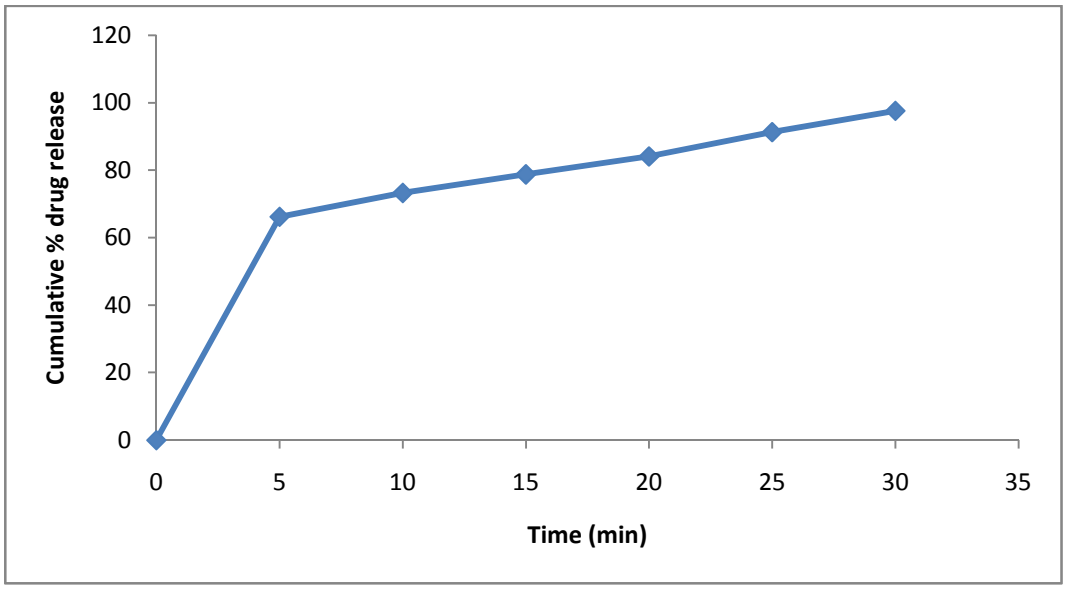


Fig.No. 30. *In-vitro* dissolution study F11

Table No.35: Dissolution profile of formulation F12

Time in minute	Cumulative Percent Drug Release (%)
0	0
5.0	83.81
10	87.17
15	88.65
20	92.60
25	96.15
30	98.99

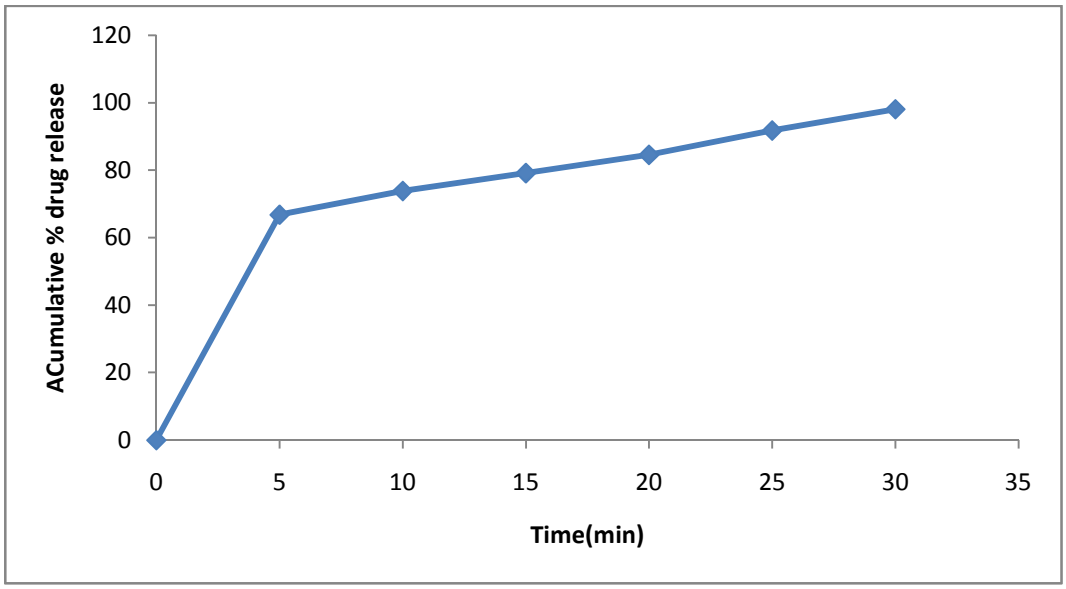


Fig.No. 31. *In-vitro* dissolution study F12

Table No: 36 Comparative dissolution study F 1 – F 12 .

Time	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	78.45	78.72	79.82	80.37	81.47	84.75	82.58	80.37	83.23	84.76	83.85	83.81
10	80.92	81.45	82.02	82.30	84.50	86.69	85.05	82.15	86.17	86.70	86.05	87.17
15	84.76	84.50	85.03	85.85	86.14	89.15	87.24	85.46	88.55	89.19	89.24	88.65
20	89.15	90.00	90.52	91.90	90.10	93.25	90.53	89.11	92.70	93.29	91.55	92.60
25	93.82	94.37	94.91	94.35	94.15	97.39	95.73	94.15	96.05	96.40	95.75	96.15
30	97.92	99.50	98.75	98.23	98.05	98.87	99.35	99.65	98.41	97.50	98.35	98.99

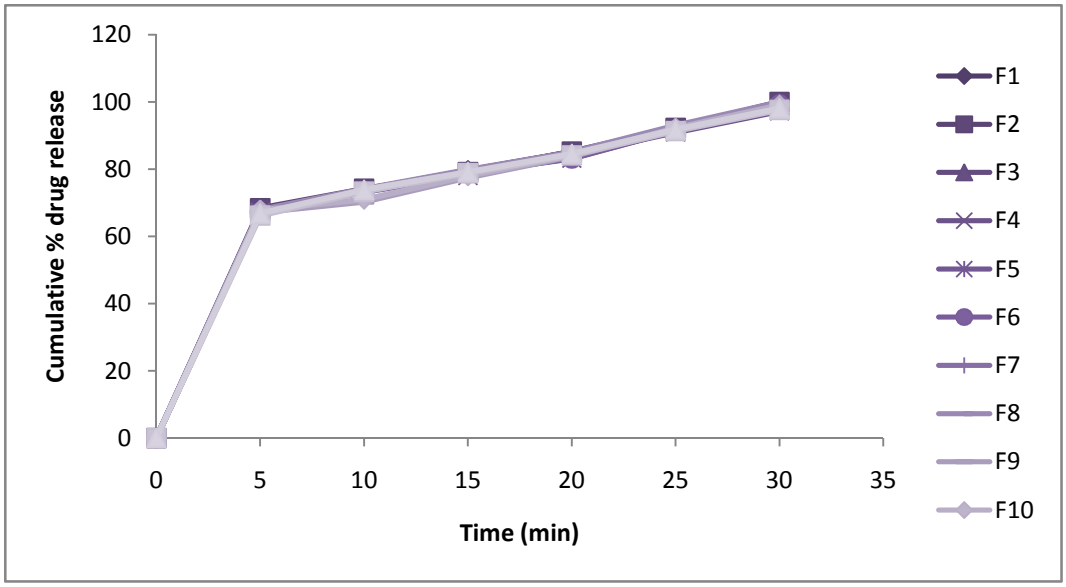


Fig.No. 32. Comparison of *In-vitro* dissolution profile of formulation F1-F12

7.8.12. KINETIC STUDY OF OPTIMIZED FORMULATION

In-vitro release data was flatted in different kinetic model and given in table 37 and figure 33 to 36.

Table No. 37 Kinetic data of Optimized Fomulation F2

Time	Log time	$\sqrt{Time}$	Cumulative % drug release	Log cumulative % drug release	Cumulative % drug remained	Log cumulative % drug remained
0	0	0	0	0	100	2.00
5	0.698	2.23	78.72	1.89	21.28	1.32
10	1.0	3.16	81.45	1.91	18.55	1.26
15	1.176	3.87	84.50	1.92	15.50	1.19
20	1.301	4.47	90.00	1.95	10.00	1.00
25	1.397	5.0	94.37	1.97	5.63	0.75
30	1.477	5.477	99.50	1.99	0.50	0.30

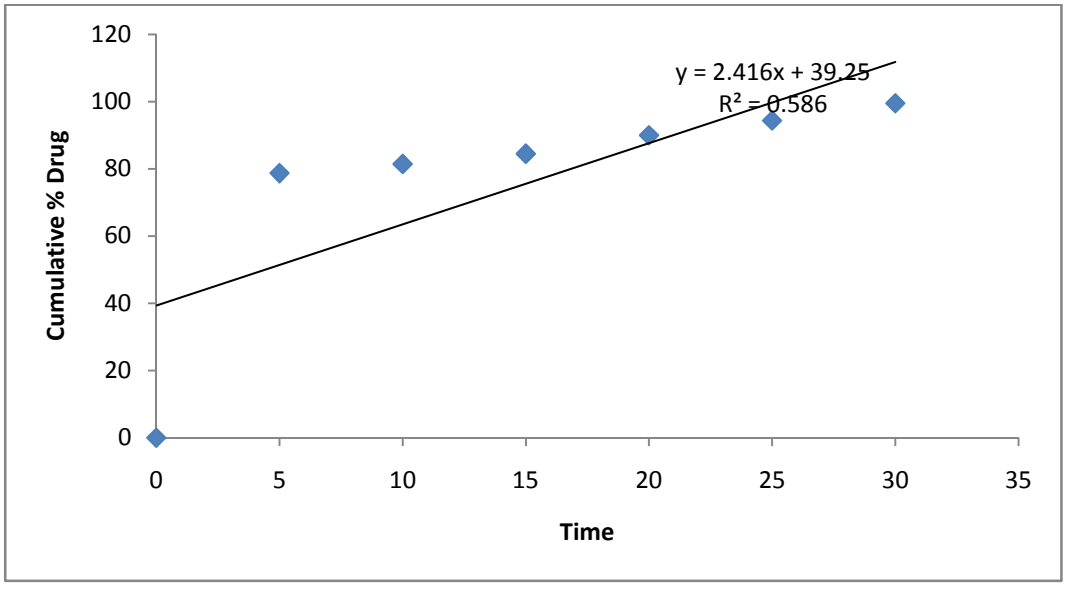


Fig. No. 33 : ZERO ORDER

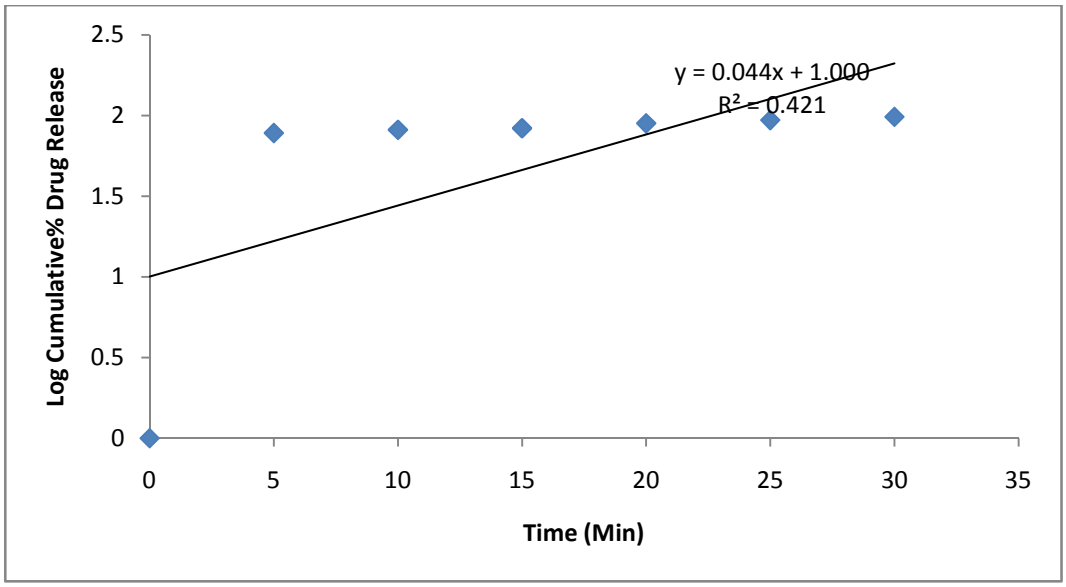


Fig. No. 34 : FIRST ORDER

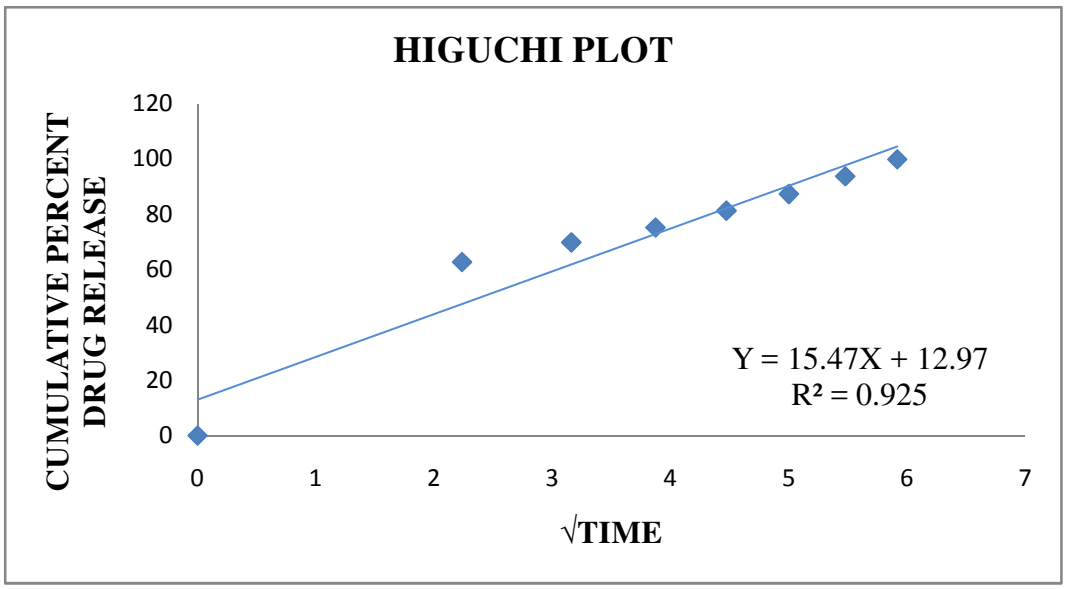


Fig. No. 35 : HIGUCHI

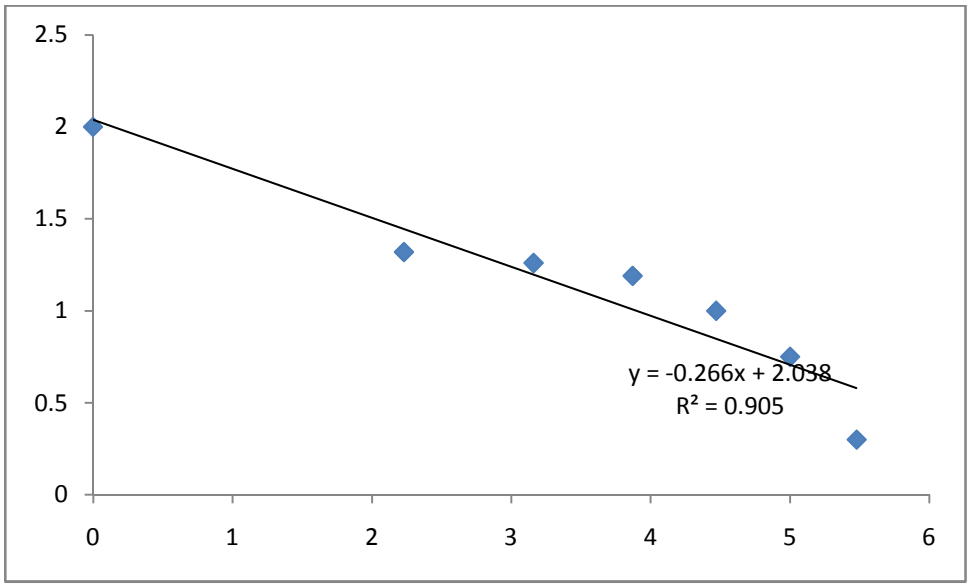


Fig. No. 36 : KORSEMEYER PEPPAS PLOT

The above studies showed that the drug release follows first order kinetics.

7.9. STABILITY STUDY

Optimized formulation (F2) was subjected to stability studies at 40°c± 2°c/75% RH ±5 % for 90 days. The product was evaluated for appearance and hardness, friability, disintegration. Drug release studies were conducted as per the planned scheduled as above.

7.9.1. Descriptions:

Table No.38: Description

Storage condition	Test	Observation	Inference
RT	Descriptions	No change of color in all strengths	Complies with stability condition
40°C + 2°C/ 75% RH	Descriptions	No change of color in all strengths	Complies with stability condition

7.9.2. Stability parameters of formulation F2 stored at 40°C + 2°C/ 75% RH

The results were illustrated in following table no. 39.

Table No.39:

Sr. No.	Parameters	Initial	30 days	60 days	90 days
1	% Friability	0.20	0.27	0.270	0.273
2	Hardness (kg / cm^2)	2.6	2.5	3.1	3.2
3	Drug Content (%)	100.01	99.10	98.51	98.21
4	*In-Vitro Disin. Time(Sec)*	21.05	21.15	23.24	24.11

All results complies with the stability condition

7.9.3. *In-vitro* Dissolution study

It was done as per procedure given in material and method part. The results were illustrated in following table no. 45.

Storage Condition at $40^oC + 2^oC$

Table No.40: *In-vitro* dissolution study

Formulation (F2)	Percentage Drug Release After 30 minutes			
	Initial (0Days)	30 Days	60 Days	90 Days
	99.50	99.60	98.54	98.60

The results showed that there was no significant change in physical and chemical parameter of the tablet, hence the formulation was found to be stable.

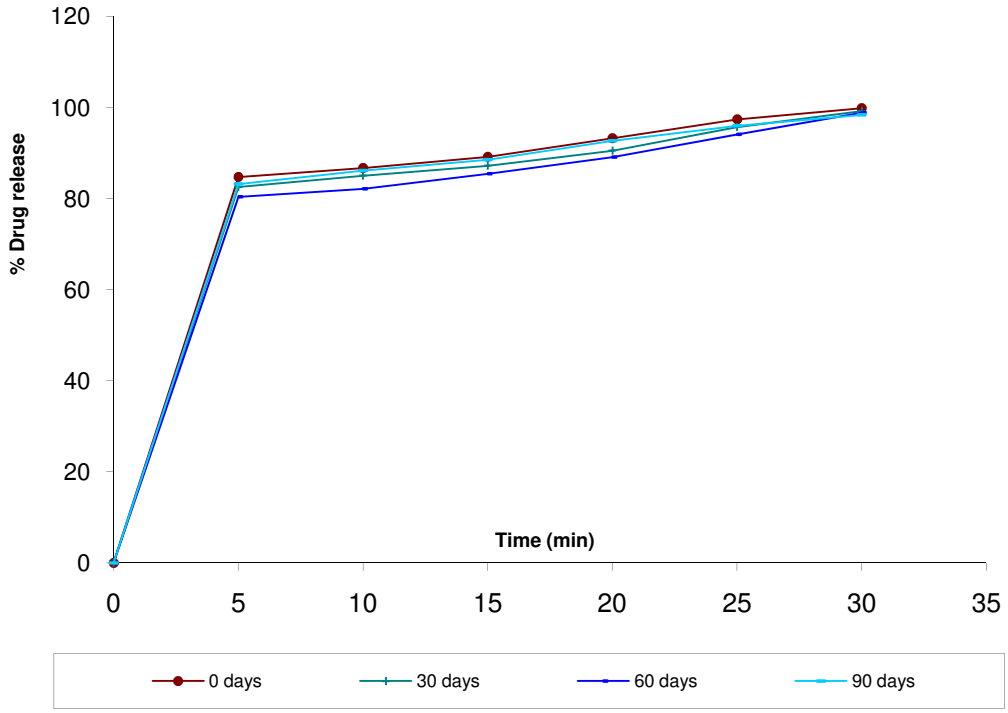


Fig. No. 37: *In-vitro* dissolution study F2 dissolution studies

8. SUMMARY AND CONCLUSION

SUMMARY

In the present study immediate release drug delivery system of repaglinide were successfully developed in the form of mouth dissolving tablets with improved dissolution characteristic by forming solid dispersion with PEG 6000, which offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increase bioavailability. Immediate release tablets of repaglinide were prepared by using natural superintegrants like microcrystalline cellulose, croscarmellose sodium, crospovidone, sodium starch glycolate and their combination as superdisintegrants.

Superdisintegrants work as an auxiliary or as a facilitator of the flowability and compressibility of the mixture and contribute to the immediate release of the tablet, due to its high solubility in water.

For the repaglinide formulation, batch No. 2 was chosen as it has disintegration time around 5-35 seconds and hardness3.5 Kg/Cm^2. IR spectra of drug with other excipients has not shown any interaction and also selected formulation was stable after stability studies.

CONCLUSION

The solubility and dissolution rate of repaglinide can be enhanced by formulating SDs of repaglinide with PEG 6000.The solubilization effect of PEG 6000, reduction of particle aggregation of the drug, formation of microcrystalline or amorphous drug, increased wetability and dispersibility, and alteration of the surface properties of the drug particles might be responsible for the enhanced solubility and dissolution rate of repaglinide from its SD and to some extent in PMs. No endothermic peak of repaglinide was present in of SDs with PEG 6000 suggesting the absence of crystalline repaglinide. From FTIR spectroscopy, it was concluded that there was no well defined chemical interaction between repaglinide and PEG 6000 in SDs and in PMs, as no important new peaks could be observed.

The identical composition of Superdisintegrants showed that a substantial shorter time require for disintegration can be obtained and immediate release tablet

were prepared. The repaglinide immediate release tablet (F2) showed 78.72% drug release within first 5 min. and 99.50% drug release with in 30 min.

The results showed that the formulation satisfied the objective of fast disintegration, dissolution, % friability, hardness, wetting time, water absorption ratio, ease of administration and safety.

Success of the present study recommends a detailed investigation in to *in-vivo* studies for its effective use in clinical practice.

9. BIBLIOGRAPHY

1. Jain N.K, Sharma S.N *A Text book of professional pharmacy* 4th edition Vallabh Prakashan, Delhi, Vol.1 , 1- 46.

2. Chatap V.K, Gupta R.D, Jaiswal N.R, "Recent advances in mouth disintegrating technology", *Asian Journal of Pharmaceutics*, vol.1 ,issue 4, Oct-Dec 2007, 191 - 195.

3. Suresh Bandari, Rajendar Kumar Mittapalli, Ramesh Gannu "Orodispersible tablets An overview'', *Asian Journal of Pharmaceutics*, Jan-2008, 2-11.

4. Prapasri Sinswath, Robert O.William, Mugul J. Yacaman, "Stabilizer choice for rapid dissolving high potency repaglinidel particles formed by evaporative precipitation in to aqueous solution", Science Direct *International Journal of Pharmaceutics* 302 (2005) 113 – 124.

5. Mohan A. ,Gosh S.K, "immediate release Tablets, past, present and future", *Indian Drugs* 47 (6), June – 2010 , 5 – 11.

6. Nandgude T. D, Saifee Maria, Bhaise K. S, "Formulation and evaluation of immediate release Tablets of repaglinidel", *Asian Journal of Pharmaceutics*, Vol.1, Oct-Dec-2006, 4

7. Liberman, Lachman and Schwartz, pharmaceutical dosage forms : Tablets 4th edition, Varghese publication, Delhi Vol.1 100 – 150.

8. Brahmakar D.M and Sunil B.Jaiswal *Biopharmaceutics and Pharmacokinetics A Treatise* 1st edition, Vallabh Prakashan, Delhi Vol.1, 19 -20, 150 – 177.

9. Chandrashekhar N .S ,Kulkarni P. K , Parimala P ; Formulation and evaluation of immediate release Tablets of repaglinide, *International Journal of Pharmaceutical Excipients*, 2006 :14- 17.

10. Chatap V.K, Gupta R.D, Jaiswal N.R, "Recent advances immediate release technology", *Asian Journal of Pharmaceutics*, vol.1 ,issue 4, Oct-Dec 2007, 191 - 195.

11. Sujimoto M, Mtusubara K, Koida Y Kobayashi M, The preparation of immediatly releasing tablets in the mouth ; *Pharmaceutical Development Technologies*, 2001,6(4) :487 – 494 .

12. Dr. Nuggehally R. Srinivas "Concept of immediate release formulations for use in acute treatment conditions – introspection, thoughts and perpectives", *Asian Journal of Pharmaceutics January* –March 2010, 87-89 .

13. Fenyvest E,Antal B, Zsadan B, Szejtli J.;Cyclodextrin (CD) polymer , a new tablet Diosintegrating agent, *Pharmazie* 1984;39(7): 473 – 475

14. Udupa N,Venkatesh, Srinivas M,Venugopal K.Nimesulide dispersible tablets from '*Direct compression* 'method,2001;38(4):208 – 10.

15. Luca Dobetti. Fast melting tablets: Developments & Technologies. Pharmaceutical Techhnology, 20001:11.

16. http://en.wikipedia.org/wiki/repaglinideRedy

17. Iman saad Ahmed, Mona Hassan Aboul - Einien, "Invitro and invivo evaluation of Fast-disintegrating lyophilized dry emulsion tablet containing nebivolol", *European Journal of Pharmaceutical Sciences* 32,(2007)58- 68.

18. Redy LH,Ghosh B,Rajneesh. Fast dissolving drug delivery systems: A review of the literature. *Indian J. Pharm. Sci,* 2002; 7: 331 -336

19. Shailesh sharma. New Generation of tablet: Fast dissolving tablet, *Pharmanifo*. net, 2008.

20. Sekiguchi. Kiobi. Studies on absorption eutectic mixture. I.A. *Comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole* in man.chem.Phann.Bul.1961;9,866 – 872.

21. Sadeghi,F.Afrasiabi Garekani, H.;Sadar, A.Influence of polymer viscosity and plasticizer addition on ethylcellulose matrix characteristics prepared from solid dispersion system. *STP Pharmaceutical Sciences*.2003;13,105 – 110.

22. Omaima A.Sammour,Mohamed A. Hamed, Nagia A. Megrab and Ahmed S. Zidan. Formulation and optimization of mouth dissolve tablets containing Rofecoxib solid dispersion, *AAPS Pharm Sci.Tech* 2006;7(2) Article 55.

23. Pignatelo.R.,Ferro.M.,DeGuidi.G.,Salemi.g.,Vaudelli.M.A.,Gucione.S.,Gepi.M.,F orte.C.,Puglisi.G.Preparation, characterization and photosensitivity studies of solid dispersion of disflunisal and Eudragit RS100 and Rl100.*International Journal of Pharmaceutics* 201; 218, 27-42.

24. Aceves.J.M., Cruz.R., Hernandez. E. Preparation and characterization of Furocemide – Eudragit controlled release system. *International Journal of Pharmaceutics*.2000;195,45 – 53.

25. Ishikawa T, Mukai B, Sriraishi S, Fuji M, ; Preparation of Rapidly disintegrating tablets using new types of Microcrystal., line cellulose (PH-M series) and low substituted Hydroxy Propyl Cellulose or spherical sugar granules by direct compression method.

26. Ishikawa T, Watanable Y, Utoguchi N, Matusumoto M; Preparation and evaluation of Rapidly disintegrating tablets in saliva containing bitter taste masked granules by direct compression method, *Chemical and Pharmaceutical Bulletin* (Tokyo);1999;47 (10): 1451 – 1454.

27. Ito A, Sugihara M,;Development of oral dosage form for elderly patients : use of Agar base of Rapidly disintegrating oral tablets, *Chemical and Pharmaceutical Bulletin*, 1996; 44 (11) : 2132-2136 .

28. Serajuddin.A.T.M. Bioavailability enhancement of porly water – soluble drugs by solid dispersion in surface – active vehicles: A recent breakthrough. La Gazette de Γ`AGI(France) 197;14,144 – 145.

29. Perissutti B, Rubesa F, Monegini M,Voinovich D.;Formulation design of carbamazepine Fast release tablets prepared by melt granulation technique, *International Journal of Pharmaceutics,* 2003, 256: 53 – 63.

30. Reddy L. H, Ghosh B, Rajeesh; Fast dissolving drug delivery systems, a review of the literature, *International Journal of Pharmaceutical Sciences*, 1997,59(4) : 331 – 336.

31. Sameer H. LAdake, "Formulation development and evaluation of Mouth Dissolving Tablets of Odancetron Hydrochloride", *Asian Journal of Pharmaceutics*, Vol.1,Isue 2 – 3 July – Sep., 207, 150 – 153.

32. Raymond C Rove, Paul J Sheakey and Sian C Owen *Text Bok of Pharmaceutical Excipients* 5th edition (2006) Royal Pharmaceutical Society of Great Britian United Kingdom page no:217 – 220, 214 – 216, 701 – 704, 118 – 120, 449 -451, 705 – 707, 132 -135, 53 – 55, 767 -769.

33. Corrigan. O. E. Mechanism of dissolution of fast release solid dispersion. *Drug Dev.Ind. Pharm.*1985; 1, 697 – 724.

34. Jinichi Fukami, Yasuo Yoshihashi, Etsuo Yonemochi, ''Evaluation of rapidly disintegrating tablets containing Glycine and Carboxy Methyl Cellulose'', Science Direct *International Journal of Pharmaceutics*, 310 (2006) 101 – 109.

35. Wang,L., F.D.Cui, and H.Sunada. Preparation and evaluation of Chem solid dispersion of nitredipine prepared with fine silica particles using the meltmixing method..*Chem. Pharm Bull (Tokyo*), 2006;54(1),37 – 43. 2006; 54(1), 37 – 43.

36. Keny R. V and Naik A Taste Masked Rapid Oro-Disintegrating Tablets of Cetirizine Hydrocloride, *Indian Drugs* 48(01) January 2011.

37. Kotteril J.V, Massei G, Cowan D.P ;Masking the bitter taste of conditioned taste Levamizole using ion exchange resin ,for practical application in wild life management, *Pet manament Sciences*, 2006, : 62(2) : 120-125.

38. Kuchekar B. S, Bandan A.C, Mahajan H.S ;Fast Dissolving Drug Delivery Systems : An update, *Pharma Times*, 2003, 35 : 7-9.

39. Mahajan H. S, Badhan A.C, Kuchekar B.S, Badhan A.C ; Mouth Dissolving Tablets of Sumatriptan succinate, *International Journal of Pharmaceutical Sciences*, 2004: 66(2) : 238-240.

40. Jatwani. *International Journal of Pharmaceutical Sceintifie Research* 2012; 3(4):942-956.

41. Bobe KR. PharmacieGlobale. *International Journal of C.Pharmaceutics*. 2011;1(02): 1 – 6.

42. Lakshmi Narasaiah V. *International Journal of Pharmaceutical Technical Research*.2011: 3(2): 652 – 659.

43. D. Karthikeyan, A.Vijayalaxmi, C. Santhosh Kumar, Formulation and evaluation of biphasic Delivery system of aceclofenac mini-tablets in Hard gelatin capsules, ISSN: 2277 – 2782, *International Journal of Novel Trends in Pharmaceutical Sciences*.

44. Noorana Tehseen, Vinay Rao, Mohd Abdul Hadi, design and characterization of twice daily mini-tablets formulation of pregabalin, *International Journal of Pharmacy and Pharmaceutical Sciences*, ISSN-0975-1491, VOL 5, Suppl 1, 2013

45. Carla M. Lopes, Jos´e Manuel Sousa Lobo, Jo˜ao F. Pinto, Paulo Costa, Compressed mini-tablets as a biphasic delivery system, *International Journal of Pharmaceutics* 323 (2006) 93–100.

46. Jitender Joshi, Lata Bhakuni and Sachin Kumar, Formulation and evaluation of solid matrix tablets of Repaglinide, Der Pharmacia Sinica, 2012, 3 (5):598-603, *Pelagia Research Library*, ISSN: 0976-8688.

47. Gross, S.T., Hoffman, A., Donbrow, M., Benita, S., 1986. Fundamentals of the release mechanism interpretation in multiparticulate systems : the prediction of the commonly observed release equations from statistical population models for particle ensembles. *International Journal of Pharmaceutics* 29, 213–222.

48. Bennett P.N.and Brown M.J.*Clinical Pharmacology*10 th edition Vol.I 293 – 31.

49. *Bentley`s Text Book of Pharmaceutics* 8th edition published by Elsevier India P Ltd New Delhi 140 – 171.

50. Betran G,Katzung, Susan B.Masters Anthony J, Trevor*, Basic and Clinical Pharmacology* 11 th edition, Vol.1.313 – 330.

51. Bhalekar M,Madgukar A,Avari J.G.;Preparation and evaluation of taste masked resinnates of Ranitidine hydrochlorides. *International Journal of Pharmaceutical Excipients*, 2005: 95 – 98.

52. Bi Y, Sunada H, Yonezawa Y, Danjo K: Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity, *Chem. Pharm.bull.* 1996; 44, (11): 221 – 2127.

53. htp:// WWW. Freshpatent.com USPTO patent application – 2070086974.

54. Kaushik D., Dureja H., Saini T.R., Mouth dissolving tablet. *A review, Indian drugs*, April204, 187 – 192.

55. Zyprexa Zydis (Olanazapine) orally disintegrating tablets, Eli Lilly and company, 1997.

56. Kei – Ichi Koizumi, Yoshiteru, watanable, Kumiko morita, Naoki, Utoguchi and Mitsuo, Matsurnoto, New method of preparing high- porosity rapidly saliva soluble compressed tablets using mannitol with camphor a subliming material, *International Journal of Pharmaceutics*, 1997; 152, 127 – 131.

57. Canada JR. USP dictionary of USAN and international drug names 198. Rockvile, *The United States Pharmacopeial Convention,* 1997;19, 159,341,342,344,744.

58. Venkadalakshi R., Sasikala C.Swathi R., "Formulation and evaluation of Granisetron Hydrochloride Mouth Dissolving Tablets", *International Journal of Pharmaceutical Sciences*, Sep – December 2009, Vol.1, Issue 2, 336 -341.

59. Ferrero C, Mufioz N, Velasco M.V; Disintegrating efficiency of Croscarmelos sodium carboxyl methyl cellulose in a direct compression formulation, *International Journal of Pharmaceutics*, 1997:47:11 – 21.

60. Crollman Pharmacology and therapeutics 11th edition 313 – 330, 626 – 630.

61. Shu T,Suzuki H, Hironaka K, Ito K; Studies on rapidly disintegrating tablets in the oral cavity using co –ground mixture of Mannitol with Crospovidone, *Chemical and Pharmaceutical Bulletin*, 2000; 50(2): 193 – 198.

62. Patel M.M., Patel D.M., Shah B.M. Fast dissolving valdecoxib tablets containing solid dispersion of valdecoxib, *Indian Journal of Pharmaceutical Science,* 2006; 68,222 – 226.

63. Shrikant P Beloshe, Dhanyakumar D Chougule, Rohit R Shah, Effect of Method Of Preparation On Pioglitazone HCL – ß – Cyclodextrin Inclusion Complexes, *Asian Journal of Pharmaceutics* – April – June 2010.

64. Dandagi P.M., Sreenivas S.A, Manvi F.V, Patil M.B, Gadad A.P, Taste masked Ofloxacin Mouth Disintegrating Tablets, *Indian Drugs*, 2005 ; 42(1): 52 – 55.

65. Raymond C Rove, Paul J Sheskey and Sian S Owen *Text Book of Pharmaceutical Excipients* 5th edition (2006) Royal Pharmaceutical Society of Great Britian United Kingdom page no: 217 – 220, 214 – 216, 701 – 704, 118 – 120, 449 – 451, 705 – 707, 132 134, 53 – 5, 767 – 769.

66. Vijayaraghavan C *A Practical Handbook of Physical Pharmaceutics,* 1 st Edition, New Century Book House, Madras 52 – 57.

67. VineetBhardwaj. Am – Euras. *Journal of Scientific Research.* 2010;5(4): 264–269.

68. Arun kumar N. *International Journal of Pharmaceutical Technical Research* 2009; 1(4): 1725 – 1730.

69. Madhura VD. *Journal of Pharmaceutical Research* 209; 2(9): 1481 – 1484.

70. Swamy. *Indian Pharmaceutical Sciences* 2007; 69 (6): 836 – 840.

71. Patel MM. *Indian Pharmaceutical Sciences* 2006; 68(2): 222 – 226.